Pharmacokinetic and economic implications when switching between hemophilia A treatments

by

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Author’s Declaration

I hereby declare that I am the sole author of this thesis. This is a true copy of the thesis, including any required final revisions, as accepted by my examiners.

I understand that my thesis may be made electronically available to the public.

Abstract

Hemophilia is a bleeding disorder in which the blood is unable to form clots, and is also classified as severe (defined as having an endogenous factor VIII [FVIII] concentration < 1 IU/dL, or 1%), moderate (1-5%) or mild (5-50%). Those with severe hemophilia may spontaneously bleed without physical trauma. If not treated appropriately, people with hemophilia may develop hemophilic arthropathy, a joint disease commonly showing signs of bleeding in the knees, ankles, or elbows, which not only impairs movement, but significantly impacts life expectancy and quality of life.

The current treatment of hemophilia involves prophylactic administration of factor concentrates. Although prophylactic treatment has improved health outcomes compared to on-demand treatment, there are still some challenges regarding the use of clotting factor concentrates. Generally, clotting factor concentrates are dosed based on international units per weight, but this one-size-fits-all dosing mechanism fails to account for pharmacokinetic variability within this population. Appropriate dosing regimens vary by patient and treatment with hemophilia A patients using FVIII concentrates should be individualized from a therapeutic and economic standpoint.

Population pharmacokinetic (PopPK) models were used as the basis for individualizing dosing regimens for patients with hemophilia while on factor concentrates. PopPK models are built using PK data from multiple participants to quantify the relationships between covariates such as age and weight to PK parameters as well as define variability between and within participants for these same PK parameters. To determine individual PK using only a few clotting factor activity levels and patient covariates, PopPK models are leveraged for Bayesian forecasting. People with hemophilia who have few sampling points are still available to be

assessed using prior knowledge available from the patient population. While PopPK models may be helpful in hemophilia, this poses a concern when switching between factor concentrates. Factor concentrate switches may be prompted by the availability of new, improved concentrates by termination of national contracts resulting in a discontinuation of drug coverage, hypersensitivity to their current drug formulation, or adverse drug reactions. The lack of PK-tailored guidance when switching from one product to another may result in a period of time where treatment may increase the risk of inappropriate dosing, leading to either an increased risk of bleeds or waste of expensive factor concentrate. The work presented in this dissertation uses knowledge of an individual's PK on a prior factor concentrate to better predict an individual's PK on a new factor concentrate using data available from the Web-Accessible Population Pharmacokinetic Service – Haemophilia (WAPPS-Hemo).

Emicizumab is a bispecific, recombinant, monoclonal antibody that bridges activated factor IX and X, mimics and partially restores the function of clotting FVIII in people with hemophilia A without inhibitors and was approved as routine prophylaxis by Health Canada in 2019. While emicizumab has its advantages over factor concentrates, such as decreased frequency of administration, and subcutaneous route of administration versus intravenous injections, the drug label recommends that any unused solution from a vial must be discarded, thereby wasting expensive resources. The use of a PopPK model of emicizumab was used to explore the implications of dosing based on vial size. This dissertation concludes that administering the entire vial of emicizumab and reducing the frequency may result in a reduction of vials used annually and consequently potential cost-savings.

With high treatment costs and the approval of emicizumab, understanding the pharmacoeconomics of hemophilia is imperative for healthcare systems for reimbursement

approval and contributing to commercial success and decision making as to whether emicizumab should be covered or not. Given the lifelong burden of the disease, the high cost of treatment in hemophilia, and the approval of emicizumab, a drug that may change the landscape of how hemophilia is treated, a cost-utility analysis studying the cost and quality-of-life of different prophylactic treatment regimens was presented in this dissertation, concluding that emicizumab is more effective and may be less costly than FVIII for patients with hemophilia A in Canada, conditional on drug cost assumptions.

The method for estimating individual PK using PopPK models developed described in this dissertation may have a high impact for patients with hemophilia taking factor concentrates, who benefit from a safer individualized dosing regimen when switching between factor concentrates, potentially reducing adverse events or medication wastage. For patients with hemophilia on emicizumab, the simulations conducted exploring the use of emicizumab dosed based on vial size may have significant economic implications in cost-savings and provide a more practical dosing regimen. Finally, the economic evaluation conducted in the Canadian healthcare landscape may provide the healthcare system insight regarding the health and economic effects of using emicizumab compared to factor concentrates.

