

Evaluating the Safety and Efficacy of Concizumab in Hemophilia A/B Patients: A Systematic Review

Clinical and Applied
Thrombosis/Hemostasis
Volume 31: 1-14
© The Author(s) 2025
Article reuse guidelines:
sagepub.com/journals-permissions
DOI: 10.1177/10760296251342968
journals.sagepub.com/home/cat



Erum Siddiqui, MBBS¹ , Maliha Khalid, MBBS¹ , Muhammad Saad Khan, MBBS¹ , Kanza Farhan, MBBS¹ , Muhammad Mohsin Khan, MBBS¹ and Aminath Waafira, MBBS²

Abstract

Background: Hemophilia A and B are X-linked recessive bleeding disorders caused by deficiencies of coagulation factors VIII and IX, respectively. These conditions lead to spontaneous bleeding, joint damage, inhibitor development, and the burden of frequent intravenous infusions. Concizumab, a monoclonal antibody targeting tissue factor pathway inhibitor (TFPI), is a novel non-factor therapy that enhances thrombin generation. This systematic review evaluates the efficacy and safety of concizumab prophylaxis in patients with hemophilia A and B.

Methods: This systematic review was conducted in accordance with PRISMA guidelines. Randomized controlled trials (RCTs) assessing the use of concizumab in hemophilia A or B were identified through a comprehensive search of electronic databases. Outcomes of interest included annualized bleeding rate (ABR), thrombin generation, bleeding episodes, immunogenicity, and adverse events. The Cochrane Risk of Bias Tool 2.0 was used for quality assessment.

Results: Five studies were included. Concizumab prophylaxis was associated with a notable reduction in ABR, with reported decreases from 9.4 to 1.3 episodes/year and from 19.6 to 2.9 episodes/year in hemophilia A, and from 14.9 to 1.6 episodes/year in hemophilia B. Thrombin generation increased in a dose-dependent manner and stabilized by week 24. Across all studies, bleeding episodes were significantly reduced. Adverse events were primarily mild to moderate. No thromboembolic events were reported.

Conclusion: Concizumab appears to be an effective and safe prophylactic treatment for patients with hemophilia A and B, demonstrating consistent reductions in bleeding rates and enhanced thrombin generation. Further long-term studies are warranted to establish its sustained safety and efficacy.

Keywords

hemophilia A, hemophilia B, factor VIII, concizumab, non-factor therapy, bleeding episodes

Received: 28 March 2025; revised: 21 April 2025; accepted: 30 April 2025

Introduction

Hemophilia A and B are the X-linked recessive bleeding disorders that are caused due to deficiencies in coagulation factor VIII (FVIII) and factor IX (FIX), respectively.¹ Joints, muscles, and soft tissues are the important areas, affected by prolonged bleeding episodes caused by deficiencies of these components, which reduce thrombin production.² Lack of sufficient prophylaxis causes patients to suffer life-threatening bleeding events, progressive joint deterioration (hemophilic arthropathy) and repeated spontaneous hemorrhages. All of these have a substantial

adverse influence on morbidity, mortality, and quality of life.³ Patient outcomes have improved with the therapy advancements, but challenges still exist, especially in terms

¹Department of Medicine, Jinnah Sindh Medical University, Karachi, Pakistan

²School of Medicine, The Maldives National University, Malé, Maldives

Corresponding Author:

Aminath Waafira, The Maldives National University, Rahdhebai Hingun, Malé, Maldives.

Email: wafiagany@gmail.com



Creative Commons Non Commercial CC BY-NC: This article is distributed under the terms of the Creative Commons Attribution-NonCommercial 4.0 License (<https://creativecommons.org/licenses/by-nc/4.0/>) which permits non-commercial use, reproduction and distribution of the work without further permission provided the original work is attributed as specified on the SAGE and Open Access page (<https://us.sagepub.com/en-us/nam/open-access-at-sage>).

of medication adherence, inhibitor development, and the cost of frequent intravenous infusions.

Factor replacement therapy, which can be given both as prophylactic to stop spontaneous hemorrhages and on-demand during bleeding episodes, is the cornerstone of conventional hemophilia management approaches.⁴ The formation of inhibitors, repeated intravenous infusions and high costs are some of the limitations of factor replacement treatment, even though it has greatly decreased bleeding-related outcomes.^{5,6} About 30% of patients with severe hemophilia A and 3%–5% of patients with hemophilia B acquire inhibitors, which are alloantibodies that neutralize foreign clotting factors.⁷ By reducing the effectiveness of conventional factor replacement therapy, the presence of inhibitors makes treatment more difficult and calls for the use of bypassing drugs like recombinant factor VIIa (rFVIIa) or activated prothrombin complex concentrate (PCC). However, these therapies often have limitations, require high doses, and carry an increased risk of thrombotic events. Consequently, there has been growing interest in non-factor-based therapies that can provide more effective and convenient alternatives for hemophilia management.^{8,9}

Concizumab is a novel monoclonal antibody that represents a significant advancement in hemophilia management.¹⁰ It works by targeting tissue factor pathway inhibitor (TFPI), a key regulator of coagulation that inhibits factor Xa (FXa) and tissue factor-mediated thrombin production. By selectively inhibiting TFPI, concizumab restores thrombin production and enhances hemostatic balance in hemophilia A and B patients irrespective of inhibitor status.^{11,12} Unlike conventional factor-based therapies, concizumab doesn't rely on FVIII or FIX replacement, which makes it beneficial, particularly for patients with inhibitors. Moreover, its subcutaneous route of administration provides a more convenient and less invasive alternative to intravenous infusions, thus improving treatment adherence and patient outcomes.¹³

Several clinical trials have evaluated the efficacy and safety of concizumab. Phase 2 trials, including the explorer4 and explorer5 studies, demonstrated that concizumab prophylaxis significantly reduced hemophilia A and B's annual bleeding rate (ABR).¹⁰ Given the concizumab promising yet developing role in hemophilia treatment, a careful assessment of the current data is necessary for future research and clinical practice. The purpose of this systematic review (SR) is to evaluate the safety and effectiveness of concizumab prophylaxis in patients with hemophilia A and B.

Methodology

This systematic review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) criteria and registered with PROSPERO (CRD420251014850) accessible at <https://www.crd.york.ac.uk/PROSPERO/view/CRD420251014850>

Data Sources and Search Strategy

This systematic review was conducted conclusively with the Preferred Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines.¹⁴ A comprehensive electronic search of PubMed (Medline), ScienceDirect, EMBASE, Scopus, and Cochrane Central databases was conducted from inception to December 2024. The following search terms were used: (“Concizumab” OR “Tissue Factor Pathway Inhibitor” OR “TFPI”) AND (“Hemophilia” OR “Hemophilia A” OR “Hemophilia B” OR “Factor VIII Deficiency” OR “Factor IX Deficiency” OR “Christmas Disease”). Two unbiased authors (ES and MK) searched without limitations or conflicts of interest. A search was conducted on “clinicaltrials.gov” for relevant published or unpublished clinical trials. Furthermore, we conducted a manual search of the reference lists of the included research, as well as related meta-analyses and review articles, to identify possibly relevant studies.

Study Selection

The eligibility criteria were randomized controlled trials (RCTs) with a target population of males aged 12–85 with hemophilia A or B, either with or without inhibitors. Eligible participants had severe hemophilia A (FVIII <1%) or moderate/severe hemophilia B (FIX ≤2%). They received concizumab or control (placebo/ no prophylaxis) with a minimum body weight of 25 kg and a BMI range of 18–30 kg/m². All males with low platelet count (<50,000–100,000/μL) or fibrinogen levels below 2 g/L, renal impairment, hepatic dysfunction or any other comorbidities were excluded. Articles such as non-randomized trials, observational studies, peer-reviewed commentaries, letters to the editor, and case reports were also excluded.

