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Outcomes of Emicizumab Treatment for Haemophilia A Paediatric Patients: A Systematic Review With Meta-Analysis

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ABSTRACT

Introduction: Haemophilia A in paediatric patients presents a lifelong risk of spontaneous and trauma-induced haemorrhage, leading to progressive joint damage, disability and impaired quality of life. Emicizumab, a bispecific monoclonal antibody administered subcutaneously, offers sustained haemostatic protection and has shown promising outcomes in children.

Aim: To systematically evaluate and quantitatively synthesise the efficacy, safety and immunogenicity outcomes of emicizumab prophylaxis in paediatric patients with haemophilia A.

Methods: This systematic review and meta-analysis was conducted according to PRISMA 2020 guidelines and registered in PROSPERO (CRD420251145633). Eligible studies reported quantitative outcomes for children with haemophilia A receiving emicizumab. Random-effects models were used to pool median annualised bleeding rates (ABR) and prevalence of joint bleeding, intracranial haemorrhage (ICH), inhibitor development and anti-drug antibodies (ADA).

Results: Eighteen studies comprising 720 paediatric patients were included. The pooled median ABR was 0.50 bleeds/year (95% CI: 0.00–1.11), and no cases of ICH were reported across all studies. The pooled prevalence of joint bleeds was 5.4% (95% CI: 1.41–10.96), reflecting effective musculoskeletal protection. Inhibitor development occurred in less than 0.01% of patients (nine cases), and ADA were reported in five cases without loss of clinical efficacy. No significant differences were observed in subgroup analyses by study design or geographic region.

Conclusions: Emicizumab prophylaxis provides robust and consistent bleed prevention with an excellent safety and immunogenicity profile in children with haemophilia A. The near-zero ABR and absence of intracranial haemorrhage highlight its potential to transform long-term outcomes and prevent haemophilic arthropathy.

Konstantina Bolou and George Triantafyllou equally contributed to this work.

1 | Introduction

Haemophilia A is an X-linked inherited bleeding disorder caused by a deficiency of coagulation factor VIII (FVIII), resulting in spontaneous or trauma-induced bleeding. These involve most commonly the joints and/or muscles, which can lead to progressive arthropathy, disability and impaired quality of life [1, 2]. Severe haemophilia A (FVIII activity < 1%) typically presents in early childhood and, if untreated or undertreated, leads to recurrent bleeds and joint damage [3].

The introduction of FVIII replacement therapy revolutionised haemophilia care in the late 20th century, first with plasma-derived concentrates and subsequently with recombinant factors [4]. Prophylaxis with regular intravenous FVIII infusions became the standard of care in children to prevent bleeding episodes and preserve joint function. This was supported by randomised trials that demonstrated significant reductions in haemarthroses and radiographic joint damage compared to episodic therapy [3, 5].

Despite these advances, conventional FVIII prophylaxis in children remains limited by several challenges. The short half-life of FVIII necessitates frequent intravenous infusions (2-4 times per week) posing considerable issues such as venous access issues, reduced adherence and impaired quality of life [6]. This is especially outlined in the paediatric population. Moreover, approximately 20%–30% of previously untreated patients (PUPs) develop inhibitory allo-antibodies against FVIII, rendering replacement therapy ineffective and complicating management [7, 8].

Emicizumab, a humanised bispecific monoclonal antibody that mimics the co-factor function of activated FVIII by bridging FIXa and FX, represents a notable shift in haemophilia A treatment that revolutionised the standard of case. Administered subcutaneously with extended dosing intervals (weekly to monthly), it provides sustained haemostatic activity regardless of inhibitor status [6, 9]. Phase III trials in adolescents and adults with and without inhibitors demonstrated dramatic reductions in annualised bleeding rates, with over 50% of patients experiencing zero treated bleeds [6]. Early real-world studies in paediatric populations suggested similarly profound efficacy and safety, with improvements in treatment adherence and quality of life. A recent meta-analysis in inhibitor-positive patients reinforced the superiority of emicizumab over bypassing agents in preventing bleeding episodes [10].

This systematic review and meta-analysis aims to synthesise the current evidence on clinical outcomes of emicizumab prophylaxis in paediatric patients with haemophilia A. We will discuss the bleeding outcomes, safety profiles and immunogenicity to provide a quantitative overview that informs clinical decision-making and long-term treatment strategies.

2 | Materials and Methods

2.1 | Methodology

The current systematic review was performed in accordance with the protocol proposed by the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) 2020 guidelines [11]. According to the guidelines, the protocol was registered into the PROSPERO database with the number CRD420251145633. Moreover, risk of bias assessment for the studies was performed according to the Newcastle–Ottawa scale tool (NOS). The studies were evaluated based on three parameters: (1) participant selection, (2) comparability of study groups and (3) assessment of outcome or exposure. A study was evaluated as 'good quality' when it had 3–4 stars in the selection domain, 1–2 stars in the comparability domain and 2–3 stars in the outcome/exposure domain. 'Fair quality' was given when 2 stars were attributed in the selection domain, 1–2 stars in the comparability domain and 2–3 stars in the outcome domain. Finally, a study was of 'poor quality' in the case of 0–1 star in the selection domain, 0 stars in the comparability domain or 0–1 star in the outcome/exposure domain [12].

