

The MAPTO survey: worldwide approaches on unmasking factor VIII inhibitors in children with emicizumab treatment: communication from the ISTH SSC Subcommittee on Factor VIII, Factor IX and Rare Coagulation Disorders

Lilianne Esmée van Stam¹  | Bridget Jane Daisy Horstman¹ |
 Pantep Angchaisuksiri²  | Manuel Carcao³  | Gili Kenet⁴  |
 Christoph Königs⁵  | Johnny Mahlangu⁶  | Maria Elisa Mancuso^{7,8}  |
 Suely Meireles Rezende⁹  | Robert Francis Sidonio Jr¹⁰  | Alok Srivastava¹¹  |
 Guy Young¹²  ✕ | Karin Fijnvandraat^{1,13}  | Samantha Claudia Gouw¹ 

¹Emma's Children Hospital, Amsterdam UMC location University of Amsterdam, Department of Pediatric Hematology, Amsterdam, the Netherlands

²Faculty of Medicine Ramathibodi Hospital, Mahidol University, Department of Medicine, Bangkok, Thailand

³Hospital for Sick Children, University of Toronto, Division of Hematology/Oncology, Department of Pediatrics, Toronto, Ontario, Canada

⁴National Hemophilia Center, Sheba Medical Center & Amalia Biron Research Institute of Thrombosis & Hemost, Tel Aviv University, Tel Hashomer, Israel

⁵Goethe University, University Hospital Frankfurt, Department of Pediatrics and Adolescent Medicine, Clinical and Molecular Hemostasis, Frankfurt, Germany

⁶Hemophilia Comprehensive Care Centre, University of the Witwatersrand and National Health Laboratory Service, Department of Molecular Medicine and Hematology, Faculty of Health Sciences, Johannesburg, South Africa

⁷Center for Thrombosis and Hemorrhagic Diseases, IRCCS Humanitas Research Hospital, Rozzano, Milan, Italy

⁸Humanitas University, Pieve Emanuele, Milan, Italy

⁹Faculty of Medicine, Universidade Federal de Minas Gerais, Belo Horizonte, Minas Gerais, Brazil

¹⁰Emory University and Children's Healthcare of Atlanta, Department of Pediatrics, Atlanta, Georgia, USA

¹¹Christian Medical College, Department of Haematology, Vellore, Tamil Nadu, India

¹²Cancer and Blood Disease Institute, Children's Hospital Los Angeles, University of Southern California Keck School of Medicine, Los Angeles, California, USA

¹³Sanquin Research and Landsteiner Laboratory, Department of Molecular Hematology, Amsterdam, the Netherlands

Correspondence

Samantha Claudia Gouw, Emma Children's Hospital, Meibergdreef 9, 1105 AZ, Amsterdam, the Netherlands, PO Box 22660, 1100 DD, Amsterdam, the Netherlands.

Email: s.c.gouw@amsterdamumc.nl

Funding information

This study was funded by an ISTH SSC small research grant.

Abstract

It might take years for previously untreated patients (PUPs) with hemophilia A on emicizumab prophylaxis to receive 50 factor VIII (FVIII) exposures. This corresponds to the time at risk for FVIII inhibitors under conventional FVIII prophylaxis. During emicizumab prophylaxis, it is unknown whether additional treatment with regular FVIII doses promotes FVIII tolerance, unmasks inhibitors, or rather, induces them. Therefore, we conducted a survey to describe the current global perspectives and practices of hemophilia health care providers (HCPs) in PUPs with severe hemophilia

Manuscript handled by: Jerrold H Levy

Final decision: Jerrold H Levy, 18 January 2026

© 2026 The Author(s). Published by Elsevier Inc. on behalf of International Society on Thrombosis and Haemostasis. This is an open access article under the CC BY license (<http://creativecommons.org/licenses/by/4.0/>).

A receiving emicizumab prophylaxis. In 2024, a survey was sent by email to 1193 hemophilia treatment centers, addressing the perceived inhibitor risk with emicizumab, the potential need for concomitant regular FVIII infusions, and the perceived parental willingness to use concomitant FVIII. In total, 102 pediatric HCPs (85% physicians, 13% nurses) from 38 countries participated. Perceived inhibitor risk data were available for 63 HCPs (62%). Compared with FVIII prophylaxis, the inhibitor risk on emicizumab was estimated to be higher by 13%, equal by 41%, lower by 32%, and unknown by 14%. Among 57 of 102 HCPs with clinical access to emicizumab for children with severe hemophilia A without inhibitors, 30 (53%) offered regular concomitant FVIII infusions. However, in the experience of the HCPs, approximately 45% of parents rejected this option due to concerns about intravenous access. Ultimately, global perspectives on FVIII inhibitor risk and concomitant FVIII use in PUPs on emicizumab prophylaxis are heterogeneous due to lack of evidence, indicating the need for further research to guide treatment strategies.

KEYWORDS

factor VIII, hemophilia A, immune tolerance, surveys and questionnaires

1 | INTRODUCTION

Hemophilia A is a hereditary hemorrhagic disorder resulting from a congenital deficiency of factor VIII (FVIII) [1]. Persons with hemophilia A mainly suffer from painful bleeding in the joints and muscles. Persons with severe hemophilia A (ie, clotting factor levels <0.01 IU/mL) often bleed spontaneously [2,3].

Bleeds are managed by intravenous administration of FVIII concentrate. To reduce bleeding in persons with hemophilia A with a severe bleeding phenotype, prophylaxis can be initiated, which traditionally consists of regular intravenous administration of FVIII concentrate [4]. In about 30% of persons with severe hemophilia A, administration of FVIII concentrate leads to the development of inhibitors (ie, anti-FVIII antibodies) that neutralize the effect of FVIII treatment [1,5,6]. The inhibitor risk is highest in the first 50 exposures to FVIII [6,7], with 79% of inhibitors detected by 20 exposures [8]. In children with inhibitors, bleeds are treated with bypassing agents, and bleeding prevention can be obtained by using emicizumab. Emicizumab is a monoclonal antibody that mimics the function of FVIII by bridging factor IXa and factor X, evading inactivation by inhibitors due to its different structure compared with FVIII [9].

