Surgical outcomes in patients with haemophilia A or B receiving extended half-life recombinant factor VIII and IX Fc fusion proteins: Real-world experience in the Nordic countries

Anna-Elina Lehtinen | Fariba Baghaei | Jan Astermark | Pål André Holme

Abstract

**Introduction:** Perioperative dosing recommendations vary across Nordic haemophilia treatment centres (HTCs) for extended half-life (EHL) factor concentrates in haemophilia A/B (HA/HB) patients.

**Aim:** To summarise Nordic real-world surgical experiences with EHL recombinant factor VIII/IX Fc (rFVIIIFc/rFIXFc) fusion proteins using retrospective data from clinical records at four HTCs in Finland, Sweden and Norway.

**Methods:** Factor dosing and surgical outcomes were recorded from HA/HB patients who underwent surgery and were treated with rFVIIIFc/rFIXFc. Perioperative factor dosing regimens were clinician-determined based on local practises.

**Results:** Twenty five surgeries were performed on 20 patients, all covered by bolus injections except one minor HA surgery; eight minor surgeries were in paediatric patients. Median preoperative rFVIIIFc dose for major HA surgeries \( (n = 8) \) was 48 IU/kg (range: 35–57), with total consumption up to Day 14 of 427 IU/kg (196–568). For the two major HB surgeries (in one patient), preoperative rFIXFc doses were 50 IU/kg and 20 IU/kg; total consumption up to Day 14 was 130 IU/kg and 40 IU/kg. Median preoperative rFVIIIFc/rFIXFc bolus doses for minor HA \( (n = 10) \) and HB \( (n = 4) \) surgeries were 50 IU/kg (24–79) and 47 IU/kg (40–71), with total consumption up to Day 5 of 138 IU/kg (49–404) and 100 IU/kg (43–125), respectively. Intraoperative and postoperative haemostatic responses were rated as at least good/excellent for 24/25 surgeries, with bleeding episodes reported in only three surgeries.

**Conclusion:** Nordic real-world experiences suggest that EHL products can be used safely and effectively for peri-operative haemostasis. Further research is required to develop local dosing guidelines for optimised treatment schedules.

**KEYWORDS**

factor IX Fc fusion protein, factor VIII-Fc fusion protein, haemophilia A, haemophilia B, recombinant fusion proteins, surgical procedures
Haemophilia A (HA) and haemophilia B (HB) are congenital clotting disorders caused by deficiencies in factor VIII (FVIII) and factor IX (FIX), respectively. Deficiencies in blood clotting can result in excessive bleeding and joint damage in patients with haemophilia, and because they are at risk of excessive bleeding during and after surgery, their care requires additional planning. The standard of care for patients with haemophilia who undergo surgery is provision of replacement clotting factor before, during and after surgery.

For major surgery, the Nordic Haemophilia Guidelines recommend preoperative target factor levels of 70–100 IU/dl, with a suggested preoperative dose of 50 IU/kg for FVIII and 60–70 IU/kg for FIX. Postoperative factor replacement therapy is recommended for 7–10 days with desired trough levels of 70 IU/dl during Days 1–3, 50 IU/dl during Days 4–6 and 30 IU/dl during Days 7–9.

For minor surgery, the guidelines recommend target preoperative factor levels of 50 IU/dl. This is to be followed with factor replacement therapy for 1–5 days, depending on the type of surgery. Factor replacement therapy can be achieved by bolus dosing or continuous infusion. Bolus dosing requires repeated injections at regular intervals, which must be sufficient to keep factor trough levels above these predetermined targets.

Extended half-life (EHL) factor concentrates have improved pharmacokinetic profiles that enable adequate trough levels to be maintained for longer in patients with haemophilia. Use of EHL products can result in higher trough levels with bolus dosing, and improved bleed protection during surgery compared with standard factor replacement products. This presents the potential for reduced factor consumption and injection frequency during surgery. EHL recombinant factor VIII Fc (rFVIIIFc) fusion protein and recombinant factor IX Fc (rFIXFc) fusion protein have been approved in Europe for the prophylactic treatment of patients with HA and HB, respectively, following the demonstration of their safety and efficacy in patients of all ages in Phase III clinical trials. Perioperative management of patients with HA or HB treated with rFVIIIFc or rFIXFc has also been found to be safe and efficacious in clinical trials.