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Dedication

I dedicate this thesis to my grandmother, Pang Shuk Kam, for her care and inspiration in pursuing my dreams to become a pharmacist, and to my parents, Ricky Yu and Marlene Yu, who have always showered me with their love and encouragement. They have shown continual support during my pursuit of higher education and all my other life aspirations, and I am forever grateful.

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List of Abbreviations

ABR	annualized bleeding rate
ADP	adenosine diphosphate
AUC	area under the curve
BDD	B-domain deleted
BLQ	below limit of quantitation
BSV	between-subject variability
BW	body weight
CADTH	Canadian Agency for Drugs and Technologies in Health
CBDR	Canadian Bleeding Disorders Registry
CBS	Canadian Blood Services
CI	confidence interval
CL	clearance
C_{max}	maximum concentration
CWRES	conditional weighted residuals
ED	exposure days
EHL	extended half-life
FFM	fat-free mass
FIX	factor IX
FVIII	factor VIII
η	eta
HQ	Héma-Québec
ICER	incremental cost-effectiveness ratio

IOV	inter-occasion variability
ISTH	International Society of Thrombosis and Hemostasis
ITI	immune tolerance induction
ka	absorption rate constant
NCA	non-compartmental analysis
PK	pharmacokinetic
PopPK	population pharmacokinetic
PROBE	Patient Reported Outcomes Burdens and Experiences
PSA	probabilistic sensitivity analysis
rFVIIa	recombinant factor VIIa
rFVIII	recombinant full-length factor VIII
rFVIIIFc	recombinant factor VIII Fc fusion protein
SD	standard deviation
SHL	standard half-life
Q	intercompartmental clearance
Q2W	every 2 weeks
Q4W	every 4 weeks
QALY	quality-adjusted life year
QW	weekly
R^2	coefficient of determination
V_1	central volume
V_2	peripheral volume
vWF	von Willebrand factor

WAPPS-Hemo	Web Accessible Population Pharmacokinetic Service – Haemophilia
WSV	within subject variability
WTP	willingness-to-pay

Chapter 1: Background

1.1 Hemophilia A

Hemophilia is a bleeding disorder in which the blood is unable to form clots. Clots are formed through a coagulation cascade, which involves clotting factors resulting in hemostasis and the formation of fibrin. However, people with hemophilia have very low amounts of or are entirely lacking in a specific clotting factor – factor VIII for hemophilia A and factor IX for hemophilia B. [1] This is generally a genetic disorder, inherited through the X chromosome, and tends to affect predominantly males. The prevalence of hemophilia A is approximately 1 in 5,000 males and 1 in 25,000 in hemophilia B. [2] Other types of hemophilia include hemophilia C and parahemophilia; however, these disease types will not be discussed.

Hemophilia is commonly associated with easy bruising or bleeding for a longer period of time after an injury. It is also classified as severe (defined as having an endogenous factor VIII concentration < 1 IU/dL, or 1%), moderate (1-5%) or mild (5-50%), depending on the type of mutation. [3] Mutations can be due to a loss-of-function mutation, deletion, or gene inversion. [3] Those with severe hemophilia may spontaneously bleed without physical trauma. If not treated appropriately, people with hemophilia may develop hemophilic arthropathy, a joint disease commonly showing signs of bleeding in the knees, ankles, or elbows, which not only impairs movement, but significantly impacts life expectancy and quality of life. [4, 5] Other signs and symptoms may include excessive bleeding after a surgical procedure, or the inability to clot after physical trauma. [1]

1.2 The Coagulation Cascade

To have a better grasp in understanding hemophilia as a genetic blood disorder, the coagulation cascade should be discussed. The coagulation cascade aids in understanding how the human body minimizes blood loss through a process called hemostasis. Hemostasis refers to the physiological response to limit the loss of blood after vascular damage by forming a clot. Blood clots are composed of activated platelets, red blood cells, and fibrin. When there is a vascular injury that occurs in the body, collagen and von Willebrand factor (vWF) are exposed from within the vessel wall to the blood. Platelets have a receptor called glycoprotein complex I and will adhere to the endothelial collagen via vWF. [6] Degranulation of both α-granules and δ-granules which were found in platelets will occur, and will release various factors, including calcium. [6] Calcium will provide a surface for coagulation factors to assemble through its binding on phospholipids. [6]