Emicizumab is highly effective in preventing bleeds, with the added convenience of relatively infrequent subcutaneous administration [8,10]. Persons with hemophilia A on emicizumab prophylaxis still require FVIII concentrates for managing breakthrough bleeds, trauma, or surgery [10]. Due to the efficacy of emicizumab and the infrequency of FVIII exposure, it may take years for people on emicizumab prophylaxis to reach a total of 50 FVIII exposures [9]. It is currently unknown how this prolonged period of FVIII exposures affects the risk

of inhibitor development in previously untreated patients (PUPs). Infrequent administration of FVIII may reduce or delay the development of inhibitors. Conversely, exposure to FVIII during tissue damage could increase the risk of developing inhibitors by activating immune-stimulating danger signals. Furthermore, it is unknown whether the traditional at-risk period related to FVIII exposures is still applicable to children under emicizumab prophylaxis who receive FVIII only occasionally. This raises the question of whether there is a way to achieve tolerance to FVIII in patients on emicizumab prophylaxis to prevent unexpected inhibitor development and treatment failure in the event of breakthrough bleeding, emergency surgery, or trauma. Previous research has shown that maintenance of immunologic tolerance requires the regular exposure to the antigen [11], suggesting that regular exposure to the FVIII protein is necessary to maintain tolerance. There are ongoing studies evaluating FVIII tolerance during emicizumab (from the [ClinicalTrials.gov](https://clinicaltrials.gov) repository, date April 4, 2025: MOTIVATE [NCT04023019], NAVIGATE [NCT05802836], PRIORITY [NCT04621916], SPIRIT [NCT07539402]).

Anecdotal information suggests that hemophilia health care providers around the world have adopted different strategies regarding the use of additional FVIII concentrate in PUPs or minimally treated patients (MTPs) on emicizumab prophylaxis. Given this heterogeneity in treatment approaches and the lack of evidence, we aimed to explore the current perspectives and practices of clinicians worldwide on unmasking inhibitors or obtaining FVIII tolerance for PUPs/MTPs with severe hemophilia A on emicizumab prophylaxis. Therefore, we conducted an online survey among hemophilia health care providers from all continents to answer the question: What is the heterogeneity in perspectives and clinical practice in PUPs/MTPs on emicizumab prophylaxis with respect to the use of concomitant FVIII?

2 | METHODS

2.1 | Study design

This study was a global online survey among hemophilia health care providers regarding real-world approaches to unmask inhibitors/obtain FVIII tolerance in PUPs/MTPs with severe hemophilia A on emicizumab prophylaxis. This study was reviewed by the Amsterdam University Medical Center Ethics Committee (METC number 2023.0903) and was deemed not to be subject to the WMO (Medical Research Involving Human Subjects Act). This study is reported following the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement for cross-sectional studies [12].

2.2 | Setting

This study was coordinated by Amsterdam UMC (the Netherlands) in close collaboration with an international steering committee of hemophilia experts and the International Society on Thrombosis and Haemostasis (ISTH) Scientific and Standardization Committee Subcommittee on Factor VIII, Factor IX and Rare Coagulation Disorders. The steering committee contributed to all project phases, including survey design, response interpretation, and manuscript drafting. Survey questions were drafted in April 2023 and pilot tested with 10 hemophilia clinicians in August 2023. Following revisions, the survey was integrated into the ISTH-managed REDCap database (USA) and distributed via email to all hemophilia treatment centers (HTCs) worldwide as listed in the World Federation of Hemophilia directory or the ISTH REDCap database [13,14]. The survey was distributed repeatedly via email and ISTH email newsletters, with reminders after 3 and 6 days for incomplete responses. Participants were contacted with additional questions if needed. Data were collected between January 19 and August 30, 2024.

2.3 | Study population

The study included hemophilia health care providers (eg, physicians, assistants, nurses) working in any of the 1193 HTCs worldwide. Eligible participants treated PUPs or MTPs with severe hemophilia A and provided consent for confidential data use. As this was an exploratory survey involving over 1000 HTCs, inclusion of around 10% of eligible participants (>100 participants) was expected.

2.4 | Outcome measures

The primary outcome was the proportion of hemophilia health care providers offering concomitant FVIII infusions besides emicizumab prophylaxis in PUPs/MTPs with severe hemophilia A. To provide a comprehensive overview of the perspectives of hemophilia experts, the survey addressed the perceived inhibitor risk with infrequent FVIII

exposure, the perceived clinical and psychosocial impact of the prolonged uncertainty inhibitor risk period, and the perceived need, potential indications, and parental willingness for concomitant FVIII use ([Supplementary Material S1](#)).

2.5 | Data analysis

Centers were classified as small (1-10 children with severe hemophilia A aged <19 years), medium (11-50 children), or large (>50 children). Countries were categorized into continents ([Supplementary Table S1](#)) and by income level based on The World Bank's method for Gross National Income per capita: high-income (>\$14 005), upper-middle-income (\$4516-\$14 005), lower-middle-income (\$1146-\$4515), and low-income (≤\$1145) ([Supplementary Table S2](#)) [15,16].

Descriptive statistics summarized the data on survey participants and study outcomes. Categorical variables were described as frequencies (*n*) and percentages (%), and continuous variables as mean with standard deviation or median with (interquartile) range. Missing data were identified as nonresponse (ie, the question was not completed). All statistical analyses were performed using IBM SPSS Statistics software version 28.0.1.1.

3 | RESULTS

3.1 | Participant characteristics

A total of 240 survey responses were received, with 120 fully completed ([Supplementary Figure S1](#)). After excluding 18 duplicate or ineligible responses, 102 pediatric hemophilia health care providers from 38 different countries were included ([Table 1](#)). Approximately half of the participants worked in Europe (49%), followed by 17% in Asia and 16% in North America. Most participants worked in high-income countries (68%). The survey included medical doctors, nurse specialists, nurse practitioners, and physician assistants ([Supplementary Table S3](#)), mainly working in academic hospitals (84%) and caring for at least 10 children with severe hemophilia A (80%).