Data reporting real-world experience of rFVIIIFc and rFIXFc in surgery have been published in several case reports and observational studies. In all studies, rFVIIIFc and rFIXFc were used effectively in the peri-operative management of HA and HB. However, details on dosage and patient outcomes were not reported consistently, and data are reported from various regions of the world with a wide range of treatment standards. Therefore, it is difficult to apply these learnings to inform clinical practice with EHL products in Nordic Countries.

Norway, Sweden and Finland include EHL products for HA and HB in their national tender or reimbursement programmes. Although Nordic Haemophilia Guidelines recommend that the same principles should be applied when using EHL products for surgery as when using standard half-life products, there is currently a lack of alignment between Nordic haemophilia treatment centres (HTCs) regarding dosing recommendations. Characterisation of real-world use of EHL products during surgery can be used to generate more data to inform treatment guidelines. Here, we report data from four Nordic HTCs on factor consumption and surgical outcomes for patients with HA and HB who were treated with EHL products during the peri-operative period in order to summarise the real world surgical experiences with rFVIIIFc and rFIXFc in the Nordic countries.

2 MATERIALS AND METHODS

2.1 Patients

This retrospective case series included surgical cases occurring between April 1, 2017 and November 30, 2019 at four HTCs in Finland, Sweden and Norway. Patients with HA or HB who had undergone major or minor surgery and were treated with rFVIIIFc (efmorcotocog alfa) or rFIXFc (eftenonacog alfa) were included. Patient characteristics and surgical data were reported in patients’ clinical records by healthcare providers during the peri-operative and postoperative (up to Day 14 for major surgeries and Day 5 for minor surgeries) periods. Later, treating physicians used an internally developed case report form to extract relevant data. Informed consent was obtained where required by national guidelines with respect to each HTC, and the protocol approved by the Swedish Ethical Review Authority, as required by national guidelines.

Major surgery was defined as any surgical procedure that usually involves general anaesthesia and/or respiratory assistance, in which a major body cavity is penetrated or exposed, or for which a substantial impairment of physical or physiologic function(s) is produced. All other surgeries were considered minor. Perioperative dosing regimens with rFVIIIFc/rFIXFc were clinician-determined based on local practices. Target intraoperative factor levels were at least 70% for major surgeries, and 50% for minor surgeries, in accordance with the Nordic Haemophilia Guidelines.

2.2 Outcomes assessed and statistical analysis

Patient characteristics for included surgical cases were assessed at the time of surgery. Mean and standard deviation (SD) were calculated for continuous variables including age (years) and weight (kg). Absolute counts and proportions were calculated for categorical variables including history of inhibitors (yes/no), haemophilia severity (mild > 5% clotting factor/moderate [1–5%]/severe [< 1%]), surgical classification (major/minor) and type of procedure (e.g. dental, orthopaedic, etc.).

Preoperative dosing, total factor consumption of rFVIIIFc/rFIXFc over the peri-operative period and FVIII activity levels (preoperative post-dose and postoperative pre-dose) for major HA surgeries were reported using descriptive statistics. Total factor consumption was reported up to Day 14 for major surgeries and up to Day 5 for minor surgeries; total consumption included any normal prophylaxis that may have been resumed during that period. Factor levels for major HA surgeries were measured by one-stage clotting factor
3 | RESULTS

3.1 Patient and surgical case characteristics

A total of 25 surgical cases were included, including 15 patients who underwent one surgery and five patients who underwent two surgeries. Outcomes for each major and minor surgery are reported in Tables S1 and S2, respectively. Nineteen surgeries were performed in patients with HA (19 severe; 0 moderate/mild) who were treated with rFVIIIFc, of which eight were major (seven orthopaedic) and 11 were minor (one orthopaedic; four dental). Six surgeries were performed in patients with HB (two mild; three moderate; one severe) who were treated with rFIXFc, of which two were major (non-orthopaedic) and four were minor (two dental). Other types of procedures included abdominal, endoscopic and ophthalmological surgery, as well as port-a-cath insertion/removal. Mean age of the patients at the time of surgery was 34.5 years (SD: 26.3) (Table 1). In total, eight surgeries (32%) were in paediatric patients, all of which were minor. Three patients (12%; Cases 1, 9a/9b and 10), all with HA, had a history of inhibitors. All three patients were considered tolerised, but one (Case 10) had a shortened FVIII half-life.