2.2 | Research Question

The present study was conducted, upon extensive literature review, to answer the following question: What are the outcomes of emicizumab treatment for the paediatric population with haemophilia A? Only studies reporting quantitative details of the outcomes, such as the annualised bleeding rate (ABR), intracranial haemorrhage (ICH) or joint bleed (JB) were considered eligible. Exclusion criteria were considered studies implicating adult sample or haemophilia B, case reports, literature reviews and conference abstracts.

2.3 | Literature Search

Two independent reviewers (KB, GT) performed the literature search and data extraction. The electronic databases, PubMed/MEDLINE, Scopus, Web of Science and Google Scholar, were used for the primary literature analysis, until September 2025. The following keywords were used in several combinations and searches: 'emicizumab', 'haemophilia A', 'children', 'infant' and 'paediatric'. There were no date or language restrictions for this process. A secondary literature analysis was performed with a hands-on search of the reference lists of all included articles. The eligible studies were gathered, and their data were extracted to Microsoft Excel sheets prior to statistical analysis.

2.4 | Statistical Meta-Analysis

Statistical analysis was conducted using the open-source R programming language and the RStudio software version 4.3.2 using the 'meta', 'metamedian' and 'metafor' packages, by a single researcher (GT) and reviewed by an expert statistician (MK). The pooled median was estimated using a sample size–weighted median of medians approach under a random-effects framework. A nonparametric bootstrap methodology was applied to derive the 95% confidence intervals of the pooled median. Because ABR was highly skewed, the primary synthesis used a non-parametric pooling of medians. However, meta-regression and funnel-plot asymmetry tests are only defined for normally distributed effect sizes with estimable variances. To enable these analyses, study-specific ABR medians were transformed into approximate mean and standard deviations. The derived means and variances

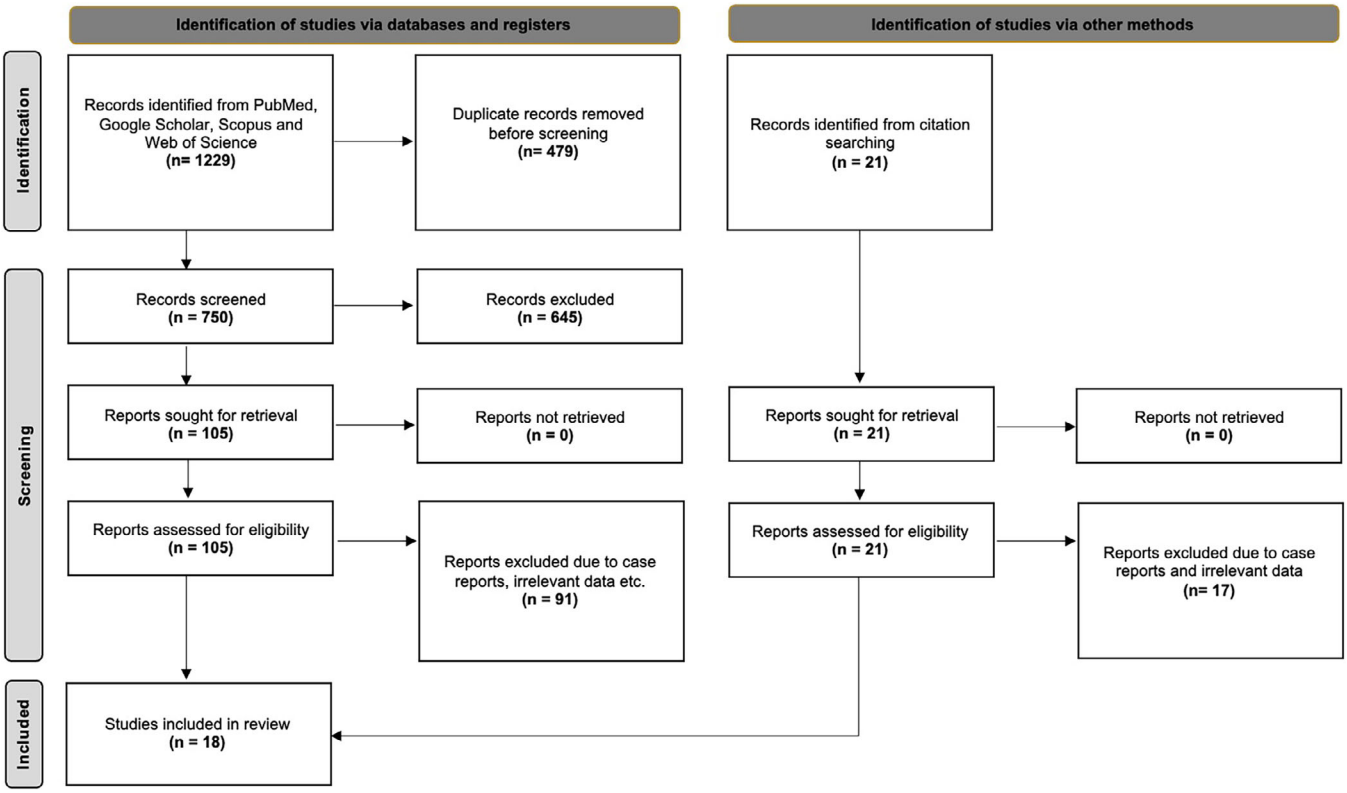

FIGURE 1 | PRISMA 2020 flow chart for literature search.