Data Extraction and Quality Assessment

Duplicate studies were removed from the list through Endnote Reference Library Software. All reviewers then carefully assessed the remaining articles, and only those that met the previously stated eligibility conditions were included. All the articles were first screened based on the abstract and title, followed by full text. A third reviewer was consulted to resolve any disagreements regarding the results. An online Microsoft Excel spreadsheet was created using data from the completed RCTs for the baseline characteristics and outcomes. Baseline parameters are as follows: age range (years), weight (kg), BMI (kg-m²), ethnicity, FVIII level (%), historical annualized bleeding rate (ABR), moderate hemophilia, severe hemophilia, number of positive inhibitor tests, race. The following outcomes were included:

Primary Outcomes

Annualized bleeding rate (ABR), Bleeding episodes, Thrombin Generation.

Secondary Outcomes

Immunogenicity (Anti-Drug Antibodies (ADAs)/antibodies against concizumab), Prothrombin Time (PT), Activated Partial Thromboplastin Time (aPTT), D dimer, prothrombin F1 + 2, TFPI Levels, safety outcomes, adverse events like injection site reaction and patient-related outcomes like pyrexia, musculoskeletal pain and upper respiratory tract infection.

The modified Cochrane Collaboration risk of bias technique was utilized to check the reliability of RCTs. Quality assessment and risk of bias were independently assessed using the Cochrane Risk of Bias Tool 2 tool on all included RCTs by two investigators, and the results were matched. Any discrepancies were resolved by team consensus.

Data Synthesis

We were unable to perform a meta-analysis of all primary outcomes due to the unavailability of complete and consistent data across the included studies. While thrombin generation, annualized bleeding rate (ABR), and bleeding episodes were reported in multiple trials, significant variations in study designs, outcome definitions, and data reporting methods limited the feasibility of statistical pooling. Some studies lacked essential measures such as standard deviations, confidence intervals, or numerical outcome data, which are necessary for meta-analysis. Additionally, differences in patient populations, including the presence or absence of inhibitors, varying age ranges, and heterogeneous dosing regimens, introduced clinical heterogeneity that further constrained direct comparisons. Given these limitations, we conducted a systematic review of randomized controlled trials (RCTs) to qualitatively synthesize the available evidence on the efficacy and safety of concizumab. However, forest plots were generated for the visual display of safety outcomes by using Review Manager (version 5.4. Copenhagen: Nordic Cochrane Centre, The Cochrane Collaboration, 2014). These outcomes were displayed as risk ratios (RR) with a 95% confidence interval using the random effects model.

Results

Study Selection

First, 25,000 records were identified via database searches like PubMed (Medline), ScienceDirect, EMBASE, Scopus, and Cochrane Central). Of these, 24,480 records remained after duplicate removal and were screened at the title and abstract levels. This resulted in 24,468 records being excluded, including review articles, abstracts, case reports, and observational studies, with 12 full-text randomised control trials remaining for eligibility evaluation. Seven studies were excluded as being out of scope,

resulting in a final selection of 5 studies to be included in the analysis. This stringent inclusion approach significantly chose the most relevant and high-quality studies for final review. The study selection steps are presented in Figure 1.

Baseline Characteristics of Studies

The five articles included^{10,15-18} were RCTs conducted on individuals suffering from Hemophilia A or B. Table 1 (Baseline Characteristics) outlines the detailed characteristics of the included studies and the results of each study.

Risk of Bias Assessment

The quality of individual studies was analyzed according to the study design using the Cochrane Risk of Bias Tool 2.0,¹⁹ a checklist for analyzing the risk of bias in studies. The results of the risk of bias assessment are presented in Figure 2.

Summary of Primary Outcomes and Key Findings from Included Studies

See Table 2.

Reported Outcomes from All Included Studies

See Table 3.

Efficacy Outcomes

Annualized Bleeding Rate (ABR): The annualized bleeding rate (ABR) was significantly reduced in patients receiving concizumab prophylaxis across multiple studies. Tadashi Matsushita (2023) reported a notable decline in spontaneous bleeding episodes, decreasing from 9.4 episodes per year without prophylaxis to 1.3 episodes per year with concizumab. Similarly, joint bleeding episodes were reduced from 9.1 to 1.4 episodes per year, while target joint bleeding episodes dropped from 1.1 to 0.1 episodes per year. P. Chowdary (2024) further demonstrated the efficacy of concizumab in reducing ABR, with median ABR decreasing to 2.9 (IQR 0.0-5.2) in hemophilia A patients and 1.6 (IQR 0.0-4.8) in hemophilia B patients, compared to significantly higher rates in those without prophylaxis (19.6 and 14.9, respectively). These findings highlight the robust hemostatic efficacy of concizumab in reducing bleeding frequency and improving clinical outcomes in hemophilia patients. In the Explorer 4 inhibitor trial, the estimated ABR was 4.5 (95% CI, 3.2; 6.4) in the concizumab arm, significantly lower than 20.4 (95% CI, 14.4; 29.1) in the rFVIIa on-demand arm. In the

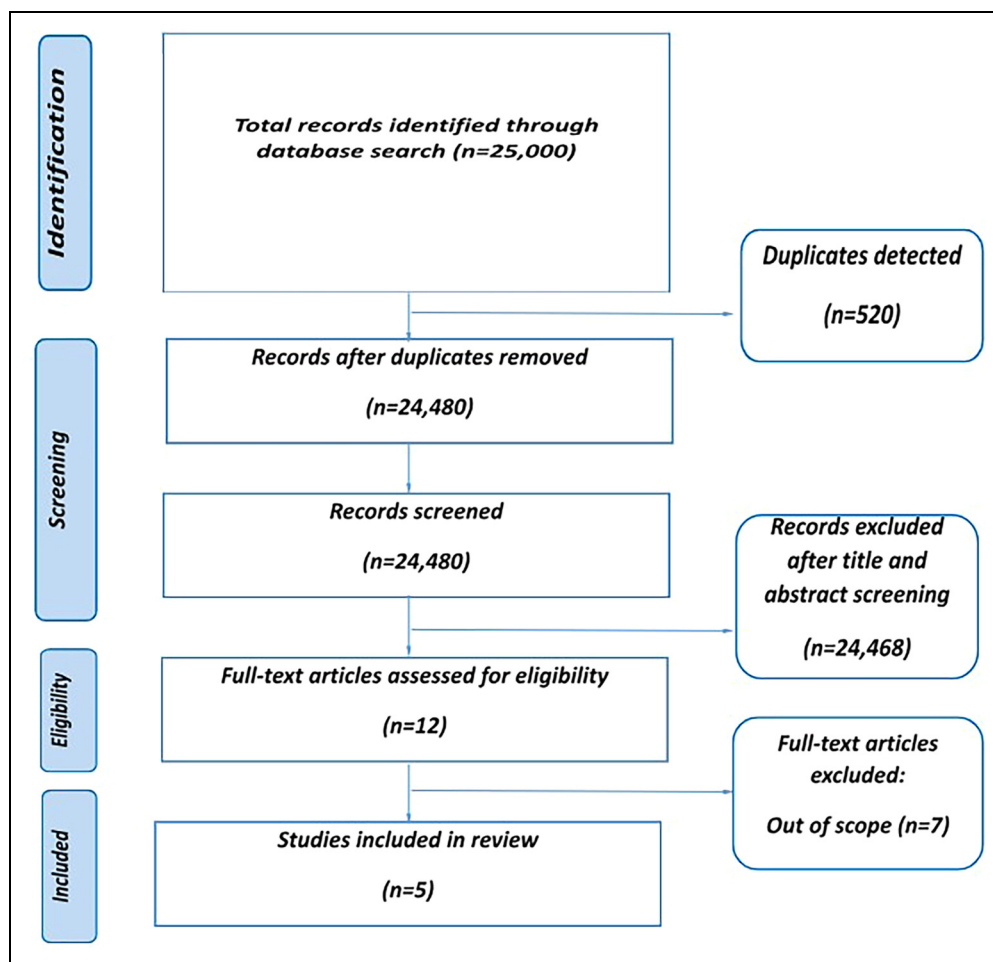


Figure 1. PRISMA Flowchart.