3.2 | Clinical practice

3.2.1 | Prophylactic treatment

Emicizumab was available to most respondents (86%) ([Table 1](#); [Figure 1](#)), mostly to those working in Europe or North America ([Table 1](#)). Emicizumab prophylaxis was reported to be available for the following clinical indications: persons with inhibitors (*n* = 80) and persons with severe hemophilia A (*n* = 74) or moderate hemophilia A (*n* = 40) without inhibitors ([Figure 1](#)). Of the 74 health care providers with access to emicizumab for severe hemophilia A without inhibitors, 57 (77%) used it as first-line prophylaxis, initiating treatment before 3 months of age (26%, 15/57), between 3 and 6 months (35%,

TABLE 1 Characteristics of survey participants.

All participating pediatric hemophilia health care providers (N = 102)	n (%)
Participant-related characteristics	
Continent of practice ^a	
Europe	50 (49)
Asia	17 (17)
North America	16 (16)
South America	11 (11)
Africa	4 (4)
Australia	3 (3)
Missing	1 (1)
Country income level ^{a,b}	
High	69 (68)
Upper-middle	22 (22)
Lower-middle	10 (10)
Low	0 (0)
Missing	1 (1)
Years of work experience in hemostasis and/or hemophilia	
>15	59 (58)
6-15	36 (35)
0-5	7 (7)
Profession ^a	
Pediatrics/Hematology	68 (67)
Internal medicine/Hematology	17 (17)
Physician assistant/Nurse (practitioner)	13 (13)
Medical doctor	2 (2)
Other ^c	2 (2)
Center-related characteristics	
Type of HTC currently working	
Academic hospital	86 (84)
General hospital	11 (11)
Free standing HTC	5 (5)
Size of center ^d	
Small	19 (19)
Medium	45 (44)
Large	37 (36)
Missing	1 (1)

(Continues)

TABLE 1 (Continued)

All participating pediatric hemophilia health care providers (N = 102)	n (%)
Treatment availability at center	
FVIII available for prophylaxis	
Yes	100 (98)
No	1 (1)
Missing	1 (1)
Emicizumab available for prophylaxis	
Yes	88 (86)
No	12 (13)
Missing	1 (1)
Pediatric hemophilia health care providers with clinical access to emicizumab (N = 88) ^e	
Emicizumab availability per continent ^a	
Europe	49 (56)
Asia	9 (10)
North America	14 (16)
South America	9 (10)
Africa	3 (3)
Australia	3 (3)
Missing	1 (1)

FVIII, factor VIII; HTC, hemophilia treatment center.

^a Percentages are rounded and thus exceed 100%.^b This classification is based on The World Bank's method for gross national income per capita: low income: ≤\$1145, lower middle income: \$1146-\$4515, upper middle income: \$4516-\$14 005, and high income: >\$14 005.^c The other two professions include: social work and physiotherapist.^d The estimated size of the center is based on the number of children (<19 years of age) with severe hemophilia A currently under their care: small (1-10), medium (11-50), or large (>50).^e For persons with hemophilia A with and without inhibitors.

20/57), between 6 and 12 months (37%, 21/57), and between 12 and 18 months (2%, 1/57).

3.2.2 | Use of concomitant FVIII

Of 57 health care providers using emicizumab as first-line prophylaxis for severe hemophilia A without inhibitors, 53% (30/57) offered families of PUPs/MTPs the option of concomitant regular FVIII concentrate infusions during emicizumab prophylaxis (Figure 1). However, only 18% (10/57) used this in practice. Additional FVIII was initiated when venous

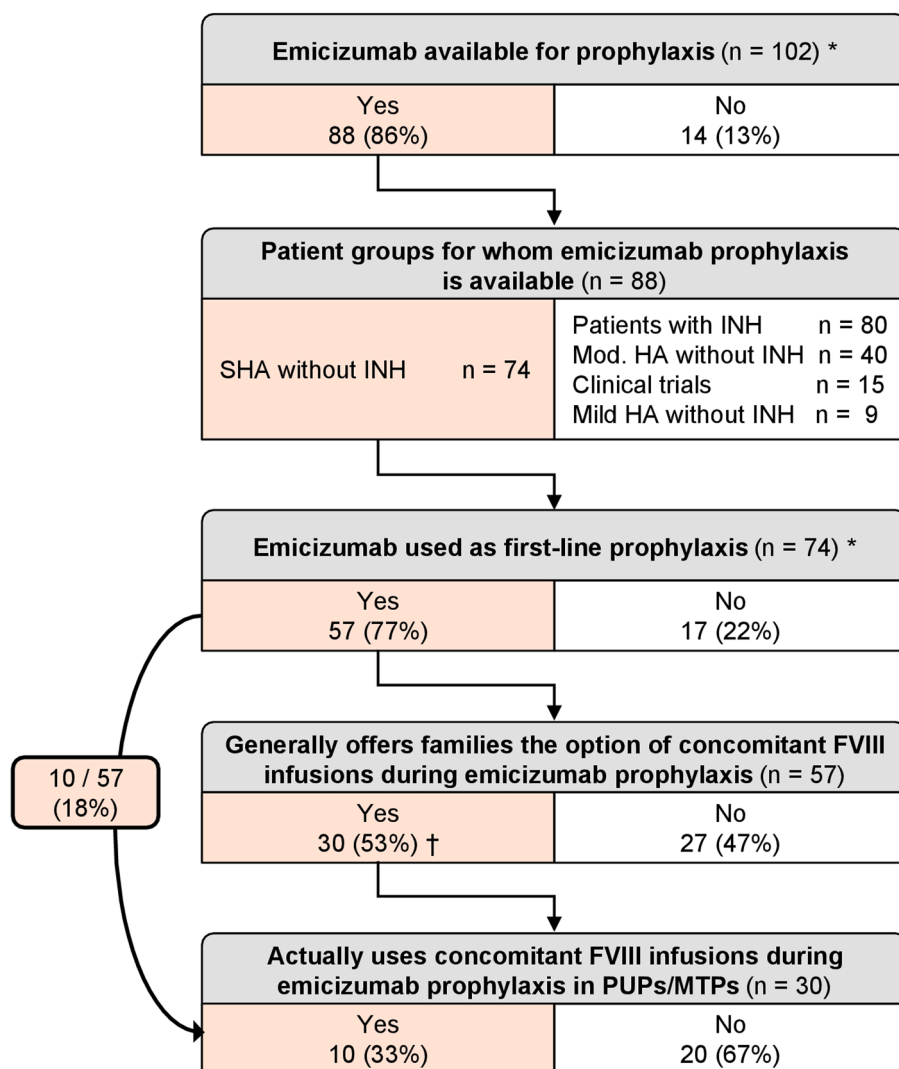


FIGURE 1 Availability and use of emicizumab prophylaxis and the use of concomitant FVIII infusions in PUPs/MTPs with severe hemophilia A

% = percentage.