3.2 Outcomes

All surgeries were covered by factor bolus injections except one minor HA surgery (Case 13) (Figure 1). For major surgeries in patients with severe HA, median preoperative rFVIIIFc dose was 48 IU/kg (range: 35–57 IU/kg), with a median preoperative post-dose FVIII level of 83 IU/dl (range: 57–108 IU/dl). Median (range) pre-dose FVIII activity levels for postoperative Day 1, 2 and 3 were 76 IU/dl (42–95 IU/dl), 82 IU/dl (47–100 IU/dl) and 85 IU/dl (57–122 IU/dl), respectively. Median total consumption up to Day 14 for major HA surgeries was 427 IU/kg (196–568 IU/kg). One patient with mild HB underwent two major surgeries (Cases 8a and 8b), the second of which was to repair a complication of the first surgery. In that patient, preoperative doses were 50 IU/kg for the first surgery and 20 IU/kg for the second. Reported consumption to Day 14 was 130 IU/kg and 40 IU/kg, respectively, but the second surgery took place on postoperative Day 13 of the first surgery. Sufficient FIX activity level data were not available for the two major HB surgeries during the peri-operative period.

For minor surgeries in patients with severe HA covered by bolus injections (n = 10), median preoperative rFVIIIFc dose was 50 IU/kg (range: 24–79 IU/kg) and median overall consumption up to Day 5 was 138 IU/kg (49–404 IU/kg). One HA patient undergoing minor surgery (Case 13) received a preoperative rFVIIIFc bolus injection of 41 IU/kg, followed by continuous infusion to postoperative Day 4; continuous infusion rate was 2.14 IU/kg/h on the day of surgery and 1.69 IU/kg/h on postoperative Days 1–4. No additional peri-operative bolus injections were required. Total consumption over the entire postoperative period was 176 IU/kg. Pre-dose FVIII activity levels were 69 IU/dl (post-bolus dose and prior to continuous infusion) on the day of surgery and 71 IU/dl, 51 IU/dl and 65 IU/dl on postoperative Days 1, 2 and 3, respectively.

Most (7/11) minor surgeries treated with rFVIIIFc were in paediatric patients. Factor consumption was not particularly high (142 IU/kg) in the patient with a shortened FVIII half-life. Four minor surgeries were reported in patients with moderate/severe HB (one paediatric), with a median preoperative dose of 47 IU/kg (range: 40–71 IU/kg) and median overall consumption up to Day 5 of 100 IU/kg (43–125 IU/kg).
Across all cases, median duration of hospitalisation was 5 days (range: 1–9 days) for major surgeries and 1 day (0–6 days) for minor surgeries. Concomitant tranexamic acid was used in 10/10 (100%) major and 13/15 (87%) minor surgeries. Thromboprophylaxis and blood transfusions were not administered for any surgeries. Both intraoperative and postoperative haemostatic response were rated as at least good/excellent by the physician or surgeon for 24/25 (96%) surgeries. Bleeding episodes were only reported in three (12%) surgeries (one major [Case 8a] and two minor [Cases 19 and 20]). Three bleeding episodes occurred in Case 20 and postoperative haemostatic efficacy was rated as poor; however, total blood loss was estimated at < 50 ml. All three surgical cases required additional postoperative bolus injections: Case 8a (wound rupture) and Case 19 received one additional dose each, whilst Case 20 received repetitive bolus injections on Days 2, 4 and 6 due to postoperative bleeds.

4 DISCUSSION

Real-world data on the use of rFVIIIFc and rFIXFc in surgery are useful to align dosage recommendations amongst Nordic treatment centres. This case series reports real world surgical outcomes in Nordic patients with HA and HB, demonstrating that rFVIIIFc and rFIXFc can be used safely and effectively for peri-operative haemostasis. Most patients did not experience any bleeding episodes, none required thromboprophylaxis, and no adverse events occurred.