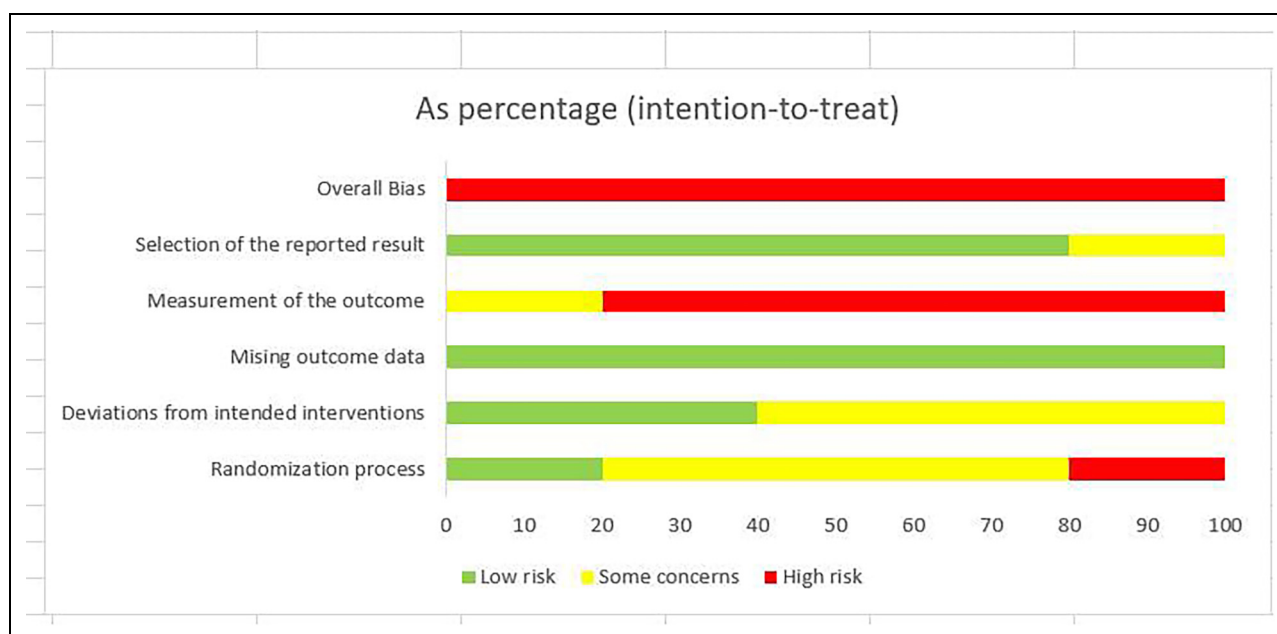


Figure 2. Risk of Bias Assessment.

Table 1. Baseline Characteristics.

Study		P. Chowdary et al 2015	H. Eichler et al 2018	Tadashi Matsushita et al 2023	P. Chowdary et al 2024	Amy D. Shapiro et al 2021	
						Explorer 4 (Inhibitor Trial)	Explorer 4 (Non-Inhibitor Trial)
No. of participants	Concizumab Control	18	18	114	42	17	36
	Total	6	6	19	21	9	no control group
Age Range (years)	Concizumab Control	24	24	133	63	33.9 (10)	36.9 (12.9)
	Concizumab Control	30-36	33.1	12-84	12-84	33.9 (10)	—
Weight (kg)	Concizumab Control	30-36	37	12-84	12-64	71 (12.1)	77.0 (20.4)
	Concizumab Control	71-77	72.8	25 kg +	25 kg +	71 (12.1)	—
	Concizumab Control	71-77	76.2	25 kg +	25 kg +	—	—
Ethnicity	Concizumab Control	—	—	5	1	—	—
	Hispanic	—	—	1	2	—	—
	Concizumab Control	—	—	106	41	—	—
	Not hispanic	—	—	16	19	—	—
BMI (kg m ⁻²)	Concizumab Control	24-26	23.8	—	—	—	—
	Concizumab Control	24-26	24	—	—	—	—
FVIII level (%)	Concizumab Control	—	0.46	—	—	—	—
	Concizumab Control	—	0.5	—	—	—	—
Historical ABR	Concizumab Control	—	8.67	—	—	—	—
	Concizumab Control	—	34	—	—	—	—
Moderate hemophilia	Concizumab Control	—	1	—	—	—	—
Severe hemophilia	Concizumab Control	—	0	—	—	—	—
	Concizumab Control	—	17	—	—	—	—
No. of positive inhibitor tests	Concizumab Control	—	6	—	—	—	—
	Concizumab Control	—	0	—	—	—	—
Race	Concizumab Control	—	0	—	—	—	—
	American Indian or Alaska Native	—	—	2	0	—	—
	Black or African American	—	—	1	0	—	—
	Asian	—	—	2	2	—	—
	Concizumab Control	—	—	1	1	—	—
	White	—	—	31	18	—	—
	Concizumab Control	—	—	6	7	—	—
	Not reported	—	—	69	21	—	—
	Concizumab Control	—	—	9	13	—	—
	Others	—	—	4	0	—	—
	Concizumab Control	—	—	2	0	—	—
	Concizumab Control	—	—	0	1	—	—
	Concizumab Control	—	—	0	0	—	—

Abbreviations: ABR, annualized bleeding rate; BMI, body mass index.

Explorer 5 non-inhibitor trial, the estimated ABR was 7.0 (95% CI, 4.6; 10.7) (Table 3).

Thrombin Generation: Across all studies, concizumab demonstrated a dose-dependent increase in thrombin generation. Chowdary (2015) and Eichler (2018) observed consistent increases with dosage increments. Matsushita (2023) reported a rise in predose thrombin peak levels from 13.5 nmol/L at baseline to 105.4 nmol/L at week 24, which remained stable thereafter. Similarly, P. Chowdary (2024) reported an increase from 23.2 nmol/L at baseline to 81.1 nmol/L at week 24. In Explorer 4 and 5, concizumab was associated with increased thrombin generation potential, as evidenced by increases in D-dimer and prothrombin fragment 1 + 2 levels. (Table 3).