Abbreviations: HA = Hemophilia A, INH = inhibitors, Mod. HA = moderate hemophilia A, n = number, MTPs = Minimally Treated Patients, n = number, PUPs = Previously Untreated Patients, SHA = severe hemophilia A.

*Missing data for 1 participant (1%)

† Answer Yes (n=30, 53%) includes Yes, always (n = 13, 23%) and Yes, sometimes (n = 17, 30%).

access improved (n = 5), after intensive FVIII treatment (≥ 3 consecutive days; n = 4), at emicizumab initiation (n = 3), or when on-demand treatment was required (n = 3). Concomitant FVIII infusions were administered once weekly (6/10) or every 2 weeks (3/10), with initial doses of ≤ 30 IU/kg (7/10) or 31-50 IU/kg (3/10). Of the 30 health care providers offering concomitant FVIII infusions, most planned a duration of 21 to 50 FVIII exposures (50%). Preferred practices are summarized in [Supplementary Table S4](#).

3.3 | Clinical perspectives

3.3.1 | Health care providers' perspectives regarding concomitant regular FVIII infusions

Among participants, 49 rated the importance of concomitant regular FVIII infusions during emicizumab prophylaxis in PUPs/MTPs with severe hemophilia A ([Figure 2](#)). Approximately half of the participants (27/49; 55%) considered it (very) important, 33% were neutral, and 12% considered it of little or no importance. Similar results were seen among

health care providers with access to emicizumab for children without inhibitors.

Reported reasons for treating PUPs/MTPs with concomitant FVIII (responses were available for 63 participants and missing for 39), included achieving tolerance (n = 29; 46%), reducing inhibitor risk (n = 26; 41%), unmasking inhibitor development (n = 25; 40%), training families (n = 18; 29%) or children in intravenous infusions (n = 12; 19%), enhancing bleed protection (n = 10; 16%), and reducing further costs in resource-limited countries (n = 7; 11%). Additionally, 27% (17/63) did not consider this approach in practice.

3.3.2 | The perceived inhibitor risk associated with emicizumab prophylaxis

Sixty-three participants estimated the lifetime inhibitor risk in PUPs/MTPs with severe hemophilia A receiving emicizumab with and without concomitant FVIII, compared with FVIII prophylaxis ([Table 2](#)). Compared with FVIII prophylaxis, the inhibitor risk of emicizumab prophylaxis without concomitant FVIII infusions was

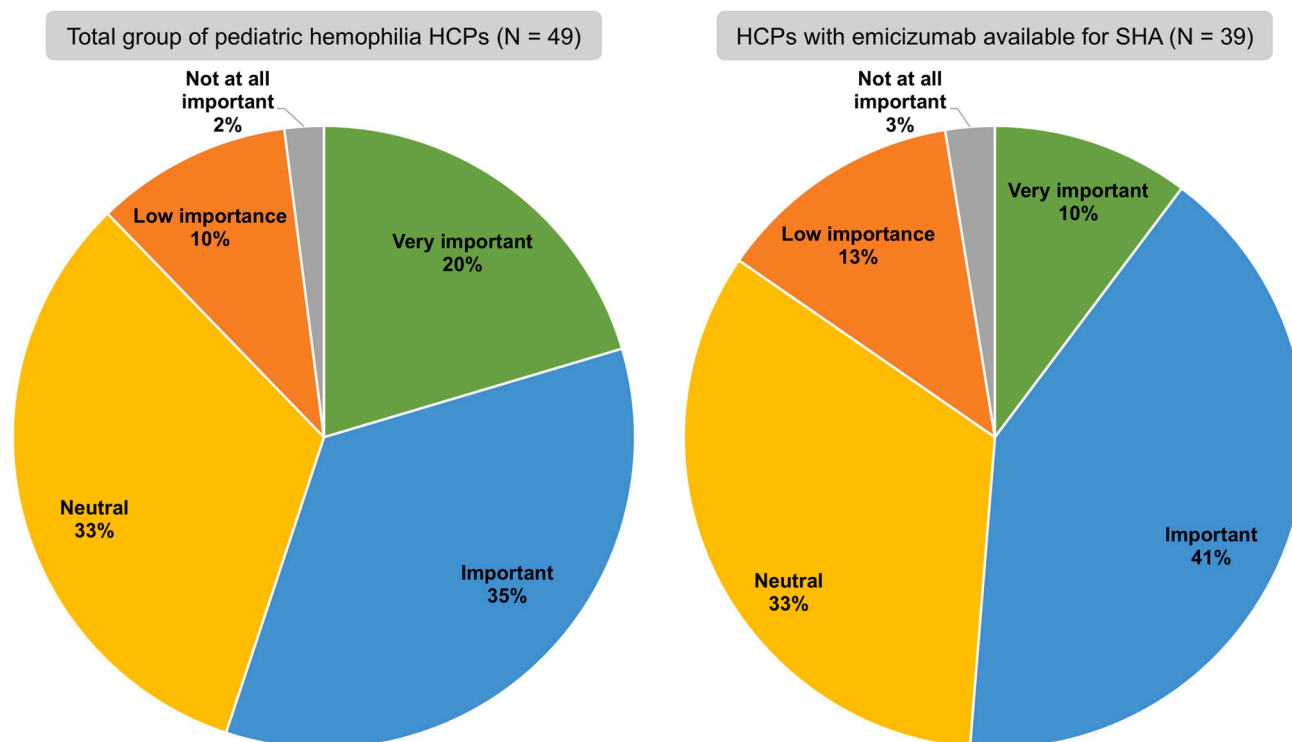


FIGURE 2 Importance to use concomitant FVIII infusions during emicizumab prophylaxis in PUPs or MTPs with severe hemophilia A. Perceived importance of using concomitant regular FVIII concentrate infusions for the total group of hemophilia health care providers (49/102) and for the subgroup who have emicizumab prophylaxis available for patients with severe hemophilia A without inhibitors (39/74). If N = 49, missing = 53, due to non-response (n = 2) or branching (n = 51, i.e., participants not using emicizumab and/or not considering treating PUPs/MTPs with concomitant FVIII infusions). If N = 39, missing = 35, due to non-response (n = 13) or branching (n = 22). % = percentage. Abbreviations: HCPs = healthcare providers, MTPs = Minimally Treated Patients, N= number, PUPs = Previously Untreated Patients, SHA = severe hemophilia A.