Preoperative doses were similar between major and minor surgeries, with median dose for all subgroups very close to the preoperative dose recommended for major surgeries in the Nordic Haemophilia Guidelines. Minor surgeries might be expected to require lower preoperative doses on average, which was not observed in this case series; however, the majority of minor surgeries treated with rFVIIIFc were in paediatric patients with HA, who may have been treated with greater caution and given a greater amount of replacement factor before surgery. Preoperative factor activity levels were available for all major HA surgeries with most post-dose FVIII levels within the target range (70–100 IU/dl) recommended in the Nordic Haemophilia Guidelines. Total factor consumption of both rFVIIIFc and rFIXFc varied considerably within surgical classifications, especially for major surgeries in patients with severe HA. This may be partially explained due to the greater bleeding risk associated with orthopaedic surgeries of the lower extremities (e.g. hip and knee arthroplasty) compared with the upper extremities (e.g., elbow arthroplasty), but also highlights the need for consensus recommendations.

Real-world treatment of patients undergoing surgery with rFVIIIFc or rFIXFc in countries with similar levels of available resources as the Nordic countries has been reported in several case reports and studies. Most of these report good surgical outcomes; however, only a few reports provide sufficient detail to compare dosing strategies. In a case report from the United Kingdom in which an adult patient with severe HA underwent a major surgery, the reported preoperative rFVIIIFc dose of 64 IU/kg was higher than the range for major surgery cases in HA reported in our results; total rFVIIIFc consumption up to Day 14 of around 279 IU/kg was lower than all but two of the major HA cases reported here. Another case report from Japan in which an adult patient with moderate HA underwent minor surgery reported preoperative dosing (50 IU/kg) and total factor consumption up to Day 5 (200 IU/kg) within the range for minor HA cases reported in
our results, whilst an Italian case report of an adult patient with moderate HB who underwent minor surgery had a preoperative dose of 80 IU/kg, slightly higher than the range for minor HB cases reported here. Whilst our case series data are generally aligned with these published data, further analyses are needed to develop standardised guidelines.

Our results can also be compared to the findings in Phase III clinical trials of rFVIIIFc and rFIXFc; as with most of the cases presented here, haemostatic responses were rated good or excellent in all patients who underwent surgery whilst taking part in a clinical trial. Patients undergoing surgery in the A-LONG and B-LONG studies were treated according to the local standard of care. In the A-LONG study and by the first interim data cut of ASPIRE, which included patients with HA, 23 major surgeries and 52 minor surgeries were reported. The loading dose for major surgeries (by type of surgery) was generally higher than the preoperative dose for major HA cases reported in our results, ranging from 41–102 IU/kg, but total consumption up to Day 14 of around 240–620 IU/kg largely overlaps with the range reported here. For minor surgeries, total dose on the day of surgery ranged from 23 to 189 IU/kg; this largely overlaps with the range for total factor consumption up to Day 5 in the minor HA cases reported in our results, but many of these cases received additional doses after the day of surgery. In the B-LONG study, which included patients with HB, 14 major surgeries and 15 minor surgeries were reported. For major surgery, total peri-operative rFIXFc consumption up to Day 14 ranged from 261–1349 IU/kg, higher than that reported in our results. These differences may partially be explained by the type of surgery. For minor surgery, preoperative doses ranged from 40–104 IU/kg, similar to the minor HB cases reported here. However, most of the B-LONG surgeries were reported to have required a single preoperative dose, whereas most of the surgeries described in our case series required additional doses. Overall, the real world surgical outcomes using rFVIIIFc and rFIXFc seen in this case series were comparable to that in clinical trials, and limited comparisons of dosing regimens did not indicate excessively high factor consumption.

This case series presents real-world data from four HTCs with consistent reporting of dosing strategies, allowing for a broad overview of the Nordic experience of EHL products in surgery for patients with both HA and HB, across a range of surgical types and classifications. However, there are some limitations. First, since haemophilia is a rare disease, only a relatively small number of patients per sub-category (type of haemophilia, haemophilia severity, type of surgery, paediatric vs. adult and presence of inhibitors) were available. Second, cases were collected retrospectively from medical records so data were not available for all outcomes, including factor levels.