Thromboxane A2 and adenosine diphosphate (ADP) aid in further increasing the number of activated platelets towards the site of injury, forming a platelet plug. [6] ADP will also cause a conformational change of GPIIb/IIIa receptors found on platelets, resulting in the deposition of fibrinogen. At the same time, tissue factor is exposed when the endothelial layer is disrupted, thus initiating the coagulation cascade (Figure 1). The tissue factor found outside the vessel wall interacts with the extrinsic pathway of the coagulation cascade, which involves a series of activating different clotting factors, starting with factor VIIa and factor Xa. [6, 7] The amount of thrombin generated by the extrinsic pathway will not be sufficient, thus thrombin acts as a positive feedback by binding to platelets. [6] This amplification process will further activate other coagulation factors which will ultimately result in increasing amounts of thrombin. [6] The extrinsic pathway is soon inhibited by tissue factor pathway inhibitor, thus the intrinsic pathway

is the more efficient pathway in the coagulation process. [8] Other inhibitors such as antithrombin will also provide a negative feedback on the coagulation cascade to stop the process. [9] Both intrinsic and extrinsic coagulation pathways will activate and lead to the production of thrombin. Thrombin will aid in converting fibrinogen to fibrin, which will ultimately end in forming the fibrin clot through the activation of factor XIII. [6, 10] In order to stop the coagulation process, thrombin also activates thrombin activatable fibrinolysis inhibitor, which acts as negative feedback to stop the clot from undergoing fibrinolysis. [6, 11, 12]