Bleeding Episodes: Chowdary (2015) observed 24 bleeds/bruises in 14 hemophilia patients (9 concizumab; 5 placebo). Eichler (2018) recorded 91 bleeding episodes across 21 patients, with a dose-dependent reduction in bleeding risk. Matsushita (2023) provided specific bleeding rate reductions: spontaneous bleeding episodes decreased from 9.4 to 1.3 episodes/year, joint bleeding episodes from 9.1 to 1.4 episodes/year, and target joint bleeding episodes from 1.1 to 0.1 episodes/year. P. Chowdary (2024) reported a median ABR reduction from 19.6 (IQR 17.3-30.4) to 2.9 (IQR 0.0-5.2) in hemophilia A patients and from 14.9 (IQR 3.3-22.1) to 1.6 (IQR 0.0-4.8) in hemophilia B patients. In Explorer 4, 47 treated bleeding episodes were reported in the concizumab arm. In Explorer 5, a total of 70 treated bleeding episodes were reported. (Table 3).

Pharmacokinetics (PK)

Half-life of Concizumab: P. Chowdary (2015) reported a half-life ranging from 31.1 to 74.2 h post-IV administration. Data for other studies were not reported (Table 3).

Maximum Plasma Concentration (C_{max}): P. Chowdary (2015) found a greater-than-dose-proportional increase in C_{max}, with 9000 µg/kg IV yielding 247 ng/mL and 3000 µg/kg SC yielding 16.7 ng/mL. Eichler (2018) reported a non-linear dose-dependent increase in C_{max} across various doses (Table 3).

Steady-State Levels: Steady-state levels were achieved before Day 42 in Eichler (2018). Other studies did not report this outcome (Table 3).

Coagulation Parameters

Prothrombin Time (PT) and Activated Partial Thromboplastin Time (aPTT): No clinically significant changes were observed in P. Chowdary (2015) and Eichler (2018). Data were not reported in the later studies (Table 3).

Endogenous Thrombin Potential (ETP): Eichler (2018) noted a dose-dependent increase in thrombin generation, with the highest dose (0.8 mg/kg) approaching normal

range values. Other studies did not report ETP values (Table 3).

D-dimer and Prothrombin F1 + 2: Chowdary (2015) and Eichler (2018) reported dose-dependent increases in D-dimer and prothrombin F1 + 2 levels. Matsushita (2023) confirmed that increased D-dimer levels correlated with concizumab plasma concentrations. P. Chowdary (2024) observed an increase in fibrin D-dimers in 8% of patients. Explorers 4 and 5 also reported increased D-dimer and prothrombin fragment 1 + 2 levels with concizumab treatment, reflecting enhanced thrombin generation (Table 3).

Fibrinogen: No significant changes in fibrinogen levels were observed in Eichler (2018) and Matsushita (2023) (Table 3).

TFPI Data

A dose-dependent decrease in free TFPI levels was consistently observed across all studies. Matsushita (2023) reported a reduction from 88.3 ng/mL (baseline) to 10.7 ng/mL (week 24), while P. Chowdary (2024) recorded a decrease from 84.8 ng/mL to 11.4 ng/mL at week 24. Similarly, Explorer 4 and 5 studies found that free TFPI levels were reduced with increasing concizumab exposure (Table 3).

Immunogenicity

Anti-Drug Antibodies (ADAs): P. Chowdary (2015) and Eichler (2018) detected no anti-concizumab antibodies. Matsushita (2023) found ADAs in 26% of concizumab-treated patients, mostly low titer, with no impact on bleeding patterns or pharmacokinetics. P. Chowdary (2024) reported low-titer ADAs in 14% of hemophilia A and 9% of hemophilia B patients, with no significant impact on outcomes. In both Explorer 4 and 5, three patients tested positive for ADAs, but these were low to medium titers and showed no clinical impact. (Table 3).

Safety Outcomes

Adverse Events (AEs): Chowdary (2015) reported mild (75%), moderate (22%), and severe (3%) AEs, none related to concizumab. Eichler (2018) observed 52 mild and 2 moderate AEs. Matsushita (2023) found AEs in 63% of concizumab-treated patients, while Prof. Pratima Chowdary (2024) reported SARS-CoV-2 infections (13%), upper respiratory tract infections (7%), and injection-site reactions. In both Explorer 4 and 5, concizumab was reported to be safe and well tolerated, with most AEs being mild and unrelated to treatment (Table 3).

Serious Adverse Events (SAEs): No SAEs related to concizumab were reported by P. Chowdary (2015) and Eichler (2018). Matsushita (2023) reported SAEs in 11% of concizumab-treated patients, whereas P. Chowdary

(2024) recorded SAEs in 9% of patients (22 events). In Explorer 4, one SAE (central venous catheter removal) was reported, but it was not related to concizumab. (Table 3).

Thromboembolic Events: None of the studies reported thromboembolic events.

Safety Analysis

Risk of Injection Site Reaction with Concizumab Versus Control. Figure 3 shows a forest plot evaluating the risk of injection site reactions in patients receiving Concizumab compared to a control group. The pooled RR using a random-effects model is 1.96 (95% CI: 0.15-25.45, $p = .61$), indicating no statistically significant difference between the groups. H. Eichler (2018) reported an RR of 0.67 (95% CI: 0.07-6.11), while T. Matsushita (2023) reported an RR of 7.65 (95% CI: 0.45-128.67). The heterogeneity analysis shows moderate variability ($I^2 = 52\%$), though the Chi^2 test ($p = .15$) does not indicate significant heterogeneity. The wide confidence intervals and the pooled estimate crossing the null line ($\text{RR} = 1$) suggest substantial uncertainty in the effect estimate. With an overall Z-test of 0.52 ($p = .61$), the results do not provide statistically significant evidence that concizumab increases the risk of injection site reactions.

Risk of Musculoskeletal Pain with Concizumab Versus Control. Figure 4 shows a forest plot assessing the risk of musculoskeletal pain in patients receiving concizumab compared to a control group. The pooled RR using a random-effects model is 1.83 (95% CI: 0.21-15.63, $p = .58$), indicating no statistically significant difference between the groups. H. Eichler (2018) reported an RR of 1.11 (95% CI: 0.05-24.07), while T. Matsushita (2023) reported an RR of 2.94 (95% CI: 0.15-58.24). The heterogeneity analysis shows no observed variability ($I^2 = 0\%$), suggesting consistency between studies, and the Chi^2 test ($p = .65$) further supports this finding. With an overall Z-test of 0.55 ($p = .58$), the results do not provide statistically significant evidence that concizumab increases the risk of musculoskeletal pain.

Risk of Pyrexia with Concizumab Versus Control. Figure 5 shows a forest plot assessing the risk of pyrexia (fever) in patients receiving concizumab compared to a control group. The pooled RR using a random-effects model is 1.13 (95% CI: 0.18-7.29, $p = .89$), indicating no statistically significant difference between the groups. H. Eichler (2018) reported an RR of 1.11 (95% CI: 0.05-24.07), while T. Matsushita (2023) reported an RR of 1.15 (95% CI: 0.11-11.87). The heterogeneity analysis shows no observed variability ($I^2 = 0\%$), suggesting consistency between studies, and the Chi^2 test ($p = .98$) further supports this finding. The wide confidence intervals and the pooled

estimate crossing the null line ($\text{RR} = 1$) indicate substantial uncertainty in the effect estimate. With an overall Z-test of 0.13 ($p = .89$), the results do not provide statistically significant evidence that concizumab increases the risk of pyrexia.