5 | CONCLUSION

This case series presents real-world data on the peri-operative management of several patients with HA and HB treated with EHL products. The Nordic experience suggests that rFVIIIFc and rFIXFc can be used safely and effectively for peri-operative haemostasis in patients with HA and HB, but further research and follow-up discussions are needed to develop local dosing guidelines.

ACKNOWLEDGEMENTS

The authors thank all the patients who were included in this case series and their treating physicians. The authors acknowledge Pia Petrini, MD, from Karolinska Hospital, Stockholm, Sweden, for input on the research question and data collection. The authors also acknowledge Marianne Clemence, DPhil, and Kristian Clausen, MPH, from Costello Medical, UK, for medical writing and editorial assistance based on the authors’ input and direction. Support for third-party writing and analyses assistance for this article, provided by Marianne Clemence, DPhil, and Kristian Clausen, MPH, Costello Medical, UK, was funded by a grant from Sobi in accordance with Good Publication Practice (GPP3) guidelines (http://www.ismpp.org/gpp3).

DISCLOSURES

Anna-Elina Lehtinen: Consultant/member of advisory board/speaker for Bayer, BioMarin, CSL-Behring, Novo Nordisk, Octapharma, Pfizer, Roche, Shire (Takeda) and Sobi; research support from Octapharma and Sobi; support for conferences from Bayer, Novo Nordisk, Octapharma, Pfizer, Roche, Shire (Takeda) and Sobi; Fabira Baghaei: Received hono-raria as a member of advisory board and/or speaker from Bayer, Novo Nordisk, Octapharma, Pfizer, Roche, Shire (Takeda), uniQure and Sobi. Jan Astarmerk: Consultant/speaker for Bayer, BioMarin, CSL Behring, Novo Nordisk, Octapharma, Pfizer, Roche, Sanofi, Shire (Takeda), uniQure, Sparks and uniQure; research grants from Bayer, CSL Behring, Shire (Takeda) and Sobi/Biogen; Pål André Holme: Consultant for Bayer, CSL, Novo Nordisk, Octapharma, Pfizer, Shire (Takeda) and Sobi; support for conferences from Bayer, Octapharma, Pfizer, Shire (Takeda) and Sobi.

AUTHOR CONTRIBUTIONS

Substantial contributions to study conception and design: Anna-Elina Lehtinen, Fabira Baghaei, Jan Astarmerk, Pål André Holme; substantial contributions to analysis and interpretation of the data: Anna-Elina Lehtinen, Fabira Baghaei, Jan Astarmerk, Pål André Holme; drafting the article or revising it critically for important intellectual content: Anna-Elina Lehtinen, Fabira Baghaei, Jan Astarmerk, Pål André Holme; final approval of the version of the article to be published: Anna-Elina Lehtinen, Fabira Baghaei, Jan Astarmerk, Pål André Holme.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

ORCID

Jan Astarmerk https://orcid.org/0000-0001-8500-2483

REFERENCES

1. Mannucci PM, Tuddenham EG. The Hemophilias — From royal genes to gene therapy. N Engl J Med. 2001;344(23):1773-1779.
2. Hermans C, Altisent C, Batorova A, et al. Replacement therapy for invasive procedures in patients with haemophilia: literature review. European survey and recommendations. Haemophilia. 2009;15(3):639-658.

3. Srivastava A, Santagostino E, Dougall A, et al. WFH guidelines for the management of hemophilia, 3rd edition. Haemophilia. 2020;26(S6):1-158.

4. Nordic Hemophilia Council Guideline Working Group. Nordic Hemophilia Guidelines; 2020; https://www.nordhemophilia.org Accessed 5 October 2021.

5. Berntorp E, Negrier C, Gozzi P, Blaas PM, Lethagen S. Dosing regimens, FVIII levels and estimated haemostatic protection with special focus on rFVIII:Fc. Haemophilia. 2016;22(3):389-396.

6. Powell J, Shapiro A, Ragni M, et al. Switching to recombinant factor IX Fc fusion protein prophylaxis results in fewer infusions, decreased factor IX consumption and lower bleeding rates. Br J Haematol. 2015;168(1):113-123.