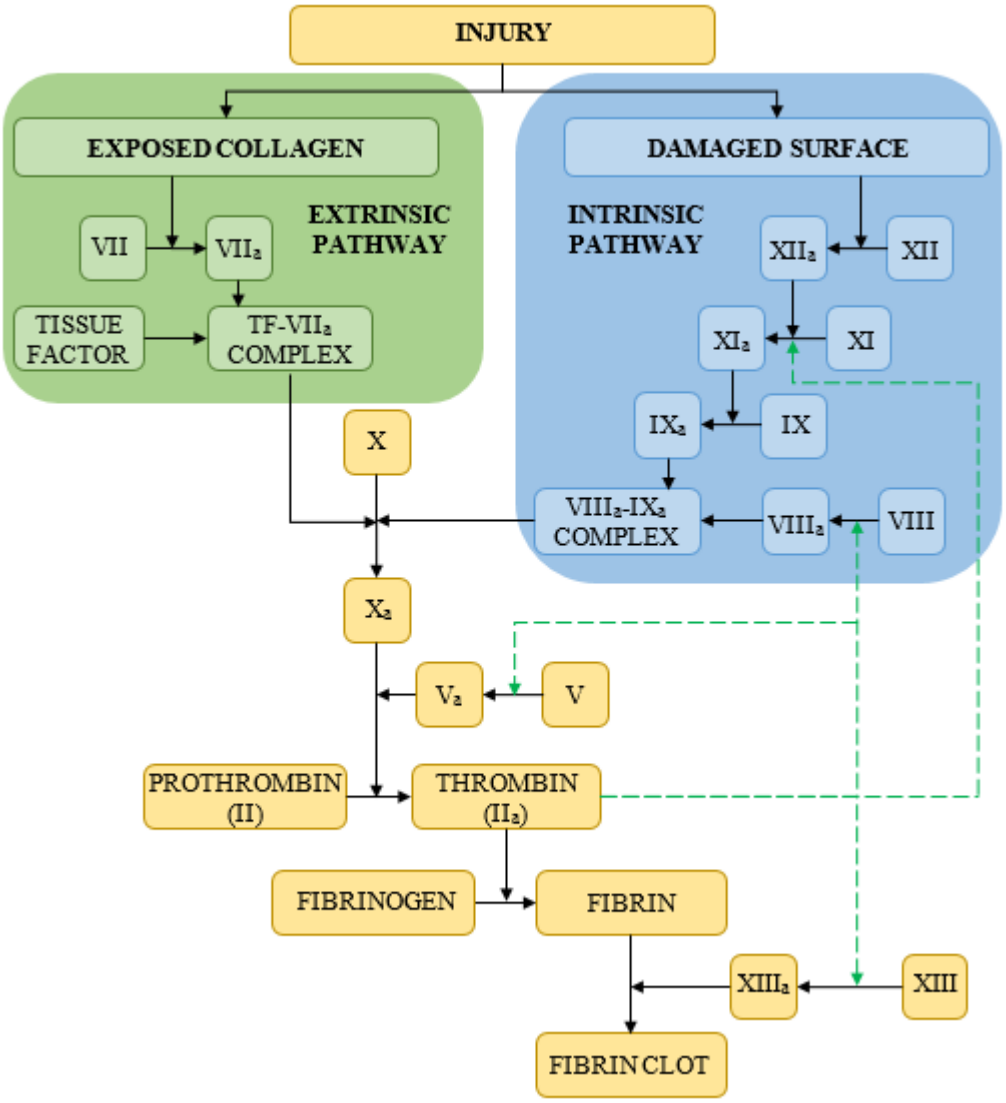

Figure 1. The coagulation cascade, differentiated between the extrinsic pathway (green) and intrinsic pathway (blue). Positive feedback of thrombin (dashed green lines) is also shown.

For hemophilia patients, low FVIII or factor IX (FIX) concentrations causes a disruption in the coagulation cascade, leading to the inability to form a clot. Depending on the site of damage, this can lead to permanent damage to the body, such as arthropathy and intracranial hemorrhages. By replenishing the human body with exogenous FVIII or FIX concentrates, one can maintain an adequate level of clotting factors to achieve hemostasis when necessary.

1.3 Current Hemophilia Therapy

The current treatment of hemophilia involves administration of factor concentrates. In the past, FVIII infusions were given during an acute bleed. This practice was commonly known as "on-demand" treatment, which aided in not only decreasing the number of patients with joint deformities, but also significantly lowering morbidity and mortality, ultimately increasing patient's quality of life. [5] However, this practice was soon to be found suboptimal. A study by Aledort et al. showed that severe hemophilia patients without inhibitors undergoing an on-demand treatment regimen still experienced reduced orthopedic outcomes and increased deteriorated joints compared to those treated prophylactically. [5, 13] Prophylactic infusions have now been accepted as the standard for preventing bleeds and treating hemophilia patients well before joint damage is apparent. [14-17] Despite these changes, an optimal dosing strategy has yet to be implemented. Due to the factor concentrates' short half-lives (approximately 10 hours), plasma-derived or recombinant FVIII products generally require about two to four infusions per week, while plasma-derived or recombinant FIX products may require less frequent infusions, up to once every 3 weeks. [1, 3] Due to the considerable variability in hemophilia treatment, dosing of factor concentrates should be individualized, thus the variations in PK parameters must be accounted for in order to provide an optimal dosing regimen. [18, 19]

Although prophylactic treatment has improved health outcomes, there are still some challenges regarding the use of clotting factor concentrates. As current hemophilia treatment involves administrating the medication intravenously, this poses a discomfort to hemophilia patients as well as an additional risk of bacterial infections. [20] In addition, due to clotting factor concentrates' relatively short half-lives (depending on the type of concentrate), clotting factor administration is required two to four times per week, which can pose adherence issues for

hemophilia patients, particularly children. [4, 20] Appropriate dosing regimens vary by patient and treatment with hemophilia A patients using FVIII concentrates should be individualized from a therapeutic and economic standpoint. [17-19] Generally, clotting factor concentrates are dosed based on international units per weight (e.g. IU/kg), but this one-size-fits-all dosing mechanism fails to account for pharmacokinetic variability within this population. Iorio et al. stated that using a "trial and error" approach without data gathered from individual PK leads to suboptimal results. [21] The "trial and error" approach involves providing a hemophilia patient with a typical prophylactic dosing regimen. [21] This dose should provide the average hemophilia patient with enough clotting factor to achieve the goal of a trough level at or above 1 IU/dL, as those with moderate hemophilia (baseline factor levels >1 IU/dL) were less susceptible to spontaneous bleeding events and subsequently joint arthropathy compared to severe hemophilia. [21, 22] This type of dosing regimen is highly variable in practice and thus presents the risk of under-dosing a patient or wasting expensive resources. [21]