Risk of Upper Respiratory Tract Infection with Concizumab Versus Control. Supplementary Figure 1 shows a forest plot assessing the risk of upper respiratory tract infection (URTI) in patients receiving concizumab compared to a control group. The pooled RR using a random-effects model is 1.38 (95% CI: 0.22-8.54, $p = .73$), indicating no statistically significant difference between the groups. H. Eichler (2018) reported an RR of 1.84 (95% CI: 0.10-33.82), while T. Matsushita (2023) reported an RR of 1.15 (95% CI: 0.11-11.87). The heterogeneity analysis shows no observed variability ($I^2 = 0\%$), suggesting consistency between studies, and the Chi^2 test ($p = .80$) further supports this finding. With an overall Z-test of 0.35 ($p = .73$), the results do not provide statistically significant evidence that Concizumab increases the risk of URTI.

Discussion

This systematic review provides a comprehensive assessment of the efficacy and safety of concizumab prophylaxis in patients with hemophilia A and B, with or without inhibitors. Concizumab serves as a novel and promising therapy for hemophilia treatment by shifting away from traditional factor replacement and it instead targets an alternative pathway of coagulation regulation. It is a monoclonal antibody that inhibits tissue factor pathway inhibitor (TFPI) which is a natural anticoagulant protein that regulates thrombin production by suppressing factor-Xa (FXa).¹⁰ In hemophilia patients, insufficient thrombin production due to FVIII or FIX deficiency results in inadequate clot formation, which leads to excessive bleeding. By inhibiting TFPI, concizumab restores thrombin production, thereby protecting hemostasis and reducing the frequency of bleeding episodes.²⁰ This mechanism of action makes concizumab particularly effective for patients with inhibitors, as its efficacy is independent of FVIII or FIX levels. Additionally, concizumab is administered subcutaneously, thus offering a more convenient and less invasive alternative option to intravenous factor replacement therapy, which requires frequent infusions and often central venous access. The availability of a subcutaneous therapy would improve treatment adherence, which is a major concern in long-term hemophilia management, particularly in younger patients or those with venous access issues.²¹

The findings from this systematic review indicate that concizumab significantly reduces the annualized bleeding rate (ABR) and overall bleeding episodes across multiple randomized controlled trials (RCTs).¹⁵⁻¹⁸ This aligns

Table 2. Primary Outcomes and Key Findings of Included Studies.

Study	Population	Intervention	Comparator	Primary Outcome	Key Findings
P. Chowdary et al 2015	28 healthy volunteers, 24 hemophilia A/B patients	Single-dose IV/SC concizumab (loading dose of 1.0 mg/kg followed by a daily dose of 0.2 mg/kg from day 2)	Placebo	Safety	No serious AEs related to concizumab were reported. 75% mild, 22% moderate, 3% severe (none related to concizumab) AEs were reported, Mild injection-site reactions, No dose-dependent AE pattern observed.
H. Eichler et al 2018	24 hemophilia A patients without inhibitors	Multiple SC concizumab doses (0.25, 0.5 and 0.8 mg/kg, once every 4 days)	Placebo	Safety	No serious AEs related to concizumab were reported, 56 adverse events (AEs) were reported in 19 of 24 patients. majority of AEs were mild (54 events), with only 2 moderate events. Common AEs included headache, nasopharyngitis (common cold), and injection site erythema.
T. Matsushita et al 2023	148 hemophilia A/B patients without inhibitors	Concizumab prophylaxis (SC) (loading dose of 1.0 mg per kilogram of body weight, followed by 0.2 mg per kilogram daily)	No prophylaxis	Annualized Rate of Treated, Spontaneous & Traumatic Bleeding Episodes	Annualized bleeding rate was significantly lower in the concizumab group (1.7 episodes vs 11.8 episodes in no prophylaxis group, Rate Ratio = 0.14, $p < .001$)
P. Chowdary et al 2024	133 hemophilia A/B patients with inhibitors	Concizumab prophylaxis (SC) (50-3000 micrograms/kg)	No prophylaxis	Annualized Bleeding Rate (ABR)	Concizumab significantly reduced bleeding versus no prophylaxis. Haemophilia A: 86% reduction (ABR ratio 0.14, $p < .0001$). Haemophilia B: 79% reduction (ABR ratio 0.21, $p < .0001$)
Amy D. Shapiro et al 2021 (Explorer 4 (Inhibitor Trial))	26 hemophilia A/B patients with inhibitors	Daily subcutaneous concizumab (0.15 mg/kg, potential escalation to 0.20 and 0.25 mg/kg)	On-demand treatment with rFVIIa	Annualized Bleeding Rate (ABR) at last dose level	Estimated ABR: HAwI: 3.0 (95% CI, 1.7; 5.3), HBwI: 5.9 (95% CI, 4.2; 8.5), HA: 7.0 (95% CI, 4.6; 10.7). - Concizumab was safe and well tolerated, with no severe AEs or thromboembolic events reported.
Amy D. Shapiro et al 2021 (Explorer 5 (Non-Inhibitor Trial))	36 hemophilia A patients without inhibitors	Daily subcutaneous concizumab (0.15 mg/kg, potential escalation to 0.20 and 0.25 mg/kg)	no control group	Annualized Bleeding Rate (ABR) at last dose level	Estimated ABR: 7.0 (95% CI, 4.6; 10.7) - Concizumab was safe and well tolerated, with no severe AEs or thromboembolic events reported. - Most patients (63.9%) reported treated bleeding episodes.

Study Findings

Outcome	Parameters	P. Chowdary et al 2015	H. Eichler et al 018	Tadashi Matsushita et al 2023	P. Chowdary et al 2024	Any D. Shapiro et al 2021
Efficacy Outcomes	Thrombin Generation	Increased in a dose-dependent manner	Increased in a dose-dependent manner	Predose thrombin peak levels rose from 13.5 nmol/L (baseline) to 105.4 nmol/L (week 24) in concizumab-treated patients, then remained stable.	Peak thrombin concentration increased from 23.2 nmol/L at baseline to 81.1 nmol/L at Week 24	Concizumab associated with increased thrombin generation potential
	Annualized bleeding rate	NR	NR	Annualized bleeding rate was significantly lower in the concizumab group (1.7 episodes vs 11.8 episodes in no prophylaxis group, ABR Rate Ratio = 0.14, <i>p</i> < .001)	Concizumab significantly reduced Annualized bleeding rate.	Concizumab associated with increased thrombin generation potential
	Bleeding Episodes	24 bleeds/bruises in 14 hemophilia patients (9 concizumab; 5 placebo).	91 bleeding episodes were recorded across 21 patients, dose-dependent reduction in bleeding risk was seen	Spontaneous bleeding episodes: No prophylaxis: 9.4 episodes/year Concizumab: 1.3 episodes/year Joint bleeding episodes: No prophylaxis: 9.1 episodes/year Concizumab: 1.4 episodes/year Target joint bleeding episodes: No prophylaxis: 1.1 episodes/year Concizumab: 0.1 episodes/year	Haemophilia A: Median ABR 2.9 (IQR 0.0-5.2) on concizumab versus 19.6 (IQR 17.3-30.4) with no prophylaxis. Haemophilia B: Median ABR 1.6 (IQR 0.0-4.8) on concizumab versus 14.9 (IQR 3.3-22.1) with no prophylaxis.	Concizumab associated with increased thrombin generation potential
Safety Outcomes	Adverse Events (AEs)	75% mild, 22% moderate, 3% severe (none related to concizumab) AEs	52 mild and 2 moderate AEs reported	AEs occurred in 63% of patients receiving concizumab	SARS-CoV-2 infection (13%), upper respiratory tract infection (7%), injection-site reactions	Concizumab was reported to be safe and well tolerated, with most AEs being mild and unlikely related to the treatment
	Serious Adverse Events (SAEs)	no SAEs due to concizumab reported	no SAEs due to concizumab reported	SAEs occurred in 11% of concizumab-treated patients.	Reported in 9% of patients (22 events).	Concizumab was reported to be safe and well tolerated, with most AEs being mild and unlikely related to the treatment
	Thromboembolic Events	No thromboembolic events reported	No thromboembolic events reported	No thromboembolic events reported.	No thromboembolic events reported.	Concizumab associated with increased thrombin generation potential

Table 3. Continued.

