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Clinical Haemophilia

Switching From Standard to Extended Half-Life Coagulation Factor Replacement in Haemophilia: Clinical Outcomes and Costs of Care in Finland

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Received: 23 January 2025 | **Revised:** 10 April 2025 | **Accepted:** 15 May 2025

Funding: Novo Nordisk provided funding for the study (collection, analyses and interpretation of the data) and writing of the manuscript.

Keywords: adherence | annual bleeding rate | coagulation factor consumption | cost | haemophilia | prophylaxis

ABSTRACT

Introduction: Real-world data are needed to evaluate treatment implementation, outcomes and costs of care in haemophilia patients switching prophylaxis from standard half-life (SHL) to extended half-life (EHL) clotting factor concentrates (CFCs).

Aim: We characterised treatment regimens, annual bleeding rate (ABR), adherence and costs in a nationwide Finnish haemophilia A (HA) and B (HB) cohort on prophylaxis, including non-switchers and switchers from SHL to EHL CFC.

Methods: This retrospective register study of adult patients with HA and HB was performed in University Hospitals during 2016–2021. Clinical and healthcare data were captured from electronic health records and national healthcare registers.

Results: Majority, 74% of HA and 71% of HB patients, switched from SHL to EHL. Thereafter, weekly mean infusions of CFC decreased (FVIII SHL 2.8, EHL 2.2; FIX SHL 1.6, EHL 0.9; $p < 0.001$). The mean annual consumption (international units, IU) increased by 18% from 219,534 per HA patient during SHL to 258,317 during EHL ($p < 0.05$) and declined per HB patient by 28% from 221,685 to 160,209 ($p < 0.01$). ABR appeared to decline after the switch in HA (mean SHL 2.8, EHL 0.9) and HB (SHL 1.6, EHL 0.8), while treatment adherence improved in HA from 81% to 95% ($p < 0.01$). The mean annual total costs of care in HA were €176,979 for SHL and €195,760 for EHL. In HB, the costs increased from €180,930 to €236,208 ($p < 0.01$).

Conclusions: Majority of patients on prophylaxis switched to EHL. The switch alleviated the infusion regimen, tended to lower bleeding rates and improved adherence with somewhat increased costs.

1 | Introduction

The standard of care for severe and some moderate haemophilia A (HA) and B (HB) has been regular prophylactic intravenous infusion of clotting or coagulation factor VIII (FVIII) and IX (FIX) concentrates (CFCs). The goal of the treatment is to maintain sufficient blood clotting factor levels (target trough levels > 3 IU/dL) to match with lifestyle needs in order to prevent serious bleeds leading to joint and muscle complications [1]. Prophylaxis with recombinant standard half-life (SHL) CFCs

requires frequent weekly intravenous infusions: typically three times with FVIII in HA and twice with FIX in HB [1, 2].

Haemophilia care has significantly changed after the introduction of recombinant extended half-life (EHL) CFCs [1, 3]. The half-life of EHL concentrates is on average 1.5 times longer for FVIII and 3–6 times longer for FIX, compared to SHL concentrates [1, 3–9]. The longer half-life reduces the burden of frequent intravenous CFC infusions while maintaining sufficient coagulation factor levels [2–4, 9–13]. Also, emicizumab is a current alternative to conventional FVIII therapies for severe and moderate HA patients with or without inhibitors [14], while rebalancing agents and gene therapies also covering FIX have been recently approved [15–18].

Clinical studies on EHL CFCs have shown excellent clinical efficacy with low bleeding rates [2, 3, 19–21]. Current real-world evidence studies have reported comparable or decreased annual bleeding rates (ABR) after switching from SHL to EHL CFCs, in both forms of haemophilia [9, 11–13, 22–25]. Switching has also improved treatment adherence [26].

A challenge in haemophilia care is to achieve optimal clinical outcomes at a reasonable CFC infusion frequency, consumption and costs. After switching from SHL to EHL, the overall CFC consumption is reduced in most real-world studies, with 13%–26% decrease of FVIII [9, 11, 27] and 15%–50% of FIX consumption [19–22, 25]. On the other hand, some studies report no changes in overall consumption [22, 23]. Also, the current information on the effect of the treatment switch on the concomitant cost of haemophilia care varies [28–32].

Our previous study showed that centralised haemophilia management in University Hospitals during 2012–2016 resulted in cost-effective care while maintaining low bleeding rates [33]. However, there are no available data on treatment outcomes and costs following the introduction of EHL therapies. This nationwide retrospective register study examined the initial years of SHL to EHL treatment switching in adult HA and HB patients treated in our University Hospitals during 2016–2021. We aimed at characterising treatment regimens, adherence, clinical outcomes and costs of haemophilia care among CFC switchers (before and after changing from SHL to EHL) and non-switchers on prophylaxis, in a real-life clinical setting.

2 | Methods

2.1 | Study Design and Population

Our nationwide, non-interventional, retrospective study utilised data from the Finnish national healthcare registers and electronic health records (EHRs) of the five University Hospitals. All adult (≥18 years of age) patients with an HA (ICD-10: D66) or HB diagnosis (ICD-10: D67) in The Register for Health Care or The Register of Primary Care Visits (The Finnish Institute for Health and Welfare), and with ≥1 haemophilia-related visit(s) in the five hospitals during 2016–2021 were identified (Figure 1). Exclusion criteria included a history of inhibitors or unknown inhibitor status in EHRs, use of emicizumab and lack of CFC use (both based on pharmacy dispensations). The main analysis focused on the HA and HB cohorts on prophylaxis, with further analysis targeting the sub-populations of switchers (from SHL to EHL CFCs) and non-switchers.