Emicizumab (HEMLIBRA®, Chugai Pharmaceutical Co, Ltd.), a bispecific, recombinant, monoclonal antibody that bridges activated factor IX and X, mimics and partially restores the function of clotting FVIII in people with hemophilia A and was approved as routine prophylaxis for those without inhibitors by Health Canada in 2019. [23] With a long half-life of approximately 4 weeks [24] and subcutaneous administration, this benefits hemophilia A patients by allowing less frequent dosing regimens and avoids intravenous infusions. [25] Emicizumab follows the general trends in the PK of monoclonal bodies, with a clearance (CL) of 3.4 mL/kg/day [26], and is dosed based on body weight at 1.5 mg/kg weekly, 3 mg/kg every 2 weeks, or 6 mg/kg every 4 weeks. The approval of three different yet equivalent dosing regimens for emicizumab in which clinical efficacy has been demonstrated lends itself the opportunity to

explore the impact of further dosing and frequency combinations. While emicizumab has its advantages, the manufacturer provided guidance on vial size selection through a website (https://www.hemlibra.com/hcp/dosing-administration/dosing.html), stating that any unused solution from a vial must be discarded, thereby wasting expensive resources. It has not yet been explored how modifying the emicizumab dose to a full vial size and correspondingly extending or reducing the injection frequency would pan out when targeting the same steady state concentration to maintain the efficacy and safety shown in clinical trials. However, a PopPK model of emicizumab is needed to explore the implications of dosing based on vial size.

1.4 Population Pharmacokinetic Modeling

PopPK is used to assess a drug's PK, and to quantify and describe the variability of a drug in a population while taking into account possible covariate effects using non-linear mixed effects regression modeling. [27] In hemophilia, PopPK has its advantages over classical PK approach to individualizing treatment. Originally in 2001, the International Society of Thrombosis and Hemostasis (ISTH) recommended that for every patient, a PK study should be completed, taking around 10-11 samples to obtain estimates of individual's PK parameters. [28, 29] However, the numerous amount of samples required in classical PK is burdensome for hemophilia patients and may not be practical for collecting PK information. [21] Unlike classical PK studies which require multiple sampling of individuals, PopPK models can be leveraged by only requiring a few sampling points to obtain individual PK. [30] Thus, people with hemophilia who have few sampling points are still available to be assessed using prior knowledge available from the patient population. [30, 31]

The PK parameters contain variability amongst the population, and can be categorized according to its predictability. Predictable variability includes known covariates that may have an influence on one's PK, for example demographic (age, sex, body weight, race), genetic (blood group or other phenotypes), or physiological (medical conditions, pregnancy) characteristics. [27] Unpredictable variability, on the other hand, includes the residual within or between patients. [27] There may be unpredictable variability between patients, known as between-subject variability (BSV), or within a patient, known as within subject variability (WSV). When unpredictable variability is high, the risk of drug concentrations appearing outside of its target range increases and thus produces unreliable dosing regimens. [32] On the contrary, if the therapeutic window of a drug is high, there is no need to be concerned with variability, and a

population dose would be adequate. In the case of FVIII concentrates, BSV is high and WSV is low. This means that individual dosing for FVIII concentrates by using patient-specific PK would be appropriate in order to provide consistent concentration-time profiles. [33]

The development of a PopPK model consists of utilizing a dataset to identify three sub-models, including a structural model (determining the shape of factor activity level vs. time profile), a covariate model (describing the relationship between PK parameters and variables, such as age, body weight, or blood type), and a statistical model (describing the variability). While PopPK models can be developed for numerous purposes, PopPK models in hemophilia are typically created for Bayesian forecasting to optimize dose selection for individuals taking factor concentrates. Bayesian forecasting typically involves using patient information, individual plasma concentrations, and prior information in the form of PopPK models to generate individual PK parameters and estimates. [34] PopPK models that are developed for Bayesian forecasting are evaluated using graphical techniques, internal, and external evaluation techniques to assess goodness-of-fit and to identify any model misspecifications. Other diagnostic plots include population/individual predicted values vs. observed values, conditional weighted residuals (CWRES) vs. predicted values, CWRES vs. time, observed/predicted values vs. time, normal QQ plots, CWRES histograms, population covariate plots, and η histograms. Bootstrap analyses are also performed to assess uncertainty in parameter estimates by assessing the confidence intervals (CI) and calculating the standard errors around the PK parameters of the PopPK model. Finally, prediction-corrected visual predicted checks are also used to assess a model's predictive capacity by splitting the original dataset into a learning subset and validation subset. The learning subset comprises of 90% of the data while the remaining 10% of the data is used for evaluation. Bayesian forecasting can be performed using population estimates of the learning subset, and

individual PK parameters are compared to using the entire modeling dataset by calculating a relative error. This process is then repeated to prevent bias from a single random split of the modeling dataset.