Study Findings					
Outcome	Parameters	P. Chowdary et al 2015	H. Eichler et al 018	Tadashi Matsushita et al 2023	Amy D. Shapiro et al 2021
				Explorer 4 (Inhibitor Trial)	Explorer 4 (Non-Inhibitor Trial)
Pharmacokinetics (PK)	Half-life of Concizumab	After i.v. administration, $t_{1/2}$ ranged 31.1 to 74.2 h.	NR	NR	NR
	Maximum Plasma Concentration (C _{max})	Higher doses led to greater-than-dose-proportional increases in C _{max} . 9000 µg/kg i.v. in hemophilia patients: C _{max} = 247 ng/mL. 3000 µg/kg s.c. in hemophilia patients: C _{max} = 16.7 ng/mL.	C _{max} increased in a non-linear, dose-dependent manner, 0.25 mg/kg : C _{max} = 52 (42; 83), 0.5 mg/kg : C _{max} = 265 (108; 2450), 0.8 mg/kg : C _{max} = 1442 (154; 4630). Geometric Mean (Min; Max) steady-state concizumab levels were achieved before Day 42	NR	NR
Coagulation Parameters	Steady-State Levels	NR	NR	NR	NR
	Prothrombin Time (PT)	No clinically significant changes observed.	No clinically significant changes observed.	NR	NR
	Activated Partial Thromboplastin Time (aPTT)	No clinically significant changes observed.	No clinically significant changes observed.	NR	NR
	Endogenous Thrombin Potential (ETP)	NR	Thrombin generation increased in a dose-dependent manner. In the 0.8 mg/kg group, ETP levels approached normal range	NR	NR
	D dimer	Dose-dependent increases in D-dimer levels were observed. Higher increases in D-dimer were seen at intravenous (i.v.) doses $\geq$ 1000 µg/kg in hemophilia patients.	Increased mostly in the highest (0.8 mg/kg) dose cohort	Increased levels observed, correlated with concizumab plasma concentrations.	D-dimer levels increased with concizumab treatment, indicating enhanced thrombin generation
TFPI (Tissue Factor Pathway Inhibitor)	prothrombin F1 + 2	Dose-dependent increase, consistent with coagulation activation.	Increased mostly in the highest (0.8 mg/kg) dose cohort.	Increased in patients receiving concizumab, reflecting enhanced thrombin generation.	Levels of prothrombin fragment 1 + 2 increased with concizumab exposure
	Fibrinogen	NR	no clinically significant depletion of fibrinogen.	No significant changes observed over time.	NR
	TFPI Levels	Dose-dependent decrease in free TFPI levels	Unbound TFPI decreased in a dose-dependent manner	Free TFPI concentration decreased from 88.3 ng/mL (baseline) to 10.7 ng/mL (week 24) in concizumab-treated	Free TFPI levels were reduced with increasing concizumab exposure

(continued)

Table 3. Continued.

Outcome	Parameters	Study Findings			
		P. Chowdary et al 2015	H. Eichler et al 018	Tadashi Matsushita et al 2023	Amy D. Shapiro et al 2021 P. Chowdary et al 2024
Immunogenicity	Anti-Drug Antibodies (ADAs)	No anti-concizumab antibodies detected in any participant	No anti-concizumab antibodies detected in any participant	patients, with no change in the no-prophylaxis group. Detected in 26% of concizumab-treated patients. Majority had low titers, one patient had a medium titer. No effect on bleeding patterns or pharmacokinetics.	baseline to 11.4 ng/mL at Week 24.
					Low-titre ADAs detected in 14% of haemophilia A and 9% of haemophilia B patients. No significant impact on bleeding rates, AEs, or pharmacokinetics.
					Three patients in this trial tested positive for ADAs, but these were of very low to medium titer and did not show clinical effects
					Three patients in this trial tested positive for ADAs, but these were of very low to medium titer and did not show clinical effects

with previous phase 2 and 3 clinical trials, including Explor4 and Explor5, which demonstrated substantial reductions in bleeding rates.¹⁰ Notably, concizumab's efficacy appears consistent across both hemophilia A and B patients, regardless of inhibitor status, making it a broadly applicable treatment option. A key observation in this review is the dose-dependent increase in thrombin generation seen across included studies, reinforcing the mechanistic rationale behind concizumab's effectiveness. This finding supports previous review studies including animal and humans, which have demonstrated that TFPI inhibition effectively restores thrombin generation to near-normal levels, even in the absence of clotting factor supplementation.²² Safety remains a critical consideration in the evaluation of any new therapeutic approach in hemophilia.²³ Across the studies included in this review, concizumab exhibited a favorable safety profile, with no thromboembolic events reported in any trial. However, the studies reported an increase in D-dimer levels, a marker of fibrinolysis, which reflects increased thrombin generation and fibrin turnover. While this finding does not necessarily indicate an increased risk of thrombosis, it highlights the importance of long-term safety monitoring to ensure that prolonged TFPI inhibition does not predispose patients to prothrombotic complications. Additionally, while adverse events (AEs) such as injection-site reactions and mild systemic effects were observed, serious adverse events (SAEs) were infrequent and were not directly attributed to concizumab use. Importantly, there were no significant changes in prothrombin time (PT) or activated partial thromboplastin time (aPTT), further supporting the conclusion that concizumab enhances coagulation in a controlled manner without significantly disrupting the overall hemostatic balance. When compared to other non-factor therapies, concizumab offers a unique advantage by being effective in both hemophilia A and B, whereas other treatments, such as bevacizumab, are currently only approved for hemophilia A.²⁴⁻²⁷ Emicizumab is a bispecific antibody that mimics FVIII function, facilitating thrombin generation in hemophilia A patients but not hemophilia B.^{28,29} The broader applicability of concizumab makes it particularly valuable for hemophilia B patients, who have fewer non-factor treatment options available.^{30,31} However, further head-to-head clinical trials comparing concizumab with emicizumab and other emerging therapies will be necessary to determine whether concizumab offers superior efficacy, safety, or convenience.

In addition to Concizumab, other non-clotting factor therapies have emerged as promising prophylactic options for individuals with congenital hemophilia A or B. A recent Cochrane systematic review by Olasupo et al (2024) evaluated the efficacy and safety of several such agents, including bevacizumab, fitusiran, and marstacimab, alongside concizumab. The review demonstrated that these therapies, particularly emicizumab and fitusiran, likely

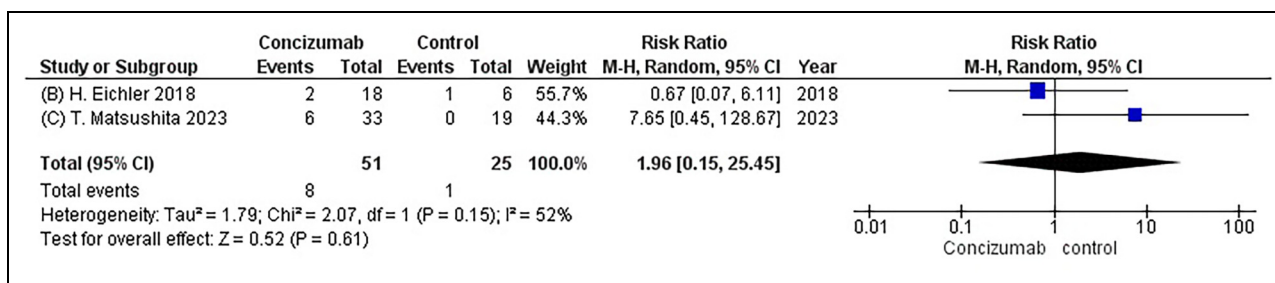


Figure 3. Forest Plot of Injection Site Reaction.