2.2 | Clotting Factor Concentrate Switches and Follow-Up Times

Switches were based on the dates of SHL and EHL CFC pharmacy dispensations reimbursed by The Social Insurance Institution. For switchers, the follow-up for the SHL period was from 1 January, 2016, until the date of the last dispensation, plus additional three calendar months (window of maximum medication supply during the study period in Finland), and for the EHL period from the date of the first dispensation until 31 December, 2021, or until death. For non-switchers, the follow-up was the entire 6-year study period (1 January, 2016 to 31 December, 2021), or until death.

2.3 | Data Collection

The data on clinical characteristics were manually collected into electronic case report forms (eCRFs) from the EHRs of the University Hospitals. Basic demographics, primary and specialty healthcare diagnoses (ICD-10, NCPC-2) and healthcare resource utilisation (HCRU) were captured from The Register for Primary Care Visits and The Care Register for Health Care (The Finnish Institute for Health and Welfare); dispensations and costs of reimbursed medications from The Register for Reimbursed Drugs (The Social Insurance Institution) and the dates of death from The Cause of Death Register (Statistics Finland).

2.4 | Outcome Measures

The basic demographic and clinical characteristics were described. Treatment type (prophylaxis/on-demand) and disease severity (severe/moderate/mild) were collected as described in Supporting Information. Comorbidities and procedures (Table S1) were reported during the study period.

The prescribed doses (IU/kg) and weekly infusion frequencies of prophylaxis were reported. The annual CFC consumption was calculated as the FVIII or FIX dispensations (international units, IU) in the reporting time window divided by the duration of the follow-up in years.

ABR was calculated by dividing the number of bleeds in the reporting time window by the duration of the follow-up in years. Bleeds were extracted from recordings (ICD-10) of bleeding events (Table S1) and self-reported bleeds from the EHRs into the eCRFs.

The overall prescription adherence (0%–100%) was calculated as the ratio of adherent (claimed) prescriptions to all prescriptions. Each prescription was defined as 0 (non-adherent) if the person did not have any related dispensations, as opposed to 1 (adherent). Medication possession ratio (MPR) was defined as the proportion of days covered (0%–100%) by drug supplies within the follow-up period [34].

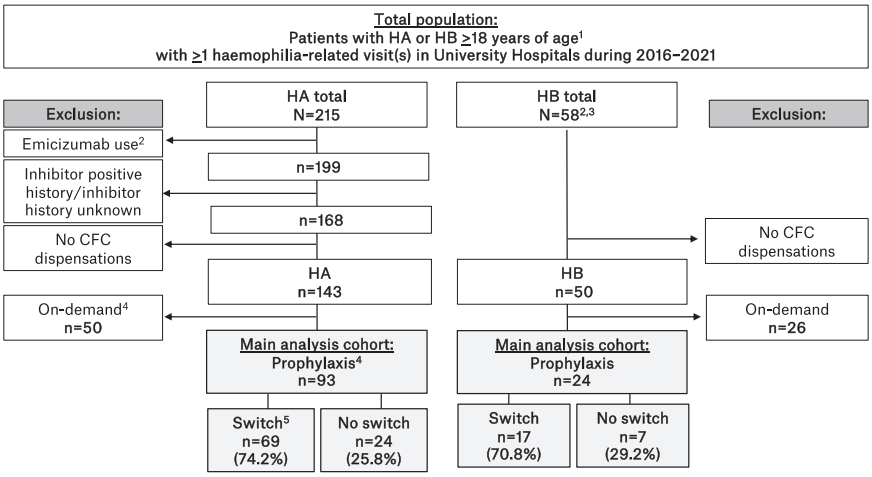

FIGURE 1 | Flow diagram showing the distribution of HA and HB populations for the main analysis. CFC, clotting factor concentrate; HA, haemophilia A; HB, haemophilia B. [1]Including patients ≥18 years of age on 1 January 2016 and patients turning 18 during the study period. [2]Emicizumab (users $n = 16$) received reimbursement status in Finland in 2018. [3]The number of HB patients with an inhibitor-positive history was <5; they were included in the analyses. [4]Treatment type was missing for 20 patients in the total haemophilia population (HA $n = 215$, HB $n = 58$), and in the main analysis population for <5 HA patients on prophylaxis. Missing treatment type was derived by comparing the CFC dispensation frequency to the dispensation frequency of those with the treatment type recorded as described in Supporting Information. [5]Treatment switches were derived from dates of pharmacy dispensations (The Social Insurance Institution).

Annual haemophilia-related HCRU rates [outpatient (follow-up and emergency room, ER) contacts, and inpatient visits] and costs (€) of haemophilia care (CFC, total haemophilia medication and HCRU costs) were calculated as the number of contacts or cost divided by duration of the follow-up in years. Details of HCRU types and cost calculations are provided in Supporting Information.

2.5 | Statistical Methods

Descriptive statistics were used by reporting numbers and percentages for categorical variables and mean with standard deviation (SD) and median with quartiles (Q1, Q3) for continuous variables. Statistical comparisons before and after the treatment switch were performed using the paired-samples *t*-test for continuous variables and the McNemar test for categorical variables. The switchers and non-switchers were compared using Welch's *t*-test for continuous variables and the chi-square test for categorical variables.

3 | Results

3.1 | Study Population

Altogether 215 adult patients with HA, and 58 with HB were treated in the five University Hospitals during 2016–2021 (Figure 1). The main analysis consisted of 93 HA and 24 HB patients on prophylaxis, while 74% ($n = 69$) of HA and 71% ($n = 17$) of HB patients switched from SHL to EHL therapy. Demographic and clinical characteristics did not differ between the switchers and non-switchers (Table 1). Mean age of the patients at first visit was 31 years for HA, and 40 for HB. In HA, the majority (88%), and in HB, approximately half (54%) of the cases had severe disease. Of all switchers, <5 switched back to SHL CFCs.

The mean length of follow-up for HA switchers was 3.7 years (SD, 1.1) for SHL and 2.3 years (1.1) for the EHL period, and for HB 4.7 years (0.6) for SHL and 1.2 years (0.6) for EHL (Table 2).