estimated to be higher by 13% of respondents (8/63), similar by 41% (26/63), lower by 32% (20/63), and unknown by 14% (9/63). The inhibitor risk of emicizumab prophylaxis with concomitant FVIII infusions was estimated to be higher by none of the respondents (0%), similar by 32% (20/63), lower by 44% (28/63), and unknown by 24% (15/63) compared with FVIII prophylaxis.

Half of the participants (49%; 17/35) indicated that the risks and efforts associated with concomitant FVIII do not outweigh the potential benefits.

3.3.3 | The perceived willingness of parents to administer intravenous injections

Twenty-five of the 30 health care providers offering concomitant regular FVIII infusions during emicizumab prophylaxis reported their experience with parental willingness toward this treatment option (Supplementary Figure S2). Experiences were mixed: 32% reported that parents were (very) willing, while 44% reported that parents were not willing. The reported percentage of parents who refused

TABLE 2 Perceived inhibitor risk associated with emicizumab prophylaxis in PUPs/MTPs with severe hemophilia A (N = 63).

Estimated inhibitor risk in PUPs or MTPs with severe hemophilia A on emicizumab prophylaxis, when only treated with FVIII for bleeds or surgery compared to FVIII prophylaxis	n (%)	Estimated inhibitor risk in PUPs or MTPs with severe hemophilia A on emicizumab prophylaxis with additional regular FVIII concentrate infusions compared to FVIII prophylaxis	n (%)
Higher – >35%	8 (13)	Higher – >35%	0 (0)
Same – about 25%-35%	26 (41)	Same – about 25%-35%	20 (32)
Lower – <25%	20 (32)	Lower – <25%	28 (44)
I do not know	9 (14)	I do not know	15 (24)

If N = 63, missing = 39 due to nonresponse (n = 2) or branching (n = 37; ie, participants not using emicizumab and/or not considering treating PUPs/MTPs with concomitant FVIII infusions).

FVIII, factor VIII; MTP, minimally treated patient; PUP, previously untreated patients.

this treatment option varied between 0 and 100%, with a mean of 45% (95% CI, 25%-65%).

3.3.4 | The perceived clinical and psychosocial impact of the prolonged inhibitor risk period with infrequent FVIII exposure

Persons with hemophilia receiving emicizumab are estimated to reach 20 FVIII exposures around 13 years [17,18]. Most respondents (61%; 23/38) reported that this long period of uncertainty regarding inhibitor development has a negative clinical impact on children, due to the risk of treatment failure from undetected inhibitor development (48%; 11/23) or an increased risk of inhibitor development (35%; 8/23) (Table 3).

Regarding the perceived psychosocial impact on families, 57% of respondents (21/37) reported a negative impact due to anxiety about

inhibitor development (62%; 13/21) and reduced confidence in FVIII efficacy (29%; 6/37), whereas 43% (16/37) perceived no psychosocial impact.

4 | DISCUSSION

This international survey among hemophilia health care providers reveals heterogeneity in clinical perspectives and practices concerning FVIII inhibitor risks and the perceived necessity of concomitant regular FVIII infusions for PUPs/MTPs with severe hemophilia A receiving emicizumab prophylaxis.

About half of the health care providers (53%) reported offering families the option of regular FVIII infusions alongside emicizumab prophylaxis. This is higher than the 9% reported in the US survey of 32 HTC Medical Doctors and the 20% reported in the European Pediatric Network on hemophilia treatment (PedNet) survey of 28

TABLE 3 Long risk period for inhibitor development with infrequent FVIII exposure on emicizumab prophylaxis: clinical impact on PUPs/MTPs and psychosocial impact on families.

Clinical impact on PUPs/MTPs (N = 38)				
Negative impact 61% (n = 23)	% ^a (n)	Positive impact 13% (n = 5)	% (n)	No impact 26% (n = 10)
Risk of treatment failure in unnoticed inhibitor development	48 (11)	Reduced risk of inhibitor development	60 (3)	
Increased risk of inhibitor development	35 (8)	Other	40 (2)	
		- Inhibitors will not occur at a young age when it is difficult to handle - Better venous access when child is older		
Postponement of treatment of surgical interventions in order to delay potential inhibitor development	9 (2)			
Other	9 (2)			
- Inhibitor occurrence at an older age will make ITI more difficult - Successful tolerization would facilitate surgical procedures				
Psychosocial impact on families (N = 37)				
Psychosocial impact 57% (n = 21)	% ^a (n)			No impact 43% (n = 16)
Anxiety about inhibitor development	62 (13)			
Lack of confidence in efficacy of FVIII concentrate used to treat bleeding	29 (6)			
Problems in coping with the diagnosis of hemophilia	10 (2)			

If N = 38, missing = 64 due to nonresponse (n = 3) or branching (n = 61; ie, participants who do not use emicizumab prophylaxis and/or participant who not offer concomitant FVIII and/or not considering treating PUPs/MTPs with concomitant FVIII and/or not discussing it with parents). If N = 37, missing = 65 due to nonresponse (n = 4) or branching (n = 61).

FVIII, factor VIII; ITI, immune tolerance induction; MTP, minimally treated patient; PUP, previously untreated patient.

^a Percentages are rounded and thus exceed 100%.

HTCs [19–21]. The difference in results may be due to the sampling of respondents to our survey, as health care providers who prioritized inhibitor unmasking or achieving FVIII tolerance in PUPs/MTPs may have been more likely to respond.