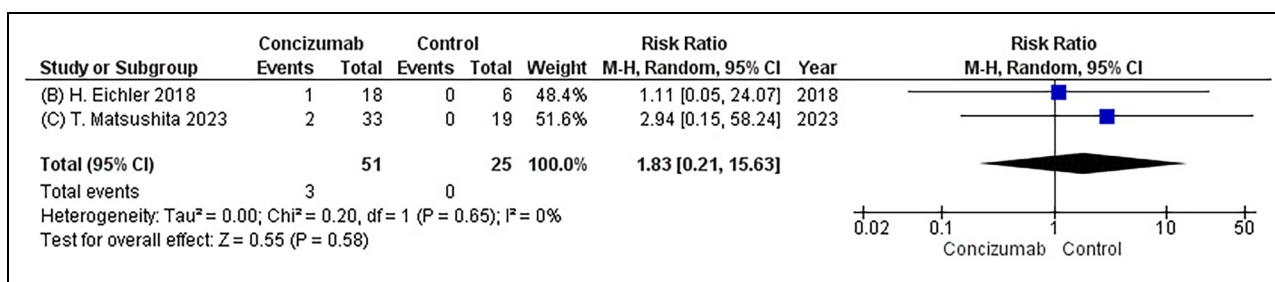


Figure 4. Forest Plot of Musculoskeletal Pain.

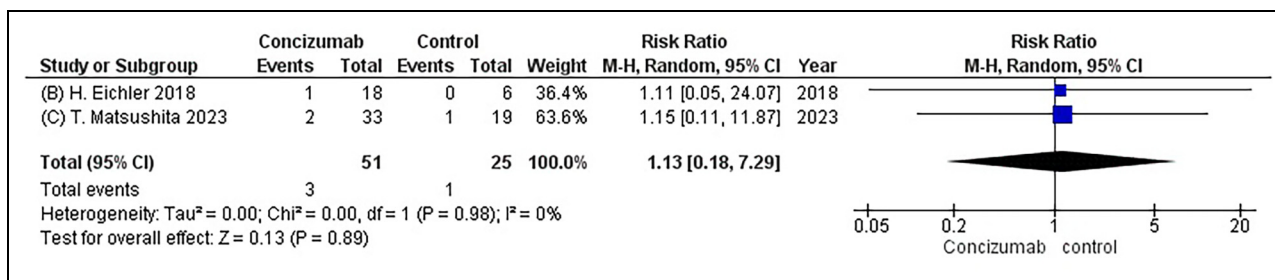


Figure 5. Forest Plot of Pyrexia.

result in a significant reduction in annualized bleeding rates and an increased proportion of patients achieving zero bleeds. Furthermore, improvements in health-related quality of life were also noted, albeit with a higher incidence of non-serious adverse events such as injection site reactions.³² These findings highlight the growing evidence base supporting multiple non-factor therapies beyond concizumab, underscoring the importance of considering the broader therapeutic landscape when evaluating bleeding prophylaxis in hemophilia

Despite the strengths of this systematic review, certain limitations must be acknowledged. One of the primary challenges encountered was the inability to conduct a meta-analysis of all primary outcomes due to inconsistencies in data reporting across studies. Several trials lacked critical statistical parameters such as standard deviations and confidence intervals, which are necessary for quantitative synthesis. Additionally, heterogeneity in study

designs, including differences in dosing regimens, patient populations (with vs without inhibitors), and inclusion criteria, introduced challenges in directly comparing results across studies. While our qualitative synthesis provides valuable insights, future trials should focus on standardized reporting of key outcomes to facilitate more robust meta-analyses. Another limitation is the relatively short follow-up duration in the included studies, which restricts the ability to assess long-term safety and efficacy. While no thromboembolic events were reported in the studies analyzed, the long-term effects of sustained TFPI inhibition remain unknown. Further research is needed to evaluate whether prolonged use of concizumab could lead to unexpected coagulation abnormalities or immune responses. In addition, although our search strategy was comprehensive, this review was limited to published RCTs, raising the possibility of publication bias. Studies with negative or neutral findings may be underrepresented,

potentially skewing the overall interpretation of concizumab's benefits and risks. Future systematic reviews should consider incorporating real-world data and registry-based studies to provide a more comprehensive assessment of concizumab's clinical impact.

Given the promising efficacy and safety profile demonstrated in this review, future research should focus on expanding the understanding of concizumab's role in routine clinical practice. Specifically, large-scale, real-world studies are needed to assess treatment adherence, patient-reported outcomes, and cost-effectiveness compared to traditional factor replacement and other emerging therapies. Additionally, studies evaluating concizumab's efficacy in pediatric populations and patients with milder forms of hemophilia will be essential to determine its full therapeutic potential.

Conclusion

Concizumab represents a transformative advancement in hemophilia management, offering an effective and convenient alternative to traditional factor replacement therapy. Its ability to significantly reduce bleeding episodes across hemophilia A and B, regardless of inhibitor status, underscores its broad clinical applicability. The subcutaneous administration of concizumab enhances treatment adherence, addressing a major limitation of frequent intravenous infusions. Furthermore, its favorable safety profile, with no reported thromboembolic events, strengthens its potential as a viable long-term treatment option. While challenges remain, including the need for long-term safety data and real-world effectiveness studies, concizumab holds promise in reshaping the treatment landscape for hemophilia. Future research should focus on expanding its indications, assessing its impact in pediatric and mild hemophilia populations, and conducting comparative studies with existing therapies. With continued investigation, concizumab can emerge as a cornerstone therapy in modern haemophilia care, improving patient outcomes and quality of life worldwide.

ORCID iDs

Erum Siddiqui  <https://orcid.org/0009-0006-7183-1022>

Maliha Khaild  <https://orcid.org/0009-0001-3413-2752>

Muhammad Saad Khan  <https://orcid.org/0009-0002-4228-6476>

Kanza Farhan  <https://orcid.org/0009-0002-6211-7522>

Muhammad Mohsin Khan  <https://orcid.org/0009-0006-2353-0276>

Aminath Waafira  <https://orcid.org/0009-0000-3283-1982>

Author Contributions

Erum Siddiqui: Data Curation, Formal analysis, Methodology, Writing-the original draft, Writing- review & editing.

Maliha Khalid: Data Curation, Formal analysis, Methodology,

Writing original draft, Writing- review & editing.

Muhammad Saad Khan: Data Curation, Formal analysis, Methodology, Writing-the original draft, Writing- review & editing.

Kanza Farhan: Data Curation, Formal analysis, Methodology, Writing original draft, Writing- review & editing.

Muhammad Mohsin Khan: Data Curation, Formal analysis, Methodology, Writing original draft, Writing- review & editing.

Aminath Waafira: Data Curation, Formal analysis, Methodology, Writing original draft, Writing- review & editing.

Funding

The authors received no financial support for the research, authorship, and/or publication of this article.