3.2 | Treatment Regimens and Clotting Factor Concentrate Consumption

In the HA switchers, the mean prescribed FVIII dose increased by 17% from 25.5 IU/kg (SD, 7.8) to 29.9 (10.6) after switching from SHL to EHL ($p < 0.001$) (Table 2). In HB, the mean FIX dose did not increase [50.5 IU/kg (19.7) before switching vs. 54.0 (16.5) after, $p = 0.39$]. The switch decreased weekly infusions from a mean of 2.8 (1.0) to 2.2 (0.8) in HA ($p < 0.001$) and from 1.6 (0.8) to 0.9 (0.4) in HB ($p < 0.001$).

Per HA switcher, the mean annual FVIII CFC consumption increased 18%, from 219,534 IU (SD, 117,259) during the SHL period to 258,317 IU (184,045) during the EHL period ($p < 0.05$) (Figure 2). In HB, the switch decreased the mean annual FIX CFC consumption by 28%, from 221,685 IU (106,864) to 160,209 IU (87,249) ($p < 0.01$).

The CFC dose, infusion frequency and annual CFC consumption of non-switchers did not differ from those of the switchers during the SHL period.

3.3 | Annual Bleeding Rates

Among the HA switchers, 77% ($n = 53$) had bleeding episodes during the SHL period, while 57% ($n = 39$) bled during EHL (Table S3). The mean ABR was initially 2.8 (SD, 8.1). After the EHL switch, the mean ABR was 0.9 (1.5), but this was not statistically significant ($p = 0.058$) (Figure 3A and Table S3).

TABLE 1 | Demographical and clinical characteristics of HA and HB patients on prophylaxis stratified based on status of switching from SHL to EHL clotting factor concentrates (CFCs) during 2016–2021.

	HA prophylaxis[a]			HB prophylaxis[a]		
	Total ***N*** **= 93**	**Switch[b]** ***N*** **= 69**	**No switch** ***N*** **= 24**	**Total** ***N*** **= 24**	**Switch[b]** ***N*** **= 17**	**No switch** ***N*** **= 7**
Disease severity[c]						
Mild, *n* (%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	<5
Moderate, *n* (%)	11 (11.8%)	6 (8.7%)	5 (20.8%)	11 (45.8%)	8 (47.1%)	<5
Severe, *n* (%)	82 (88.2%)	63 (91.3%)	19 (79.2%)	13 (54.2%)	9 (52.9%)	<5
Age[d]						
Mean (SD)	31.3 (15.7)	30.3 (15.6)	34.1 (15.9)	40.1 (21.5)	37.7 (17.7)	50.7 (27.4)
Median (Q1, Q3)	26.0 (18.0, 40.0)	25.0 (18.0, 35.0)	29.5 (21.5, 42.5)	40.08 (21.50)	35.71 (17.73)	50.71 (27.35)
BMI (kg/m^2)[d]						
Data available, *n* (%)	84	63	21	20	13	7
Mean (SD)	26.5 (5.9)	26.6 (6.4)	26.0 (4.4)	24.5 (6.4)	24.6 (7.0)	24.3 (5.5)
Median (Q1, Q3)	25.3 (22.5, 29.6)	25.3 (22.6, 29.7)	26.5 (22.2, 28.3)	23.7 (19.6, 26.8)	23.5 (19.3, 26.0)	23.9 (20.3, 27.0)
Smoking status[d]						
Data available, *n* (%)	73	55	18	18	14	<5
Yes, *n* (%)	25 (34.2%)	18 (32.7%)	7 (38.9%)	8 (44.4%)	7 (50.0%)	<5
Comorbidities[e]						
Diseases of teeth, periapical tissues and jaw	70 (75.3%)	56 (76.8%)	17 (70.8%)	13 (54.2%)	10 (58.8%)	<5
Haemophilic arthropathy and/or arthrosis	56 (60.2%)	39 (56.5%)	17 (70.8%)	17 (70.8%)	13–16 (70.6–94.1%)[f]	<5
Joint imaging and surgeries	52 (55.9%)	41 (59.4%)	11 (45.8%)	15 (62.5%)	11 (64.7%)	<5
Hypertension	17 (18.3%)	14 (20.3%)	<5	6 (25.0%)	<5	<5
Psychiatric disorders	24 (25.8%)	17 (24.6%)	7 (29.2%)	<5	<5	0 (0.0%)
HCV	12 (12.9%)	7 (10.1%)	5 (20.8%)	8 (33.3%)	0 (0%)	<5
Diabetes and its complications	6 (6.5%)	<5	<5	<5	<5	<5
Haematuria	8 (8.6%)	7 (10.1%)	<5	<5	<5	<5
Hemarthrosis	8 (8.6%)	6 (8.7%)	<5	<5	<5	<5
Cancers	6 (6.5%)	<5	<5	<5	<5	<5

Abbreviations: CFC, clotting factor concentrate; eCRF, electronic case report form; EHL, extended half-life; HA, haemophilia A; HB, haemophilia B; HCV, hepatitis C virus; SD, standard deviation; SHL, standard half-life; Q1, 1st quartile; Q3, 3rd quartile.

[a]Treatment type was missing in eCRFs for 20 patients altogether in total haemophilia population (HA $n = 215$, HB $n = 58$), and in the main analysis population for <5 HA patients on prophylaxis. Missing treatment type was derived by comparing the CFC dispensation frequency to the dispensation frequency of those with the treatment type recorded in eCRFs, as described in Supporting Information.

[b]$n < 5$ patients were switched back to SHL.

[c]Disease severity was missing in eCRFs for 17 patients altogether in the total haemophilia population (HA $n = 215$, HB $n = 58$), and in the main analysis population for <5 HA patients and for <5 HB patients on prophylaxis. Missing disease severity was estimated by XGBoost as described in Supporting Information.

[d]The first recording at the start of the study period.