were then used to fit DerSimonian–Laird random-effects models and to perform meta-regression with study design and continent as moderators. The proportions meta-analysis (prevalence meta-analysis) was conducted using the Freeman–Tukey double arcsine transformation, the DerSimonian–Laird estimator for the between-study variance tau^2, and the Jackson method for confidence interval of tau^2 and tau. Cochran's Q statistic was used to evaluate the presence of heterogeneity across studies, and the Higgins I^2 statistic was used to quantify heterogeneity. Cochran's Q p value < 0.10 was considered significant. Higgins I^2 values between 0% and 40% were regarded as might not be necessary, 30%–60% as moderate heterogeneity, 50%–90% characterised as substantial heterogeneity and 75%–100% may represent considerable heterogeneity. A p value less than 0.05 was considered statistically significant. To evaluate the presence of small-study effect (the phenomenon that smaller studies may show different effects than large ones), the DOI plot with LFK index was generated [13]. Funnel plot asymmetry was tested using the Thomson–Sharp method [14].

3 | Results

3.1 | Selection Process

The databases retrieved 1229 results that were exported to Mendeley version 2.10.9 (Elsevier, London). After excluding irrelevant and duplicate papers, 105 studies underwent full-text retrieval and screening. Finally, 14 studies were considered eligible for our initial meta-analysis questions. Furthermore, four studies were identified from references and a hands-on search. Hence, 18 studies were included in the current systematic review. In accordance with the PRISMA 2020 guidelines [11], the Figure 1 presents the flow diagram of the selection process.

3.2 | Studies' Characteristics

The main characteristics of the studies are summarised in Table 1. Eighteen studies with a total sample of 720 paediatric patients (mean sample = 40). The year of publication ranged from 2019 to 2025. Sixty-six patients were previously untreated; thus, they treated with emicizumab prior to factor VIII. Six studies belonged to the Asian population, five studies to the American population, three studies to the European population, three studies were multicontinental and one to the African population. The age and the dose of the patients ranged significantly (Table 1). Risk of bias assessment depicted 14 studies with 'good quality' [15–28], 4 studies with 'fair quality' [29–32] and 0 studies with 'poor quality'.

3.3 | Meta-Analysis Outcomes

Ten studies (n = 515) reported the median (and IQR) ABR value. The pooled median ABR analysis was calculated at 0.50 (95% CI: 0.00–1.11) bleeds per year (Figure 2). Meta-regression analysis for the type of study and geographical distribution did not depict statistically significant results ($p = 0.9622$ and $p = 0.1837$, respectively). The funnel plot is presented in Figure 2, while its test for asymmetry had a p value of 0.152, indicating no asymmetry.

TABLE 1 | Characteristics of the included studies. PUP- previously untreated patients.

Authors (Year)	Country	Type	Sample	Age (mean or median)	PUP	Dose
Barg et al. (2019) [15]	Israel	Prospective single-centre cohort	11	26 months	0	Loading 3 mg/kg QW ×4 → 1.5 mg/kg QWmaintenance
Barg et al. (2020)[16]	Israel	Prospective cohort (single centre)	40	5.5 years (0.15–18.5)	0	Loading 3 mg/kg QW ×4 → 1.5 mg/kg QW maintenance
Cohen et al. (2021) [17]	USA	Retrospective cohort	27	6.7 years (0.2–20.4)	2	3 mg/kg weekly ×4, then Q2W maintenance
Garcia et al. (2021) [29]	USA	Case series	3	3 days, 6 months, 6 months	0	3 mg/kg weekly → 1.5 mg/kg weekly
Glonnegger et al. (2022) [18]	Germany	Retrospective cohort	13	5.3 years (0.26–17.5)	2	3 mg/kg weekly loading → 1.5 mg/kg QW maintenance
Hasan et al. (2025) [19]	UK	Retrospective cohort	78	7 years (2.2–11.8)	11	3 mg/kg weekly loading → 3 mg/kg Q2W (most common)
Hassan et al. (2022) [30]	UK	Case series	5	15.8 months, 7.6 months, 8.3 months, 4 months and 10.3 months	3	3 mg/kg Q2W maintenance
Hassan et al. (2024) [20]	Egypt	Prospective cohort	88	6 years (2–15)	0	3 mg/kg QW loading → 3 mg/kg Q2W maintenance
Lemos et al. (2024) [21]	Uruguay	Retrospective cohort	32	1–11 years	8	3 mg/kg QW loading → 6 mg/kg Q4W maintenance
Levy et al. (2024) [22]	Israel	Prospective cohort	27	7 months (5–10)	0	3 mg/kg QW → 1.5 QW / 3 Q2W
Liu et al. (2022) [23]	China	Retrospective cohort	13	3.51 years (0.73–6.65)	4	3 mg/kg QW → Q2W/Q10D/Q15D/Q4W
Mao et al. (2024) [24]	China	Retrospective cohort	34	1.9 years (0.1–9.1)	9	Reduced individualised dosing
Mashiach et al. (2024) [25]	USA	Retrospective cohort	15	9.7 years (4)	0	3 mg/kg Q2W
Mason et al. (2021) [31]	USA/Australia	Case series	4	7 days, 5 weeks, 15 months, 14 months	1	1.5 mg/kg QW or 3 mg/kg Q2W
Pipe et al. (2024) [26]	Multicontinental	Phase 3b trial	55	4 months (9 days–11.5 months)	25	3 mg/kg QW → 3 mg/kg Q2W
Shima et al. (2019) [32]	Japan	Open-label trial	13	6.6 years (1.5–10.7)/4.1 years (0.3–8.1)	1	3 mg/kg QW → Q2W/Q4W
Van der Zwet et al. (2024) [28]	Multicontinental	Prospective cohort (registry)	177	8.6 years (4.8–13.1)	0	6 mg/kg Q4W (label-based)
Young et al. (2019) [27]	Multicontinental	Phase 3 trial	85	7 years (1–15)	0	3 mg/kg QW / Q2W / Q4W