The perceived inhibitor risk associated with emicizumab prophylaxis and on-demand FVIII was estimated to be higher by 13% and lower by 32% compared with FVIII prophylaxis. This shifted with the use of concomitant FVIII. More health care providers considered the risk to be lower (32% vs 44%) or were uncertain (14% vs 24%). It is important to distinguish a *lower risk* from *postponement of risk*. Currently, PUPs on emicizumab have a reduced annual inhibitor incidence due to infrequent FVIII exposure [22], but the risk period may extend over decades. Furthermore, it is unclear whether the inhibitor risk diminishes after a period of 50 exposures or whether a lifelong risk persists due to very infrequent FVIII exposures in people receiving emicizumab prophylaxis. Therefore, the question of whether the lifetime cumulative incidence is increased or decreased remains unanswered. As a result, delayed inhibitor development may have been misinterpreted as a lower risk.

A systematic literature review on inhibitor incidence in PUPs receiving emicizumab prophylaxis found that only 15 of the 32 included patients received FVIII, with a median cumulative exposure days of 1 (range 0–10) over 51.2 cumulative person-years at risk [23]. Cumulative inhibitor incidence rates in PUPs are not informative until at least 20 to 50 exposures have been reached. Therefore, it is currently not possible to determine the inhibitor risk or the timing of inhibitor development in PUPs on emicizumab prophylaxis.

Parental willingness to administer concomitant regular FVIII infusions varied widely. It should be noted that these findings reflect the perception of the health care providers, and it would be more precise to directly ask parents and children. Concomitant use of emicizumab and FVIII imposes a treatment burden and economic costs, while the efficacy of this approach remains unknown. Currently, there is no evidence from studies evaluating the effect of concomitant FVIII use during emicizumab prophylaxis on the development of FVIII inhibitors. Furthermore, it remains unknown whether unmasking potential inhibitors or shortening the risk period actually affects patient safety and the psychosocial well-being of families.

The prolonged period of uncertainty regarding inhibitor risk can have both clinical and psychosocial implications. In our survey, most respondents reported a negative clinical impact on children (61%), due to concerns about treatment failure from undetected inhibitors, and a negative psychosocial impact on families (56%), due to anxiety about the inhibitor risk. However, this reflects the perceived impact of health care providers rather than that of the families themselves. The level of concern of families may be significantly influenced by the level of concern expressed by the health care provider. Treatment decisions on concomitant FVIII administration may also be influenced by individual characteristics, including inhibitor risk factors (eg, positive family history of inhibitors or high-risk *F8* gene mutations),

factors associated with treatment burden (eg, venous access or family circumstances), and economic aspects (eg, treatment affordability).

This study has several limitations. First, the limited response may have introduced selection bias, making the study population unrepresentative of all hemophilia health care providers worldwide [24]. Health care providers who prioritize unmasking inhibitors or achieving tolerance may have been more likely to respond, potentially overestimating the proportion of health care providers who consider concomitant regular FVIII infusions important. Furthermore, HTCs in low-income countries, those in North America compared with Europe, and smaller-sized HTCs were underrepresented. We cannot exclude that this was associated with the perspectives of health care providers and may have influenced our results. A second limitation was the branching design of the survey, which excluded health care providers not using emicizumab as first-line prophylaxis or not offering concomitant FVIII from parts of the survey, resulting in data loss. Efforts to address this, including removing branching for some questions and emailing participants to complete the additional survey questions, yielded limited responses. This may have led to an overestimation of concomitant FVIII use and a higher proportion of health care providers perceiving a reduced risk when adding FVIII to emicizumab prophylaxis.

Therefore, it should be emphasized that the distribution of the perspectives of health care providers in this study does not reflect the distribution of global perspectives of an unselected sample of the global hemophilia health care providers. However, our study highlights the diversity in clinical perspectives and practices in hemophilia care worldwide, reflecting the uncertainty regarding the best approach. Our study emphasizes the need for more evidence regarding the effects of concomitant FVIII exposure during emicizumab prophylaxis on inhibitor risk. Emerging evidence and changes in FVIII treatment modalities may influence future views and decision-making processes. Similar to current standard half-life and extended half-life products, the impact of ultra-long half-life FVIII products with sustained FVIII levels is also unknown. Nevertheless, weekly prophylaxis with these ultra-long half-life FVIII products may change the acceptance of FVIII exposures, which could offer an alternative to non-factor therapy prophylaxis combined with FVIII infusions. Evidence from long-term follow-up studies and large registries are essential to guide optimal treatment strategies.

ACKNOWLEDGMENTS

We thank Cary Clark and Clarence Potter who built and managed the online survey in REDCap.

AUTHOR CONTRIBUTIONS

K.F. and S.G. conceived the project; L.v.S., P.A., M.C., G.K., C.K., J.M., M.M., S.M.R., R.S., S.S., A.S., G.Y., K.F., and S.G. developed survey questions; L.v.S., B.H., and S.G. contributed to data analysis; all

authors contributed to data interpretation; L.v.S., B.H., K.F., and S.G. wrote the article; all authors had full editorial control, critically reviewed the manuscript, and approved the contents for publication.