[e]Comorbidities listed in Table S1 were analysed during the entire study period. Results are shown for comorbidities with a minimum prevalence of 5% of HA or HB total population on prophylaxis.

[f]Results cannot be shown if either 'yes' or 'no' of a categorical variable is <5.

In the HA patients over 30 years of age, however, the switch to EHL decreased the mean ABR from 4.7 (8.1) to 1.1 (1.6) ($p < 0.05$) (Table S4). Among HB switchers 71%–100% (n = 12–17) (imprecise due to masking rules) suffered from bleeding events during SHL, while 53% ($n = 9$) had bleeds during the EHL period (Table S3). The ABRs before, mean 1.6 (1.5), and after the switch, mean 0.9 (1.2), were comparable ($p = 0.155$) (Figure 3B).

The mean ABR of 1.8 (3.2) in HA non-switchers did not differ from the ABR during the SHL period of switchers. The bleeds for HB non-switchers were <5.

TABLE 2 | Follow-up times and treatment regimens of HA and HB switchers and non-switchers on prophylaxis during 2016–2021.

	HA prophylaxis $N = 93$			HB prophylaxis $N = 24$		
	Switch $N = 69$		No switch $N = 24$	Switch $N = 17$		No switch $N = 7$
	SHL period	EHL period	SHL	SHL period	EHL period	SHL
Follow-up (years)						
Mean (SD)	3.7 (1.1)	2.3 (1.1)	5.7 (1.0)	4.7 (0.6)	1.2 (0.6)	5.5 (0.8)
Median (Q1, Q3)	3.5 (2.8, 4.2)	2.5 (1.8, 3.1)	6.0 (6.0, 6.0)	4.9 (4.1, 5.1)	1.0 (0.8, 1.9)	6.0 (5.2, 6.0)
Dose, IU/kg						
Data available, *n* (%)	63 (91.3%)	67 (97.1%)	24 (100.0%)	16 (94.1%)	16 (94.1%)	7 (100.0%)
Mean (SD)	25.5 (7.8)***	29.9 (10.6)***	25.7 (7.9)	50.5 (19.7)	54.0 (16.5)	58.5 (24.4)
Median (Q1, Q3)	25.8 (20.8, 29.6)***	27.0 (24.0, 34.7)***	25.9 (20.0, 31.4)	44.6 (35.7, 61.1)	51.5 (44.6, 58.6)	52.1 (40.7, 72.6)
Infusions/week						
Data available, *n* (%)	63 (94.0%)	64 (92.8%)	24 (100.0%)	17 (100.0%)	17 (100.0%)	7 (100.0%)
Mean (SD)	2.8 (1.2)***	2.2 (0.8)***	2.8 (0.7)	1.6 (0.8)***	0.9 (0.4)***	2.8 (1.9)
Median (Q1, Q3)	3.0 (2.0, 3.4)***	2.0 (1.8, 2.6)***	2.8 (2.3, 3.5)	1.0 (1.0, 2.1)***	1.0 (0.7, 1.0)***	2.3 (1.5, 3.5)

Note: Statistical comparisons did not reveal differences between non-switchers and the SHL period of the switchers.
Abbreviations: CFC, clotting factor concentrate; EHL, extended half-life; HA, haemophilia A; HB, haemophilia B; IU, international unit; SD, standard deviation; SHL, standard half-life; Q1, 1st quartile; Q3, third quartile.
*** $p < 0.001$ between SHL and EHL period of the switchers.

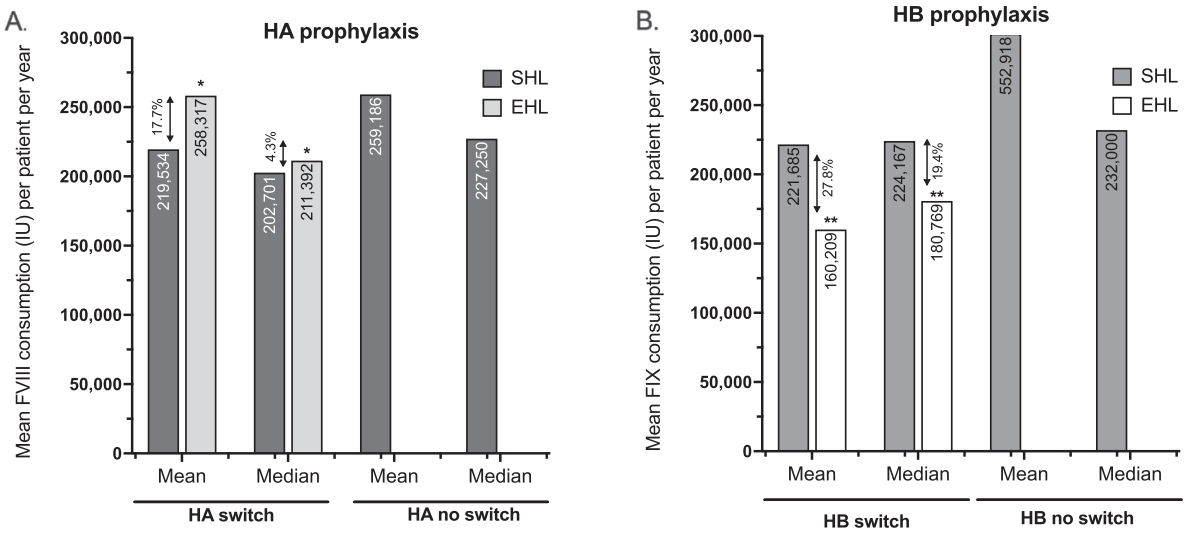

FIGURE 2 | Annual consumption (IU per patient year) of clotting factor concentrates (CFCs)[1] in HA and HB switchers and non-switchers on prophylaxis during 2016–2021. (A) HA, (B) HB. CFC, clotting factor concentrate; EHL, extended half-life; HA, haemophilia A; HB, haemophilia B; IU, international units; SHL, standard half-life. *$p < 0.05$, **$p < 0.01$ between SHL and EHL period of the switchers. [1]Consumption was calculated from pharmacy dispensations (The Social Insurance Institution).