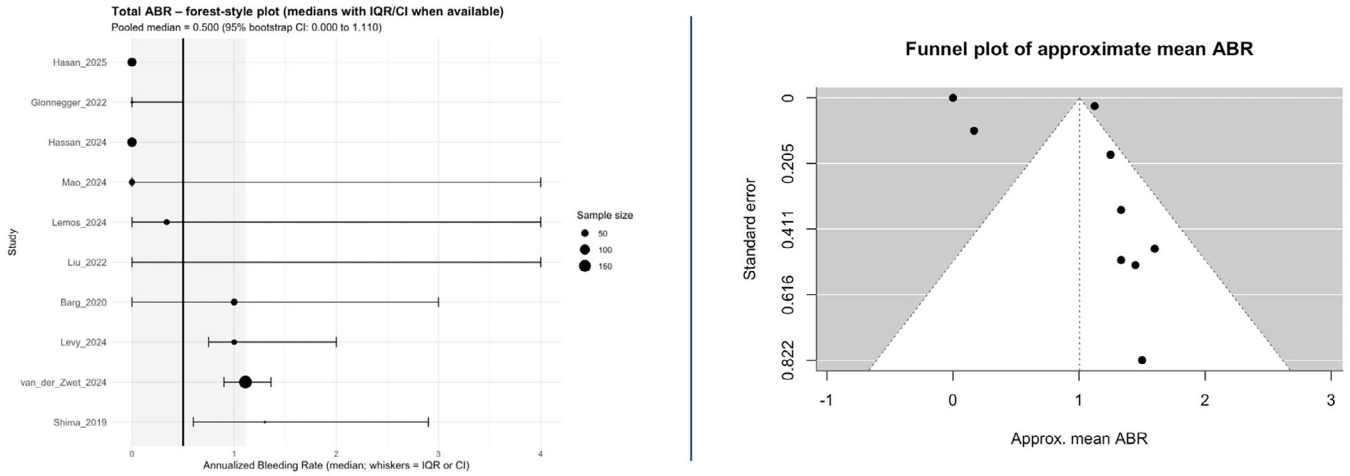

FIGURE 2 | Forest-style (left) and funnel (right) plots for the annualised bleed rate (ABR) pooled median analysis.