DECLARATION OF COMPETING INTERESTS

L.v.S. and B.H. have no conflicts of interest to disclose. P.A. reports project-based funding via research or service agreements from Novo Nordisk, Sanofi, and Spark Therapeutics; and served as President of the ISTH. M.C. has received research support from Novartis, Novo Nordisk, Pfizer, Roche, Sanofi, and Takeda; and honoraria for speaking/advisory board from Bayer, LFB, Novo Nordisk, Pfizer, Roche, Sanofi, and Takeda. G.K. received research funding to institutions from BSF, Novo Nordisk, Pfizer, and Roche; consulting fees and/or honoraria from CSL, Novo Nordisk, Pfizer, Roche, Sanofi-Genzyme, and Sobi; participated on a Data Safety Monitoring Board/Advisory Boards for Biomarin, CSL, Novo Nordisk, Pfizer, Roche, Sanofi-Genzyme, Spark, and Uniquore; and served as CEO from PedNet Research Foundation. C.K. received research funding to institutions from Bayer, Biotest, CSL Behring, Intersero, Novo Nordisk, Pfizer, Roche/Chugai, Sobi/Sanofi, EU H2020 ITN, State of Hesse, and FUSE e.V.; and acted as a consultant or speaker for Bayer, CSL Behring, Florio, Novo Nordisk, Pfizer, Roche/Chugai, Sobi/Sanofi, and Takeda. J.M. has received research grant/research support from Biomarin, LFB, Novo Nordisk, Pfizer, Roche, Sanofi, Spark Therapeutics, and Vega Therapeutics; and has been a consultant/scientific board for Biomarin, Novo Nordisk, Roche, Sanofi, Spark Therapeutics, and Takeda. M.M. received research funding to institutions from Bayer, CSL Behring, and Novo Nordisk; and acted as consultant, advisor and/or speaker for Bayer, Biomarin, CSL Behring, Kendrion, LFB, Novo Nordisk, Octapharma, Pfizer, Regeneron, Roche, Sanofi, Sobi, and Takeda. S.M.R. has received research funding/support from Brazilian Association of Hematology, Brazilian Ministry of Health (Fundo Nacional de Saúde), CNPq (Brazilian Ministry of Science), FAPEMIG (State agency for science), and ISTH congress 2023 and 2024; and served in leadership or fiduciary roles for Bleeding Disorders Committee of the Brazilian Ministry of Health, Hematology Committee of the Brazilian Association of Thrombosis and Hemostasis, ISTH Leadership Committee, and Thrombosis and Hemostasis Committee of the Brazilian Association of Hematology. R.S. has received research funding/support from Hema Biologics, LFB, Octapharma and Takeda; honoraria for consulting and advisory boards from Bayer, HEMAB, LFB, Novo Nordisk, Octapharma, Pfizer, Sanofi, Sobi, Star, Takeda, and Vega; participated on a Data Safety Monitoring Board or Advisory Board for Uniquore/CSL Behring; and had a role as American Thrombosis and Hemostasis Network board member and ISTH Chair. A.S. has received research funding from Roche, Novo Nordisk, Sanofi, and Pfizer; and served on advisory committees/grant review committees from Sanofi, Takeda, Novo Nordisk, Roche, Pfizer, and Bayer Healthcare. A.S. has received research funding/support from Biomarin, Novo Nordisk, Octapharma, Pfizer, Regeneron, Roche, Sanofi, and Takeda; consulting fees from Biomarin, Novo Nordisk, Octapharma, Pfizer, Regeneron, Roche, Sanofi, Spark, and Takeda; honoraria from Biomarin, Novo Nordisk,

Octapharma, Pfizer, Regeneron, Roche, Sanofi, and Takeda; and had a role as board/committee member for World Federation of Hemophilia, ISTH, and Association for Haemophilia and Allied Disorders – Asia Pacific, Indian Association for Haemophilia and Allied Disorders. G.Y. reports receiving royalties/licensing fees from Viatrix; consulting fees from Alnylam, ASC Biotherapeutics, Bayer, BioMarin, CSL Behring, Genentech/Roche, Hema Biologics/LFB, Novo Nordisk, Octapharma, Pfizer, Sanofi Genzyme, Spark, and Takeda; honoraria from BioMarin, CSL Behring, Genentech/Roche, Hema Biologics, Novo Nordisk, Octapharma, Pfizer, Sanofi Genzyme, Spark, and Takeda; and participation on a Data Safety Monitoring Board/Advisory Boards for ASC Biotherapeutics. K.F. has received unrestricted research grants from CSL Behring, Sobi, and Novo Nordisk and consulting fees from Sobi, Novo Nordisk, Sanofi, and Roche, all fees paid to the institution. S.G. received unrestricted research funding from Sobi.

ORCID

Lilianne Esmée van Stam  <https://orcid.org/0000-0001-8278-9428>

Pantep Angchaisuksiri  <https://orcid.org/0000-0001-5607-3485>

Manuel Carcao  <https://orcid.org/0000-0001-5350-1763>

Gili Kenet  <https://orcid.org/0000-0003-3494-9823>

Christoph Königs  <https://orcid.org/0000-0003-4597-2439>

Johnny Mahlangu  <https://orcid.org/0000-0001-5781-7669>

Maria Elisa Mancuso  <https://orcid.org/0000-0002-7113-4028>

Suely Meireles Rezende  <https://orcid.org/0000-0002-3083-7093>

Robert Francis Sidonio  <https://orcid.org/0000-0002-9509-9415>

Alok Srivastava  <https://orcid.org/0000-0001-5032-5020>

Guy Young  <https://orcid.org/0000-0001-6013-1254>

Karin Fijnvandraat  <https://orcid.org/0000-0003-0904-4360>

Samantha Claudia Gouw  <https://orcid.org/0000-0002-1957-4122>

X

Guy Young  @GuyYoungMD

REFERENCES

- [1] Tomeo F, Mariz S, Brunetta AL, Stoyanova-Beninska V, Penttilä K, Magrelli A. Haemophilia, state of the art and new therapeutic opportunities, a regulatory perspective. *Br J Clin Pharmacol*. 2021;87:4183–96.
- [2] Iorio A, Stonebraker JS, Chambost H, Makris M, Coffin D, Herr C, Germini F, Data and Demographics Committee of the World Federation of Hemophilia. Establishing the prevalence and prevalence at birth of hemophilia in males: a meta-analytic approach using national registries. *Ann Intern Med*. 2019;171:540–6.
- [3] O'Hara J, Walsh S, Camp C, Mazza G, Carroll L, Hoxer C, Wilkinson L. The impact of severe haemophilia and the presence of target joints on health-related quality-of-life. *Health Qual Life Outcomes*. 2018;16:84. <https://doi.org/10.1186/s12955-018-0908-9>
- [4] Srivastava A, Brewer AK, Mauser-Bunschoten EP, Key NS, Kitchen S, Llinas A, Ludlam CA, Mahlangu JN, Mulder K, Poon MC, Street A, Treatment Guidelines Working Group on Behalf of The World Federation Of Hemophilia. Guidelines for the management of hemophilia. *Haemophilia*. 2013;19:e1–47. <https://doi.org/10.1111/j.1365-2516.2012.02909.x>
- [5] Fischer K, Carcao M, Male C, Ranta S, Pergantou H, Kenet G, Kartal-Kaess M, Königs C, Carvalho M, Alvarez MT, Brakenhoff T,