3.4 | Medication Adherence

In HA, CFC prescription adherence increased from a mean of 81% (SD, 29%) during the SHL period to 95% (16%) during EHL ($p < 0.01$) (Figure 3C and Table S3). Similarly, the MPR increased from a mean of 87% (18%) of days covered by the medication supply from the SHL period to 95% (14%) during the EHL period ($p < 0.01$). Among HB switchers, the mean prescription adherence (86%–94%) remained comparable before and after switching (Figure 3D and Table S3). The average treatment adherence among HA non-switchers was 86% (24%) and among HB 91% (14%), aligning with the SHL period of the switchers.

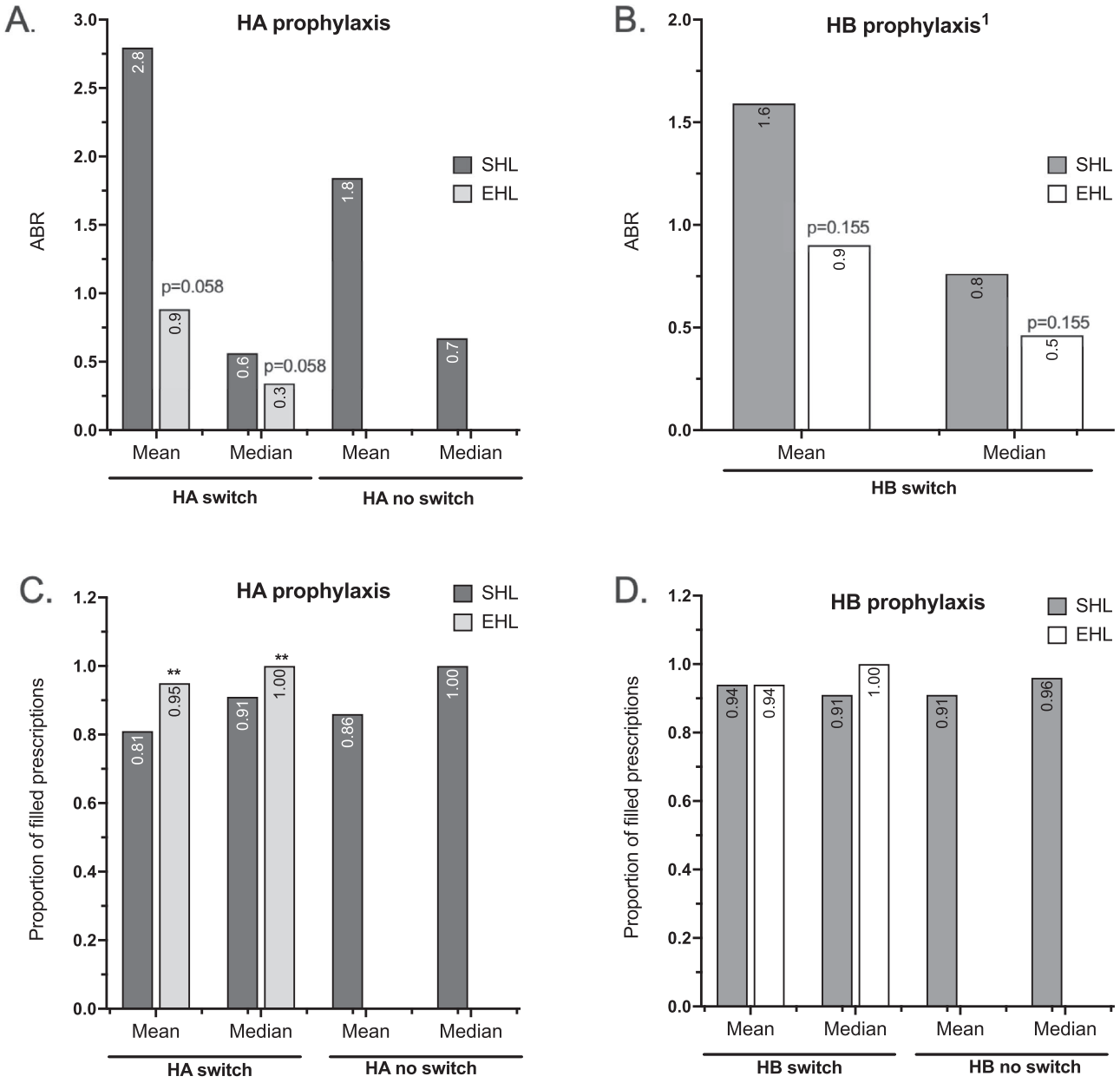

FIGURE 3 | Annual bleeding rates (ABRs) and prescription adherence to clotting factor concentrates (CFCs) among HA and HB switchers and non-switchers on prophylaxis during 2016–2021. (A) ABR for HA, (B) ABR for HB, (C) proportion of filled CFC prescriptions in HA, (D) proportion of filled CFC prescriptions in HB. ABR, annual bleeding rate; CFC, clotting factor concentrate; EHL, extended half-life; HA, haemophilia A; HB, haemophilia B; SHL, standard half-life. [1]Among HB non-switchers, the number of patients with bleeds was <5. **$p < 0.01$ between SHL and EHL period.

3.5 | Healthcare Resource Utilisation

The frequency of haemophilia-related specialty care outpatient contacts increased after switching to EHL treatment due to agreed follow-up intensity. In HA, the mean annual number of specialty care outpatient contacts was 3.8 per patient (SD, 4.6), while it was 5.7 (11.0) after switching (Table 3). In HB, the number of the contacts doubled early after switching, from a mean of 3.1 (2.3) to 6.3 (3.7) ($p < 0.01$). The mean number of specialty care outpatient contacts in all non-switchers did not differ from those of the switchers during the SHL period (Table 3).