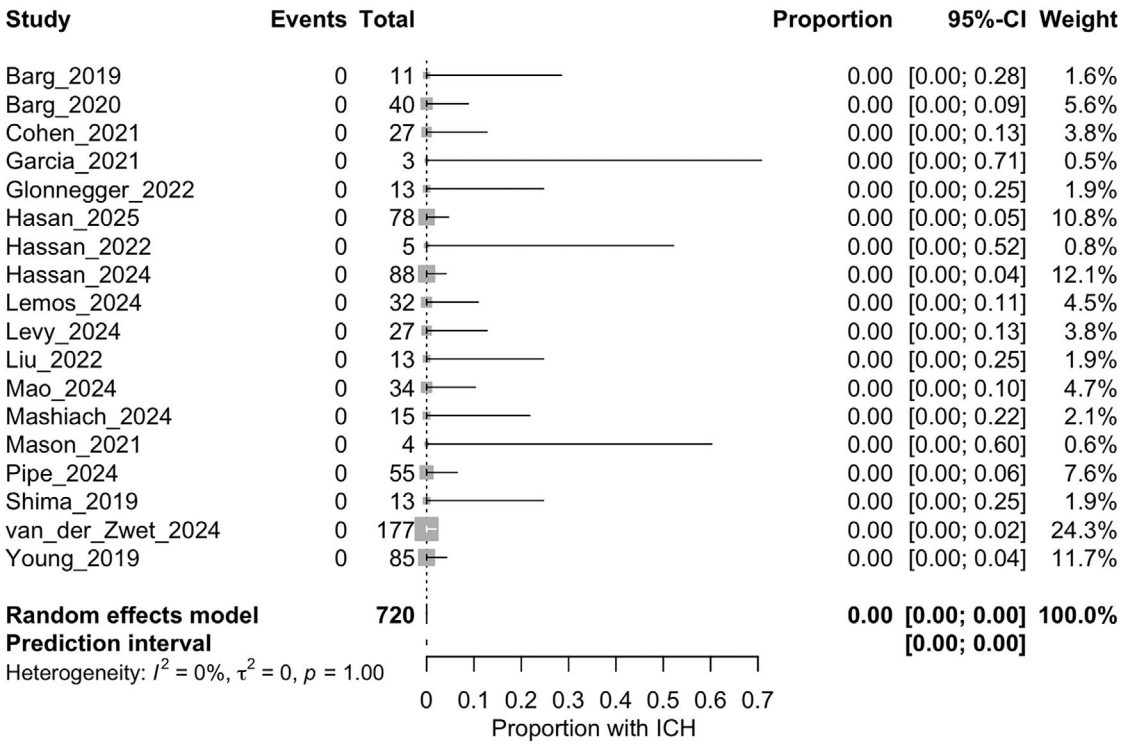

FIGURE 3 | Forest plot for the pooled prevalence estimate of intracranial haemorrhage (ICH) for haemophilia A paediatric patients under emicizumab treatment.

All the studies ($k = 18$, $n = 720$) reported zero incidence of ICH for patients under emicizumab treatment (Figure 3).

Sixteen studies ($n = 516$) recorded incidences of JB for the patients. The pooled prevalence of JB was calculated at 5.40% (95% CI: 1.41–10.96) bleeds (Figure 4). The I^2 was estimated as 69.3% indicating moderate heterogeneity. The DOI plot depicted a LFK index of −1.8, indicating minor asymmetry (Figure 4). Subgroup analysis for the type of study and geographical distribution did not retrieve statistically significant difference ($p = 0.790$ and $p = 0.747$, respectively).

Seventeen studies ($n = 693$) recorded incidences of inhibitor development for the patients. The pooled prevalence was estimated at less than 0.01%, with only nine cases of inhibitors reported between the studies (Figure 5). Low heterogeneity was recorded ($I^2 = 32\%$), but the LFK index was +3.21, indicating a substantial small-study effect (Figure 5).

Sixteen studies ($n = 690$) reported incidences of anti-drug antibodies (ADA) development. The pooled prevalence was estimated at less than 0.01%, with only five cases of ADA development reported between the studies (Figure 6).

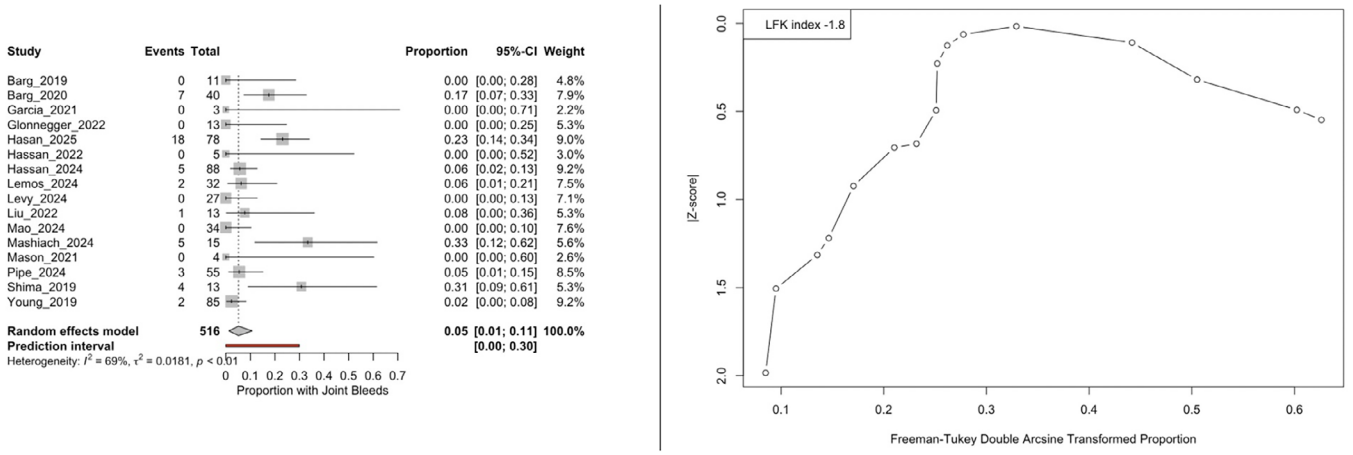

FIGURE 4 | Forest (left) and DOI (right) plots for the pooled prevalence estimate of joint bleeds (JB) for haemophilia A paediatric patients under emicizumab treatment.