- Chambost H, van den Berg HM. Different inhibitor incidence for individual factor VIII concentrates in 1076 previously untreated patients with severe hemophilia A: data from the PedNet cohort. *J Thromb Haemost*. 2023;21:700–3.
- [6] Gouw SC, van den Berg HM, Fischer K, Auerswald G, Carcao M, Chalmers E, Chambost H, Kurnik K, Liesner R, Petrini P, Platokouki H, Altisent C, Oldenburg J, Nolan B, Garrido RP, Mancuso ME, Rafowicz A, Williams M, Clausen N, Middelburg RA, et al. Intensity of factor VIII treatment and inhibitor development in children with severe hemophilia A: the RODIN study. *Blood*. 2013;121:4046–55.
- [7] Fischer K, Lassila R, Peyvandi F, Gatt A, Gouw SC, Hollingsworth R, Lambert T, Kaczmarek R, Carbonero D, Makris M, European HAemophilia Safety Surveillance (EUHASS) participants. Inhibitor development according to concentrate after 50 exposure days in severe hemophilia: data from the European HAemophilia Safety Surveillance (EUHASS). *Res Pract Thromb Haemost*. 2024;8:102461. <https://doi.org/10.1016/j.rpth.2024.102461>
- [8] van den Berg HM, Fischer K, Carcao M, Chambost H, Kenet G, Kurnik K, Königs C, Male C, Santagostino E, Ljung R, PedNet Study Group. Timing of inhibitor development in more than 1000 previously untreated patients with severe hemophilia A. *Blood*. 2019;134:317–20.
- [9] Lillicrap D, Fijnvandraat K, Young G, Mancuso ME. Patients with hemophilia A and inhibitors: prevention and evolving treatment paradigms. *Expert Rev Hematol*. 2020;13:313–21.
- [10] Srivastava A, Santagostino E, Dougall A, Kitchen S, Sutherland M, Pipe SW, Carcao M, Mahlangu J, Ragni MV, Windyga J, Llinás A, Goddard NJ, Mohan R, Poonnoose PM, Feldman BM, Lewis SZ, van den Berg HM, Pierce GF. WFH Guidelines for the Management of Hemophilia panelists and co-authors. WFH guidelines for the management of hemophilia, 3rd edition. *Haemophilia*. 2020;26(Suppl 6):1–158.
- [11] Ramsdell F, Fowlkes BJ. Maintenance of in vivo tolerance by persistence of antigen. *Science*. 1992;257:1130–4.
- [12] Vandembroucke JP, von Elm E, Altman DG, Gøtzsche PC, Mulrow CD, Pocock SJ, Poole C, Schlesselman JJ, Egger M. STROBE initiative. Strengthening the Reporting of Observational Studies in Epidemiology (STROBE): explanation and elaboration. *Ann Intern Med*. 2007;147:W163–94.
- [13] World Federation of Hemophilia. The Global Treatment Centre Directory. <https://wfh.org/find-local-support/#HTCs>; [accessed June 6, 2025].
- [14] International Society on Thrombosis and Haemostasis. REDCap. <https://www.isth.org/page/redcap>; [accessed June 6, 2025].
- [15] The World Bank. World Bank Country and Lending Groups <https://datahelpdesk.worldbank.org/knowledgebase/articles/906519-world-bank-country-and-lending-groups>; [accessed June 6, 2025].
- [16] Maldonado L, Olivo V. Is Venezuela still an upper-middle-income country? Estimating the GNI per Capita for 2015–2021. IDB. <https://doi.org/10.18235/0004612>; 2022. [accessed June 6, 2025].
- [17] Patel AM, Corman SL, Chaplin S, Raimundo K, Sidonio RF. Economic impact model of delayed inhibitor development in patients with hemophilia a receiving emicizumab for the prevention of bleeding events. *J Med Econ*. 2019;22:1328–37.
- [18] Abdi A, Kloosterman FR, Eckhardt CL, Male C, Castaman G, Fischer K, Beckers EAM, Kruip MJHA, Peerlinck K, Mancuso ME, Santoro C, Hay CR, Platokouki H, van der Bom JG, Gouw SC, Fijnvandraat K, Hart DP, INSIGHT Study Group. The factor VIII treatment history of non-severe hemophilia A. *J Thromb Haemost*. 2020;18:3203–10.
- [19] Cohen CT, Tarango C, Powers JM. Efficacy of emicizumab use in infancy: a survey of United States pediatric hemophilia treatment center medical directors. *Haemophilia*. 2024;30:848–51.
- [20] Ranta S, Motwani J, Blatny J, Bührlen M, Carcao M, Chambost H, Escuriola C, Fischer K, Kartal-Kaess M, de Kovel M, Kenet G, Male C, Nolan B, d'Oiron R, Olivieri M, Zapotocka E, Andersson NG, Königs C. Dilemmas on emicizumab in children with haemophilia A: a survey of strategies from PedNet centres. *Haemophilia*. 2023;29:1291–8.
- [21] Ranta S, Zapotocka E, Andersson NG, Fischer K, Kenet G, de Kovel M, Königs C, Labarque V, Male C, Olivieri M, Motwani J. A survey on clinical practice in monitoring and management of bleeding in children with haemophilia A on emicizumab prophylaxis in the PedNet centres. *Thromb Res*. 2025;249:109307.
- [22] Fischer K, Lassila R, Peyvandi F, Gatt A, Gouw SC, Hollingsworth R, Lambert T, Kaczmarek R, Carbonero D, Makris M, participants E. Trends in treatment of severe haemophilia and impact on inhibitor assessment by the EUHASS Registry. *Haemophilia*. 2025;31:433–40.
- [23] van Stam LE, Lacroix-Desmazes S, Fijnvandraat K, Gouw SC. Tolerance to factor VIII in the era of nonfactor therapies: immunologic perspectives and a systematic review of the literature. *J Thromb Haemost*. 2025;23:1169–84.
- [24] Delgado-Rodríguez M, Llorca J. Bias. *J Epidemiol Community Health*. 2004;58:635–41.

SUPPLEMENTARY MATERIAL

The online version contains supplementary material available at <https://doi.org/10.1016/j.jtha.2026.01.006>.