3.6 | Costs of Haemophilia Care

The mean annual costs of care for the total haemophilia study population (Figure 1) were analysed between 2016 and 2021 (Figure 4). Due to CFC switching, the proportion of total costs attributed to EHL products increased from 14% in 2018 to 57% in 2021 for HA, and from 5% in 2019 to 59% in 2021 for HB. However, the proportion of HCRU costs was only 2%–4% of all costs.

For the HA switchers, the mean annual total costs of haemophilia prophylaxis were €176,979 (SD, 96,023) per patient during the SHL period and €195,760 (131,990) during the EHL period (Table 3).

TABLE 3 | Haemophilia-related healthcare resource utilisation (HCRU) and costs of haemophilia care among HA and HB switchers and non-switchers on prophylaxis during 2016–2021.

	HA prophylaxis *N* = 93			HB prophylaxis *N* = 24		
	Switch *N* = 69		No switch *N* = 24	Switch *N* = 17		No switch *N* = 7
	SHL period	EHL period	SHL	SHL period	EHL period	SHL
Haemophilia-related healthcare contacts per patient per year						
Specialty healthcare: Outpatient contacts (follow-up + ER)						
Mean (SD)	3.8 (4.6)	5.7 (11.0)	3.2 (2.4)	3.1 (2.3)**	6.3 (3.7)**	2.3 (1.3)
Median (Q1, Q3)	3.0 (1.9, 4.4)	3.5 (2.2, 5.8)	2.3 (1.7, 3.6)	2.8 (2.0, 3.7)**	6.2 (3.7, 7.8)**	2.2 (1.3, 3.0)
Specialty healthcare: Follow-up contacts						
Mean (SD)	3.7 (4.2)*	5.5 (10.0)*	3.2 (2.4)	3.0 (2.3)**	6.3 (3.7)**	2.2 (1.2)
Median (Q1, Q3)	2.9 (1.9, 4.3)*	3.2 (2.2, 5.7)*	2.3 (1.7, 3.6)	2.3 (1.8, 3.7)**	6.2 (3.7, 7.8)**	1.8 (1.3, 3.0)
Specialty healthcare: ER visits						
Mean (SD)	0.2 (0.6)	0.2 (0.6)	0.1 (0.2)	0.1 (0.2)*	0.0 (0.0)*	0.1 (0.1)
Median (Q1, Q3)	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	0.0 (0.0, 0.2)*	0.0 (0.0, 0.0)*	0.0 (0.0, 0.1)
Specialty healthcare: Inpatient periods						
Mean (SD)	0.2 (0.6)	0.2 (0.7)	0.06 (0.1)	0.05 (0.1)	0.05 (0.2)	0.3 (0.6)
Median (Q1, Q3)	0.0 (0.0, 0.2)	0.0 (0.0, 0.0)	0.0 (0.0, 0.04)	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	0.0 (0.0, 0.3)
Primary healthcare: Outpatient contacts (follow-up + ER)						
Mean (SD)	0.04 (0.1)	0.04 (0.25)	0.03 (0.08)	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)
Median (Q1, Q3)	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)

(Continues)

TABLE 3 | (Continued)

	HA prophylaxis $N = 93$			HB prophylaxis $N = 24$		
	Switch $N = 69$		No switch $N = 24$	Switch $N = 17$		No switch $N = 7$
	SHL period	EHL period	SHL	SHL period	EHL period	SHL
Costs (€) per patient per year						
Haemophilia-related HCRU cost						
Mean (SD)	€2115 (3370)	€2457 (4305)	€1368 (1019)	€1478 (1308)*	€2492 (1417)*	€2859 (4852)
Median (Q1, Q3)	€1207 (675, 2141)	€1361 (872, 2410)	€1085 (701, 1636)	€1178 (788, 1559)*	€2464 (1481, 3117)*	€904 (500, 2021)
CFC cost[a]						
Mean (SD)	€174,642 (94,948)	€193,284 (130,982)	€200,856 (138,176)	€179,437 (86,954)**	€233,693 (93,872)**	€445,452 (634,664)
Median (Q1, Q3)	€165,681 (96,481, 232,297)	€160,762 (120,289, 206,214)	€173,057 (89,101, 282,953)	€181,210 (97,949, 238,137)**	€228,184 (190,099, 310,407)**	€184,614 (123,400, 379,816)
Total haemophilia medication cost[a,b]						
Mean (SD)	€174,864 (95,772)	€193,303 (130,996)	€200,884 (138,179)	€179,453 (86,960)**	€233,716 (93,881)**	€445,530 (634,821)
Median (Q1, Q3)	€165,770 (96,495, 232,310)	€160,768 (120,289, 206,214)	€173,064 (89,114, 282,955	€181,214 (97,957, 238,162)**	€228,184 (190,099, 310,463)**	€184,622 (124,012, 379,849)
Total cost of haemophilia care						
Mean (SD)	€176,979 (96,023)	€195,760 (131,990)	€202,252 (138,800)	€180,930 (86,589)**	€236,208 (94,360)**	€448,389 (639,590)
Median (Q1, Q3)	€166,977 (98,037, 233,110)	€162,334 (120,600, 215,020)	€174,084 (89,530, 284,908)	€183,518 (98,216, 239,847)**	€230,684 (190,099, 311,983)**	€186,046 (124,731, 381,335)

Abbreviations: CFC, clotting factor concentrate; EHL, extended half-life; ER, emergency room; HA, haemophilia A; HB, haemophilia B; HCRU, healthcare resource utilisation; Q1, 1st quartile; Q3, 3rd quartile; SD, standard deviation; SHL, standard half-life.

[a]CFC cost was based on pharmacy dispensations and costs available from The Social Insurance Institution.

[b]Including other haemophilia-related medications: von Willebrand factor (VWF) + FVIII, desmopressin, antifibrinolytic agents (Table S2).

*$p < 0.05$, **$p < 0.01$ between SHL and EHL period of switchers.