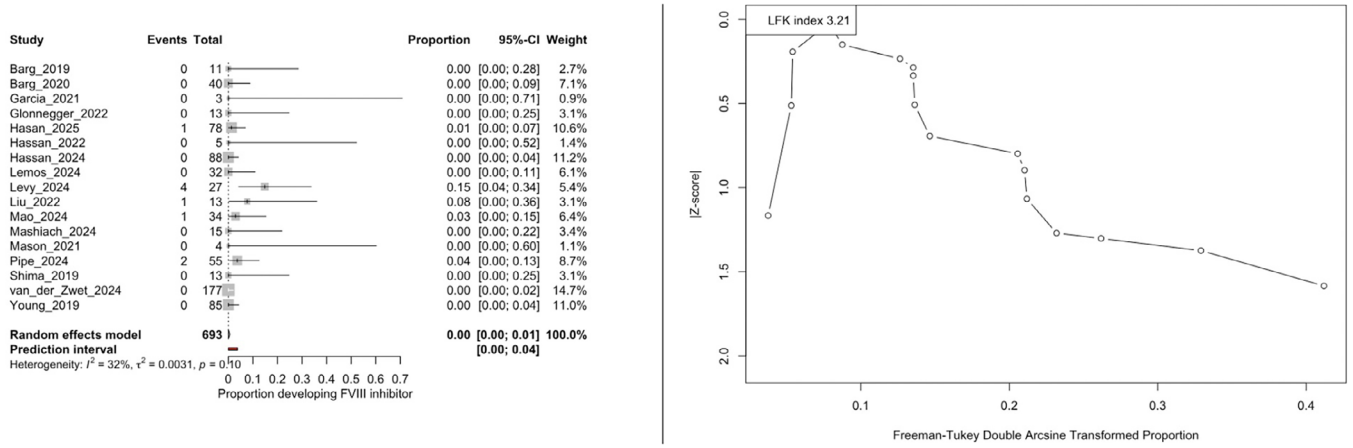

FIGURE 5 | Forest (left) and DOI (right) plots for the pooled prevalence estimate of inhibitors development for haemophilia A paediatric patients under emicizumab treatment.

4 | Discussion

This systematic review and meta-analysis provides the most comprehensive synthesis to date of emicizumab prophylaxis outcomes in paediatric patients with haemophilia A. Across 18 studies involving 720 children, emicizumab demonstrated a profound low numbers in bleeding events, with a pooled median ABR of 0.50 bleeds per year and a 95% confidence interval that included zero. Notably, no cases of ICH were reported in any study, underscoring the protective effect of emicizumab against life-threatening bleeds. JB events were infrequent, with a pooled prevalence of 5.4%, indicating strong musculoskeletal protection in a population at critical risk for hemarthroses and arthropathy. Immunogenicity outcomes were likewise favourable with inhibitor development occurred in less than 0.01% of patients, and anti-drug antibodies were exceedingly rare.

The findings of this meta-analysis are consistent with and build upon the growing body of clinical trial and real-world evidence demonstrating the transformative efficacy of emicizumab in paediatric haemophilia A care. In the HAVEN 2 trial, involving children with FVIII inhibitors, emicizumab prophylaxis reduced the ABR to 0.3, with 77% of patients experiencing zero treated bleeds [27]. Similarly, in the HAVEN 7 trial assessing previously untreated and minimally treated infants without inhibitors, the model-based ABR was 0.4 and no ICH were reported, highlighting the potential of early prophylaxis to prevent first joint damage and life-threatening bleeds [26]. These results align with initial cohort studies [33] and our pooled median ABR of 0.50 and universal absence of ICH, reinforcing the profound haemostatic efficacy observed. Real-world studies further corroborate these findings. In the PedNet registry, which followed 177 children treated with emicizumab across 19 countries, both inhibitor-positive and inhibitor-negative cohorts demonstrated statistically significant reductions in ABR (from 5.08 to 0.75 post therapy, and 2.41 to 1.11, respectively) and annualised joint bleeding rate (from 1.90 to 0.34 post therapy, and 0.74 to 0.31, respectively) compared with prior FVIII or bypassing agent prophylaxis [28].

A critical clinical question is how emicizumab performs relative to conventional FVIII prophylaxis in paediatric patients. Unfortunately, the current literature did not compare these data for the paediatric population to add these details on our meta-analysis. The findings of our paediatric meta-analysis are aligned with the