7. Hermans C, Apte S, Santagostino E. Invasive procedures in patients with haemophilia: review of low-dose protocols and experience with extended half-life FVIII and FIX concentrations and non-replacement therapies. Haemophilia. 2020;00:1-7.

8. EMA. Eltocta® (Emtoroctocog alfa) Summary of Product Characteristics. EMA; 2021. https://www.ema.europa.eu/en/documents/product-information/eltocta-epar-product-information_en.pdf Accessed: 5 October 2021.

9. EMA. Alprolix® (Eftrenonacog alfa) Summary of Product Characteristics. EMA; 2021. https://www.ema.europa.eu/en/documents/product-information/alprolix-epar-product-information_en.pdf Accessed: 5 October 2021.

10. Mahlangu J, Powell JS, Ragni MV, et al. Phase 3 study of recombinant factor VIII Fc fusion protein in severe hemophilia A. Blood. 2014;123(3):317-325.

11. Powell JS, Pasi KJ, Ragni MV, et al. Phase 3 study of recombinant factor IX Fc fusion protein in hemophilia B. N Engl J Med. 2013;369(24):2313-2323.

12. Young G, Mahlangu J, Kulikarni R, et al. Recombinant Factor VIII Fc fusion protein for the prevention and treatment of bleeding in children with severe hemophilia A. J Thromb Haemost. 2015;13(6):967-977.

13. Fischer K, Kulikarni R, Nolan B, et al. Recombinant Factor IX Fc fusion protein in children with haemophilia B (Kids B-LONG): results from a multicentre, non-randomised phase 3 study. Lancet Haematol. 2017;4(2):e75-e82.

14. Mahlangu JN, Ragni M, Gupta N, et al. Long-acting recombinant factor VIII Fc fusion protein (rFVIIIFc) for perioperative haemostatic management in severe haemophilia A. Thromb Haemost. 2016;116(1):1-8.

15. Powell JS, Apte S, Chambost H, et al. Long-acting recombinant factor IX Fc fusion protein (rFIXFc) for perioperative management of subjects with haemophilia B in the phase 3 B-LONG study. Br J Haematol. 2015;168(1):124-134.

16. Hermans CR, Eeckhoudt S, Van Damme A, Lambert C. Successful use of EHL-FIX in hemophilia B carriers with FIX deficiency: a single center experience. Haemophilia. 2019;25(S1):66.

17. O’Donovan M, Johnston K, Singleton E, et al. Extended half-life recombinant facitIrIXFc is effective in preventing bleeding after major and minor surgery in severe Factor IX deficiency. Res Pract Thromb Haemost. 2019;3(S1):285.

18. Lienhart A, Meunier S, Nougier C, Which FVIII:c assay for the monitoring of patients with hemophilia undergoing surgery under the cover of FVIII:Fc fusion protein? Presented at: ECTH 2019. Glasgow, UK; 2019.

19. Hellal M, Alvi A, Campbell Tait R, Experience of major orthopaedic surgery in severe haemophilia A with extended half life factor FVIII Fc fusion protein. Presented at: WFH 2018, Glasgow, UK; 2018.

20. Patil V, Chandrakala S, Jijna F, Shetty S, Mohanty S, Wasekar N. Recombinant factor VIII Fc fusion protein in surgeries in hemophilia A. EHA Lib. 2019;26:6127.

21. Kanematsu T, Suzuki N, Ogawa M, et al. Continuous infusion of recombinant factor IX Fc fusion protein during major surgery. Res Pract Thromb Haemost. 2017;15(1):726-737.

22. Kremer Hoving ICL, Schutgens REG, van der Valk PR, van Vulpen LFD, Mauser-Bunschoten EP, Fisher K. Continuous infusion of extended half-life factor VIII (efmoroctocog alpha) for surgery in severe haemophilia A. Haemophilia. 2018;24(4):e280-e283.

23. Okamoto A, Yamamoto K, Eguchi G, et al. Perioperative management of haemophilia A using recombinant factor VIII Fc fusion protein in a patient undergoing endoscopic nasal pituitary adenomectomy for a growth hormone-producing pituitary adenoma. Haemophilia. 2017;23(6):e525-e527.