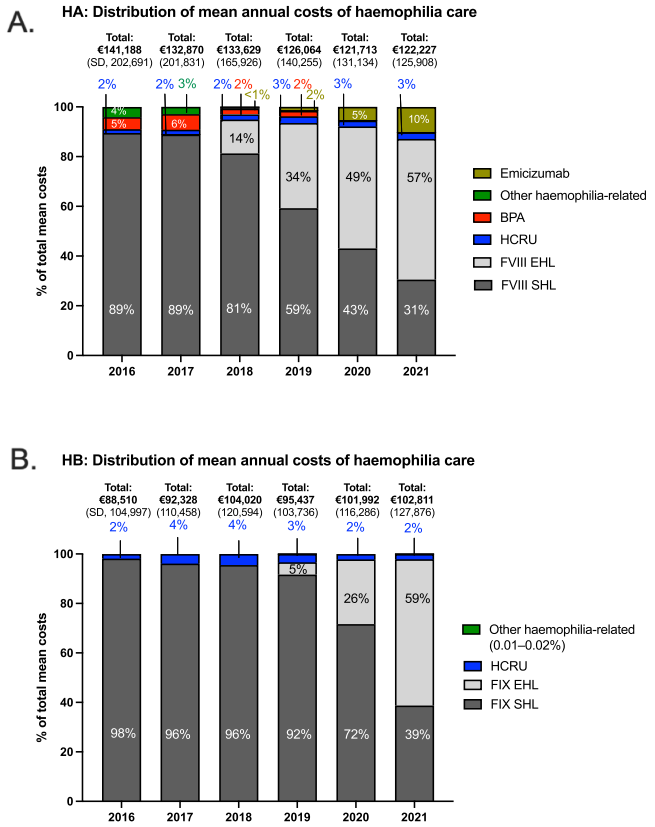

FIGURE 4 | Annual distribution of mean costs of haemophilia care (costs related to haemophilia medication and healthcare resource utilisation, HCRU) for the total population with (A) HA and (B) HB treated in the University Hospitals and alive during 2016–2021. BPA, bypassing agent; FIX, factor IX; FVIII, factor FVIII; HA, haemophilia A; HB, haemophilia B; HCRU; healthcare resource utilisation; SD, standard deviation.

CFC costs comprised 99% of the mean total costs during both SHL (€174,642) and EHL (€193,281) periods. In HB, the mean annual total costs increased by 23% from €180,930 (86,589) during the SHL period to €236,208 (94,360) during the EHL period ($p < 0.01$). Again, CFC costs were 99% of the mean total costs during both SHL (€179,437) and EHL (€233,693).

The mean HCRU costs of HA switchers were €2,115 (3370) per patient during SHL, and €2,457 (4305) during EHL period without a statistically significant increase ($p = 0.19$) (Table 3). Due to the early follow-up intensity after the switch, in HB, there was a significant 40% increase from €1478 (1308) before the switching to €2492 (1417) after switching ($p < 0.05$).

The mean annual total direct costs among haemophilia non-switchers (Table 3) were not different from the SHL period of the switchers.

4 | Discussion

This is the first Finnish nationwide study to assess treatment outcomes, treatment adherence and costs of care in patients with haemophilia A and B during 2016–2021, when switching from SHL to EHL CFC prophylaxis was initiated. The transition to EHL therapy succeeded well, along with reduced infusion regimen and ABR, likely partly due to improved treatment adherence. Based on our short-term follow-up, switching to EHL can elevate CFC costs during the initial post-switch years, possibly due to initial updosing and improved adherence. Patients may also become physically more active, requiring higher CFC trough levels. As treatment practices are likely to become more established over time, there is a need for studies assessing the long-term impact of EHL therapies on the cost of care and quality of life.

The goal in clinical practice has been to switch all feasible patients to EHL because of pricing tenders, the reduced burden of infusions and excellent bleeding control [1, 3, 35]. Majority (>70%) of haemophilia patients switched from SHL to EHL prophylaxis during 2016–2021. The available data of the switchers and non-switchers did not reveal differences between the characteristics of the groups that could provide reasons for switching. This suggests that the non-switchers had a stable disease, and also, during 2016–2021, some patients did not yet have an opportunity to transition to EHL therapy.

We showed that switching from FVIII SHL to EHL reduced the infusion frequency from three to two weekly infusions, and with FIX from two to one weekly infusion. These results align well with the reported weekly rate of 1.4–2.4 infusions with FVIII EHLs, and once every 7–10 days with FIX EHLs [2–4, 9, 11–13, 21]. Notably, since the end of the study period in 2021, individualised pharmacokinetic (PK) monitoring of FVIII/FIX levels and regular follow-ups suggest that the infusion frequency can be decreased even further to every 7 days in HA and every 14 days in HB.

In accordance with others, we observed an increase in FVIII and FIX CFC dose per infusion after the switch [9, 11, 13, 36]. Enhancement of EHL dosing may initially balance the decrease in infusion frequency to ensure sufficient haemostasis, and may also be applied to support new physical lifestyle alterations. Also, higher factor trough levels (3%–5%) are preferred to control bleeding if response to SHL has been inadequate, or if warranted by PK monitoring [1, 37]. After the initial experience, the CFC dosing has gradually been tailored down if haemostasis remains stable.

According to the literature, ABRs decrease or remain constant and low following the transition from SHL to EHL [9, 11–13, 22–25]. Our findings aligned well with these. Notably, in patients >30 years of age, ABR decreased after switching, suggesting that younger patients may have been on a better treatment regimen initially, possibly also with fewer joint bleeds.

We observed improved adherence in HA and a similar trend in HB after switching, as previously reported [13, 26, 36]. The overall adherence rates (86%–100%) were within the reported range, despite varying definitions across studies [38]. Cut-offs for adherent versus non-adherent are based on estimates of levels considered clinically significant, which vary by medicines and individuals, but often an approximate 80% cut-off is used [39, 40]. Based on this, the adherence was considered good during both periods of SHL and EHL. The plausible reason for improved adherence after EHL was the reduced treatment burden, leading to better bleed control and improved quality of life.