Declaration of Conflicting Interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Supplemental Material

Supplemental material for this article is available online.

References

1. Franchini M. The modern treatment of haemophilia: A narrative review. *Blood Transfus = Trasfusione del Sangue [Internet]*. 2013;11(2):178-182. Available from <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3626468/>.
2. Quintana Paris L. Foundations of hemophilia and epidemiology. *Blood Coagul Fibrinolysis [Internet]*. 2023;34:S35. Available from https://journals.lww.com/bloodcoagulation/fulltext/2023/06001/foundations_of_hemophilia_and_epidemiology.11.aspx.
3. Acharya SS. Exploration of the pathogenesis of haemophilic joint arthropathy: Understanding implications for optimal clinical management. *Br J Haematol*. 2011;156(1):13-23.
4. Coppola A. Treatment of hemophilia: A review of current advances and ongoing issues. *J Blood Med [Internet]*. 2010;1:183. Available from <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3262316/>.
5. Peyvandi F, Makris M. Inhibitor development in haemophilia. *Haemophilia*. 2016;23:3-3.
6. Young G, Aledort L. Therapy for haemophilia: Recent advances and goals for the future. *Expert Opin Emerg Drugs*. 2005;10(1):173-184.
7. Franchini M, Lippi G. Recent improvements in the clinical treatment of coagulation factor inhibitors. *Semin Thromb Hemost*. 2009;35(08):806-813.
8. Shapiro AD, Hedner U. Advances in bypassing agent therapy for hemophilia patients with inhibitors to close care gaps and improve outcomes. *Ther Adv Drug Saf*. 2011; 2(5):213-225.
9. Franchini M, Mannucci PM. Non-factor replacement therapy for haemophilia: A current update. *Blood Transfus [Internet]*. 2018;16(5):457-461. Available from <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6125230/>.

10. Shapiro AD. Concizumab: A novel anti-TFPI therapeutic for hemophilia. *Blood Adv [Internet]*. 2021;5(1):279. Available from <https://pubmed.ncbi.nlm.nih.gov/33570646/>.
11. Chowdary P. Anti-tissue factor pathway inhibitor (TFPI) therapy: a novel approach to the treatment of haemophilia. *Int J Hematol*. 2018.
12. Chowdary P. Inhibition of tissue factor pathway inhibitor (TFPI) as a treatment for haemophilia: Rationale with focus on concizumab. *Drugs [Internet]*. 2018b [cited 2022 Nov 15];78(9):881-890. Available from: <https://pubmed.ncbi.nlm.nih.gov/29845491/#:~:text=Tissue%20factor%20pathway%20inhibitor%20%28TFPI%29%20is%20a%20multivalent>
13. Frei-Jones M, Cepo K, d'Oiron R, Goh AS, Mathias M, Odgaard-Jensen J. Subcutaneous concizumab prophylaxis in patients with hemophilia A or B with inhibitors: Efficacy and safety results by hemophilia subtype from the phase 3 Explorer7 trial. *Blood*. 2022;140(Supplement 1):466-468.
14. Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: An updated guideline for reporting systematic reviews. *Br Med J*. 2021;372:n71. doi: 10.1136/bmj.n71. PMID: 33782057; PMCID: PMC8005924.
15. Chowdary P, Lethagen S, Friedrich U, et al. Safety and pharmacokinetics of anti-TFPI antibody (concizumab) in healthy volunteers and patients with hemophilia: A randomized first human dose trial. *J Thromb Haemost: JTH [Internet]*. 2015 [cited 2023 Feb 20];13(5):743-754. Available from: <https://pubmed.ncbi.nlm.nih.gov/25641556/>
16. Eichler HJ, Angchaisuksiri P, Kavakli K, et al. A randomized trial of safety, pharmacokinetics and pharmacodynamics of concizumab in people with hemophilia A. *JTH*. 2018;16(11):2184-2195.
17. Matsushita T, Shapiro AD, Abraham A, et al. Phase 3 trial of concizumab in hemophilia with inhibitors. *N Engl J Med*. 2023;389(9):783-794.
18. Chowdary P, Angchaisuksiri P, Apte S, et al. Concizumab prophylaxis in people with haemophilia A or haemophilia B without inhibitors (explorer8): a prospective, multicentre, open-label, randomised, phase 3a trial. *Lancet Haematol [Internet]*. 2024. Available from [https://www.thelancet.com/journals/lanhae/article/PIIS2352-3026\(24\)00307-7/fulltext](https://www.thelancet.com/journals/lanhae/article/PIIS2352-3026(24)00307-7/fulltext).
19. Risk of bias tools - Current version of RoB 2. sites.google.-com. <https://sites.google.com/site/riskofbiastool/welcome/rob-2-0-tool/current-version-of-rob-2?authuser=0>
20. Jewell MP, Ashour Z, Baird CH, et al. Concizumab improves clot formation in hemophilia A under flow. *J Thromb Haemostasis*. 2024;22(9):2438-2448.
21. Hampton K, Knoebl P, Odgaard-Jensen J, et al. Treatment burden and patient preference in patients with hemophilia A or B with inhibitors on concizumab prophylaxis: Results from the phase 3 explorer7 study. *Hematol Transfus Cell Ther*. 2023;45:S458-S459.
22. Pasca S. Concizumab as a subcutaneous prophylactic treatment option for patients with hemophilia A or B: A review of the evidence and patient's perspectives. *J Blood Med [Internet]*. 2022;13:191-199. Available from <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9020573/#:~:text=Concizumab%2C%20an%20anti%2Dtissue%20factor>.
23. Recht M. Safety first: Tracking adverse events associated with new therapies for people with hemophilia. *J Thromb Haemostasis*. 2020;19(S1):3-5.
24. Mahlangu J. Emicizumab for the prevention of bleeds in hemophilia A. *Expert Opin Biol Ther*. 2019;19(8):753-761.
25. Young G, Callaghan M, Dunn A, Kruse-Jarres R, Pipe S. Emicizumab for hemophilia A with factor VIII inhibitors. *Expert Rev Hematol*. 2018;11(11):835-846.
26. Yoneyama K, Schmitt C, Portron A, et al. Clinical pharmacology of emicizumab for the treatment of hemophilia A. *Expert Rev Clin Pharmacol*. 2023;16(9):775-790.
27. Oldenburg J, Mahlangu JN, Kim B, et al. Emicizumab prophylaxis in hemophilia A with inhibitors. *N Engl J Med*. 2017;377(9):809-818.
28. Shima M, Hanabusa H, Taki M, et al. Factor VIII-mimetic function of humanized bispecific antibody in hemophilia A. *N Engl J Med*. 2016;374(21):2044-2053.
29. Knight T, Callaghan MU. The role of emicizumab, a bispecific factor IXa- and factor X-directed antibody, for the prevention of bleeding episodes in patients with hemophilia A. *Ther Adv Hematol*. 2018;9(10):319-334.
30. Young G. Nonfactor therapies for hemophilia. *HemaSphere [Internet]*. 2023;7(6):e911-e911. Available from <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC10247213/>.
31. Spadarella G, Di Minno A, Milan G, et al. Paradigm shift for the treatment of hereditary haemophilia: Towards precision medicine. *Blood Rev*. 2020;39:100618.
32. Olasupo OO, Noronha N, Lowe MS, Ansel D, Bhatt M, Martino D. Non-clotting factor therapies for preventing bleeds in people with congenital hemophilia A or B. *Cochrane Database Syst Rev*. 2024;2(2):CD014544. doi: 10.1002/14651858.CD014544.pub2