24. Valeri F, Giacchello J, Valpредa A, et al. Eftrenonacog alfa (rFIXFc) in major surgery: a case report. Blood Transfus. 2018;16(Suppl 4):s542.

25. Abraham A, Srivastava A. Surgical prophylaxis using long acting factor concentrate in a cohort of haemophilia patients [WP-P-008 (684)]. Haemophilia. 2018;24(Supplement 5):20-21.

26. Amelia N, Gatot D, Susanah S, et al. Utilization of extended half-life recombinant of Fc-Fusion protein concentrate from WFH donation in Indonesia. Haemophilia. 2018;24(Supplement 5):154.

27. Apte S, Phatiale R, Joshi A, Subramanian K. Bilateral, simultaneous total knee replacement (TKR) surgery for hemophilia A with eloctate (extended half life product) – a feasible and cost effective approach. Blood. 2018;132(Supplement 1):4684.

28. Echenagucia M, Jimenez T, Dos Santos ML, et al. Clinical and laboratorial evaluation of recombinant FVIII Fc fusion protein treatment in hemophilia A patients: a real-life in a single center. Haemophilia;2016(Supplement 4):79.

29. Ruiz-Saez A, Echenagucia M. Use of extended half-life rFVIII-Fc or rFIX-Fc in previously treated patients with hemophilia A or B. A single center experience [PO30]. Haemophilia. 2019;25(Supplement 1):50-51.

30. Helseforetakenes Innkjøpservice AS (HINAS). Avtaler LIS 1712 og 1812a. Helseforetakenes Innkjøpservice AS (HINAS); 2019; https://sykehusinnkjop.no/Documents/Legemidler/Avtaler%20og%20anbefalinger/2019/Helseforetakenes%20anbefalinger%20for%20LIS%201712%20og%201812a%20Blodkoagulasjonsfaktorer%20oppdatert%20feb%202019.pdf Accessed: 5 October 2021.

31. Tandvårds- och läkemedelsförsäkringsverket. Alprolix ingår i högkostnadsskyddet med uppföljningsvillkor. Tandvårds- och läkemedelsförsäkringsverket; 2018; https://www.tlv.se/beslut/beslut-lakemedel/generell-subvention/arkiv/2018-09-28-alprolix-ingar-i-hogkostnadsskyddet-med-uppfoljningsvillkor.html Accessed: 5 October 2021.

32. Tandvårds- och läkemedelsförsäkringsverket. Elctoca ingår i högkostnadsskyddet med uppföljningsvillkor. Tandvårds- och läkemedelsförsäkringsverket; 2016; https://www.tlv.se/beslut/beslut-lakemedel/generell-subvention/arkiv/2016-04-27-elctoca-ingar-i-hogkostnadsskyddet-med- uppfoljningsvillkor.html Accessed: 5 October 2021.

33. Lääkkeiden hintalautakunta. Reimbursable Authorized Medicinal Products and their Prices. Lääkkeiden hintalautakunta; 2021; https://www.hila.fi/en/notices/reimbursable-authorized-medicinal-products-and-their-prices/ Accessed: 5 October 2021.

34. Bierbaum BE, Callaghan JJ, Galante JO, Rubash HE, Tooms RE, Welch RB. An analysis of blood management in patients having a total hip or knee arthroplasty. J Bone Joint Surg Am. 1999;81(1):2-10.

35. Ramampusendrahova JB, Andrianony A, Andrianina Ismaël R, Rado R, Gaétán Duval S. Evaluation of blood loss during the perioperative period in orthopedic and trauma surgery. EPH – Int J Med Health Sci. 2021;7(3):01-08.

36. O’Donovan M, Singleton E, Roche S, et al. Single centre, real-world experience of perioperative rFIXFc use in adult patients with haemophilia B undergoing major and minor surgery. Haemophilia. 2021;27(6):e690-e697. 1-8.
SUPPORTING INFORMATION

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

How to cite this article: Lehtinen A-E, Baghaei F, Astermark J, Holme PA. Surgical outcomes in patients with haemophilia A or B receiving extended half-life recombinant factor VIII and IX Fc fusion proteins: real-world experience in the Nordic countries. Haemophilia. 2022;28:713–719. https://doi.org/10.1111/hae.14585