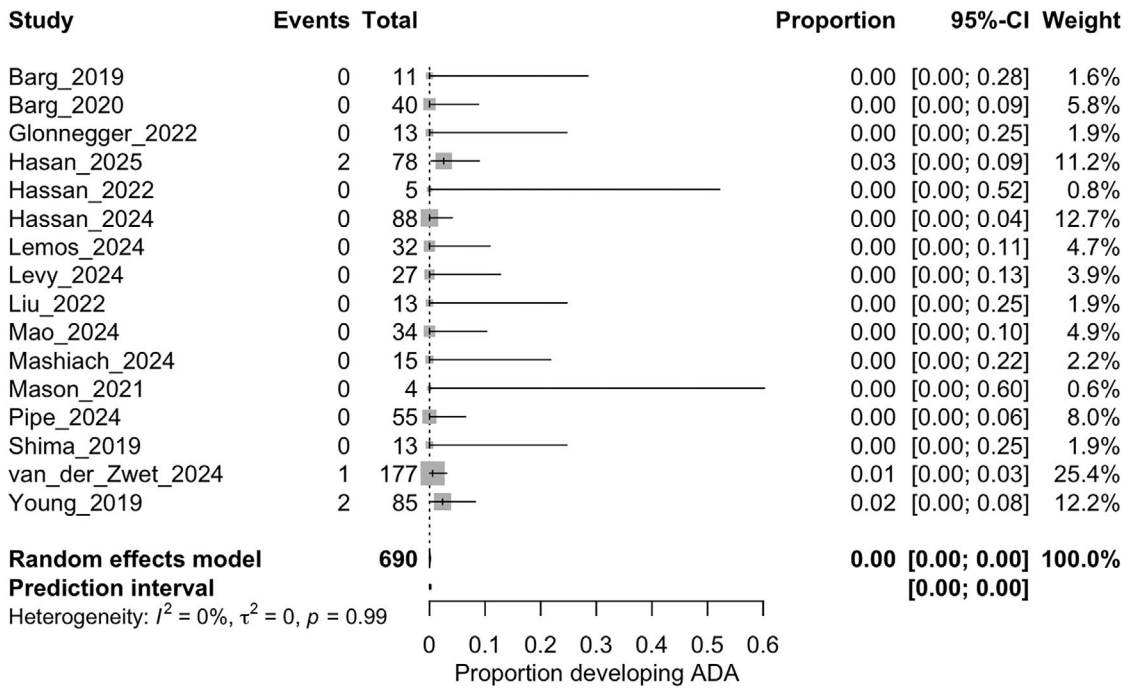

FIGURE 6 | Forest plot for the pooled prevalence estimate of anti-drug antibodies (ADA) for haemophilia A paediatric patients under emicizumab treatment.

broader systematic review and meta-analysis by Muniz et al. [34], which directly compared emicizumab prophylaxis with FVIII prophylaxis in non-inhibitor adult patients. Their pooled analysis of 11 studies demonstrated that emicizumab significantly reduced total treated ABR compared with FVIII, with a standardised mean difference of −0.6 ($p < 0.001$) in patients without inhibitors and −1.7 ($p < 0.001$) in the inhibitor subgroup. These results corroborate our pooled findings and suggest that emicizumab not only offers clinically superior bleed protection but also simplifies treatment administration, potentially improving adherence and long-term joint outcomes compared with intravenous FVIII therapy [34].

Although recent indirect comparisons suggest that next-generation FVIII therapies, such as efanesoctocog alfa, may achieve even lower ABRs than emicizumab in the adult and adolescent population >12 years without inhibitors [35], these therapies still require intravenous administration, while their inhibitor risk is not yet known, if any. In contrast, emicizumab offers a unique non-factor mechanism with subcutaneous delivery and near-elimination of inhibitor development or postponing of the development of FVIII inhibitors to older ages close to puberty, making it particularly advantageous in young children, where venous access, treatment adherence, and early joint protection are paramount [35].

The results of this meta-analysis have significant implications for the evolving management of paediatric haemophilia A. The profound low rates in ABR observed with emicizumab, coupled with the complete absence of ICH and exceptionally low rates of inhibitor or ADA development, indicates that emicizumab may provide superior haemostatic protection compared with conventional FVIII prophylaxis during the most vulnerable period of musculoskeletal development. Early and sustained suppression of bleeding is essential for preserving joint architecture and health, as even a few haemarthroses during childhood can establish a trajectory of chronic arthropathy despite subsequent intensive prophylaxis [36]. Emicizumab ability to maintain a constant haemostatic state without peaks and troughs and to convert the severe and moderate haemophilia A to mild, associated with FVIII pharmacokinetics aligns directly with the World Federation of Hemophilia recommendation to sustain protective factor levels >3–5 IU/dL to prevent subclinical joint bleeding [37].

A particularly important finding of our meta-analysis is the complete absence of ICH among 720 emicizumab-treated paediatric patients. This is clinically significant given that ICH has historically been one of the most devastating complications of haemophilia A in infancy and early childhood. Prior to the introduction of emicizumab, ICH incidence in children with haemophilia A was substantially higher. A systematic review and meta-analysis of 45 studies estimated a pooled ICH incidence of 7.4% per 1000 patient/years in children and young adults, and a neonatal cumulative incidence of 2.1% per 100 births in the pre-emicizumab era [38]. Similarly, Zanon and Pasca [39] summarised that ICH remains a leading cause of morbidity and mortality, with neonatal incidence 40–80 times higher than in non-haemophilic infants, and with nearly half of childhood ICH cases occurring within the first 2 years of life despite conventional factor prophylaxis [39]. Against this historical background, the finding of zero ICH events in all 18 included emicizumab studies strongly underscores the protective effect of early emicizumab prophylaxis.