The centralised model of haemophilia care in Finland has resulted in comprehensive follow-ups [33]. We showed an increased number of haemophilia-related specialty care contacts due to follow-ups and concomitant HCRU costs after the treatment switch, which is expected based on clinicians' guidance to enable appropriate CFC dosing adjustments and evaluation of treatment response.

Assessing clinical outcomes should be accompanied by analysis of the cost-effectiveness of haemophilia care, following our previous efforts [33]. The main cost driver is the factor replacement therapy, which is sensitive to the intensity (dose and frequency) of prophylaxis. To date, information on how treatment switching impacts real-world CFC consumption and costs remains conflicting. In HA, the overall FVIII consumption has been reported to decrease by 13%–26% after switching [9, 11, 27], or remain stable [13, 22, 23]. Real-world data on post-switch costs are conflicting as savings have been associated with both staying on FVIII SHL [32, 41], and conversely switching to EHL [30]. We observed an increase in post-switch FVIII consumption (mean 18%), aligning with reports from the United States and Australia [36, 41], but the increased consumption did not lead to a cost increase. Possible explanations for the increased consumption are the initial EHL updosing before titration of the therapy and improved adherence. Notably, since we observed a considerable difference in mean and median values in consumption and costs, the interpatient variability in consumption seems substantial.

In HB, the switch decreased FIX consumption (mean 28%), aligning with most real-world studies reporting 15%–50% reductions [22–25, 28, 29, 31]. However, the total costs increased (mean 23%) after switching. The literature on the effect of switching upon the FIX costs is again conflicting. In the United States, almost doubling of CFC costs after the switch in HB (35% increase in prophylaxis) occurred [28, 29], whereas a Canadian study showed a 9% cost reduction (3% in prophylaxis) [31]. Several factors may explain the discrepancies in findings. First, instead of using wholesale prices or hypothetical, threshold-set costs, we used the actual cost of dispensed CFCs. Second, the cost impact of switching to EHL can vary widely across countries due to different healthcare systems, pricing strategies, procurement and reimbursement policies and the baseline cost of SHL therapies. The EHL follow-up time will also impact the costs of after the CFC switch.

One limitation of our study is the short EHL period (median of 2.5 years in HA, 1.0 in HB), which likely primarily captures the initial phase of updosing and frequent patient visits. Since the cost per unit of FIX EHL exceeds that of SHL, the observed post-switch cost increase in HB may reflect this short follow-up, during which the dosing may not yet have been optimised. Since the end of 2021, the overall CFC consumption and costs are expected to have plateaued, and even declined upon the practices becoming more established and treatment tailoring more individualised [9]. Limitations also include unknown reasons for treatment switching, a small patient population affecting, in particular, ABR assessment in HB due to data masking rules, and reliance on self-reported bleeds, which all may introduce bias. Our results highlight the importance of individualised and PK-based management to control the costs of haemophilia care [42]. Future research on the long-term effects of the EHL switch is needed, covering potentially different cost implications and patients' quality of life.

The main strengths of this study are the nationwide real-world cohort, comprehensive data from Finnish registers, including the actual CFC dispensations and costs, and capture of the key clinical data from the main haemophilia treatment centres.

5 | Conclusions

Switching from SHL to EHL haemophilia treatment has improved outcomes in Finland with reduced infusion burden, improved treatment adherence and a trend towards a decreased bleeding rate. The findings set a foundation for future standards in haemophilia care, not only in Finland but also in other healthcare systems, by highlighting the benefits of EHL treatment in improving disease management. Analyses along longer EHL follow-ups are required to evaluate the effect of the treatment switch on CFC prophylaxis and costs, and to set future standards for haemophilia care in Finland and similar healthcare systems.

Acknowledgements

Maarit Taskinen and Maria Patronen from Helsinki University Hospital, Elina Ellilä from Tampere University Hospital and Kirsi Kvist-Mäkelä and Satu Vaihoja from Oulu University Hospital are warmly acknowledged for the manual data collection, and Monica Ferreira from MedEngine Oy for medical writing and Harlan Barker from MedEngine Oy for language review.

Ethics Statement

This study was approved by the Finnish Social and Health Data Permit Authority, Findata, with the approval number: THL/4729/14.02.00/2021. The study was conducted in accordance with the Helsinki Declaration of 1975, Good Pharmacoepidemiology Practices, and Data Protection Directive.

Consent

Informed consent or review and/or approval by an ethics committee was not required because according to the Finnish legislation (Act on the Secondary Use of Health and Social Data (552/2019) by the Ministry of Social Affairs and Health), the patients included in the study cohort were not contacted, and the study did not affect the treatment of the patients.

Conflicts of Interest

M.K., A.V. and J.M. are employees of MedEngine Oy, T.K. was an employee of MedEngine Oy at the time of the study. N.S. and J.H. are employees of Novo Nordisk. T.Sz. has received honoraria as a consultant or speaker from SOBI, Roche and Novo Nordisk. T.Si. is a member of the advisory board for Amgen, Abbvie, GSK, Otsuka Pharma, BMS and Celgene, and has received honoraria as a consultant or speaker from Abbvie and Jansen-Cilag. A.-E.L. has received honoraria as a consultant or speaker from Bayer, Biomarin, CSL Behring, Novo Nordisk, Octapharma, Roche, SOBI and Takeda. R.L. is CMO and CSO of Aplagon Oy, a drug development company for antithrombotics, a lecturer and a member of the advisory board of Astra Zeneca, Biomarin, CSL Behring, Novo Nordisk, Pfizer, Sanofi and SOBI. A.P., O.L. and M.V. declare no conflicts of interest.

Data Availability Statement

The aggregated 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.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.