From a safety perspective, this analysis confirms the favourable immunogenicity profile of emicizumab. While conventional FVIII prophylaxis carries a 20%–30% risk of inhibitor development in PUPs [7], our pooled estimate showed

inhibitor emergence in <0.01% of cases, consistent with the mechanistic understanding that emicizumab does not present antigenic epitopes for anti-FVIII antibodies [40]. This reduced immunogenicity is of particular relevance in infants, where early exposure to FVIII is linked to peak inhibitor risk. Expert opinion supports considering emicizumab as first-line therapy in PUPs with the aim of delaying or even preventing inhibitor formation, although the long-term outcomes regarding inhibitor formation and implications for immune tolerance induction remain under investigation [41]. Furthermore, interpretation of inhibitor incidence in our meta-analysis is limited by the fact that most included studies did not systematically report key variables known to influence inhibitor development, such as the number of FVIII exposure days, type of FVIII concentrate, or indications and frequency of FVIII administration. Where available, these details varied considerably between cohorts. For example, in the HAVEN 7 trial, the only study providing full exposure data, infants had a median of 1 on-study FVIII exposure day (range 0–10), typically administered for traumatic bleeding, and two PUPs developed inhibitors after 3 and 10 non-consecutive exposure days, respectively, both following treatment with standard- or extended-half-life FVIII [26]. Outside HAVEN 7, reporting was far less consistent. Several real-world cohorts only noted whether FVIII was used '*as needed*', without specifying exposure days number or product type, while some case series reported FVIII use but not cumulative exposure [23].

Emicizumab dosing is another important detail of the treatment. However, the data were not available for quantitative analysis. Standard emicizumab prophylaxis is based on the phase III dosing regimens (3 mg/kg weekly for 4 weeks followed by 1.5 mg/kg weekly, 3 mg/kg every 2 weeks, or 6 mg/kg every 4 weeks) [26]. Emerging real-world data suggest that flexible or reduced dosing strategies are increasingly being explored, particularly in resource-limited settings. Several studies in our review maintained on lower-intensity or individualised dosing schedules [23]. Liu et al. [23] reported children transitioned to extended dosing intervals, including Q10-day, Q15-day and Q4-week regimens with maintained bleed protection. Mao et al. [24] described a cohort treated with individualised reduced-dose regimens, reflecting clinical attempts to balance haemostatic efficacy with drug accessibility [24]. Future research comparing dosing should be considered carefully.

Quality-of-life improvements associated with emicizumab are also clinically meaningful. Across trials and observational studies, caregivers report improved psychosocial functioning, reduced anxiety around venipuncture, and greater participation in physical, educational and social activities compared with FVIII therapy [37, 40]. These outcomes have direct relevance for adherence, as poor adherence to FVIII prophylaxis in adolescents is a well-documented predictor of increased bleeding and disability [42]. Emicizumab ease of administration offers a practical route to achieving optimal prophylaxis in real-world paediatric settings.

This meta-analysis has several limitations that should be considered when interpreting the findings. The majority of included studies were observational in nature, and only a limited number were randomised or controlled. This inherently increases the risk of bias due to confounding variables, treatment selection preferences, and reporting heterogeneity. Moreover, significant heterogeneity and small-study effect was evident in a few outcomes. This variability likely reflects differences in baseline patient characteristics, including inhibitor status, history of target joints, physical activity of the patients, age at initiation of prophylaxis, loading protocols and follow-up durations. Emerging comparator therapies such as high-sustained FVIII molecules (such as, efanesoctocog alfa) were not directly evaluated in this paediatric cohort. As a result, while our data strongly support emicizumab as a preferred prophylactic option in children, the rapidly evolving therapeutic landscape necessitates cautious interpretation in the context of long-term decision-making.

5 | Conclusion

This systematic review and meta-analysis demonstrates that emicizumab prophylaxis provides highly effective and safe bleed prevention in paediatric patients with haemophilia A, resulting in a pooled median ABR approaching zero, absence of ICH, low rates of JB and exceptionally low immunogenicity. These outcomes were consistent across study designs, geographic regions and patient populations, including those with and without inhibitors. Importantly, emicizumab overcomes challenges and limitations of recombinant FVIII. Collectively, these findings position emicizumab as a transformative therapy, capable of shifting the treatment from bleed reduction to near elimination of prophylaxis-related bleeds in children. While long-term data are still needed to confirm sustained joint protection, inhibitor incidence, immune tolerance strategies and comparative performance against emerging FVIII, the current evidence supports emicizumab as the preferred first-line prophylactic option for infants and children with haemophilia A.

Author Contributions

Konstantina Bolou: conceptualisation, data collection, data analysis, writing – original draft, final edition approval. **George Triantafyllou**: project development, data collection, data analysis, statistical analysis, writing – original draft, final edition approval. **Athina Dettoraki**: data analysis, writing – review and editing, final edition approval. **Aikaterini Michalopoulou**: data analysis, writing – review and editing, final edition approval. **Miltiadis Kyprianou**: statistical analysis, writing – review and editing, final edition approval. **Olympia Papakonstantinou**: data analysis, writing – review and editing, final edition approval. **Helen Pergantou**: supervision, data analysis, writing – review and editing, final edition approval.

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