The end purpose of PopPK models in the context of hemophilia is to estimate clinically relevant individual PK parameters (e.g. half-life, time to 1%, etc.) from sparse patient samples as well as demographic data using Bayesian forecasting, with PopPK model parameters (e.g. typical values and variances) serving as prior information. These FVIII PopPK models may highly impact patients with hemophilia, in which individualized dosing is more beneficial compared to a trial-and-error approach due to the high BSV and low WSV of FVIII concentrates, which results in fewer adverse events by allowing for targeting a threshold FVIII concentration >1%.

1.5 Switching Between Treatment in Hemophilia Therapy

When a person with hemophilia switches between factor concentrates, the person is switching from a product with known PK parameters, or at least with known outcomes (e.g. dose required to reduce bleeding events), to one with unknown PK parameters (Figure 2). Dosing a factor concentrate with unknown PK parameters introduces the risk of under-dosing or resource wastage, leading to increased risk of bleeds or unnecessary use of factor concentrates, respectively. Current practice does not include a procedure or guideline in terms of how to safely switch from one factor concentrate to another. It is crucial to understand the concept of switching in order to provide safer and efficacious treatments for people undergoing changes in their drug regimen.

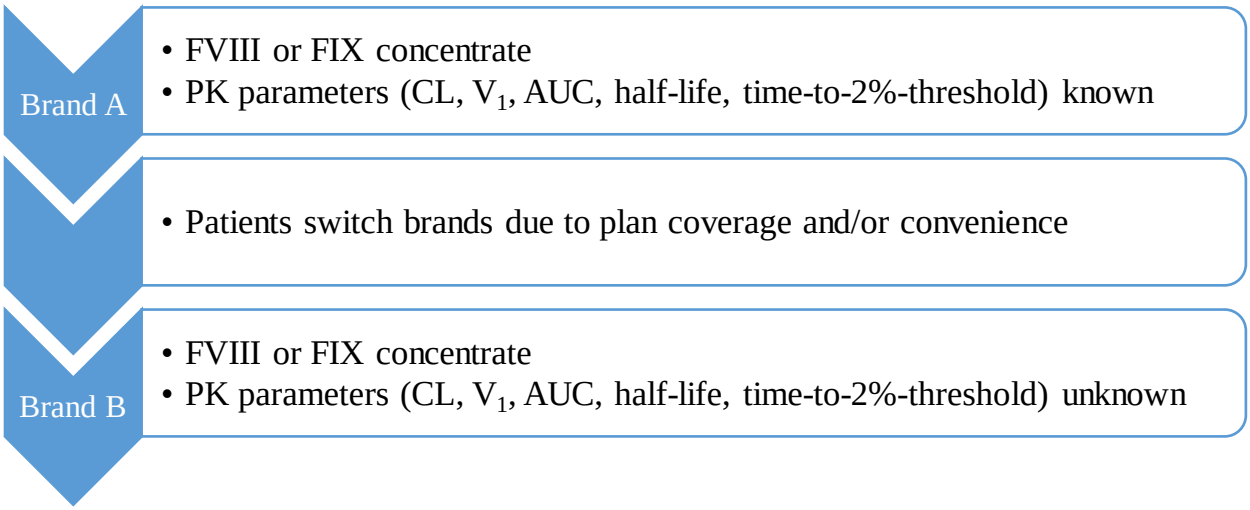

Figure 2. Known PK parameters of Brand A switching to unknown PK parameters of Brand B.

The availability of newer and safer FVIII concentrates has resulted in switching between different plasma-derived or recombinant FVIII concentrates throughout the course of hemophilia treatment. [35] Newer FVIII products typically have better PK in terms of longer half-life and thus may provide the advantage of fewer infusions. [35] Patients who are infusing three times a week may switch to another clotting factor concentrate for twice a week infusions or other less

frequent dosing regimens, resulting in a significant decrease of infusions per year. Other reasons for switching FVIII products may include national plan coverage, side effects, drug shortages, or hypersensitivity to the formulation. [35]

The decision to switch between factor concentrates depends on a variety of factors, but requires collaboration between the patient and their healthcare provider. Shared decision making while assessing the product's safety, efficacy, cost, and convenience is essential before introducing a new product. However, the lack of literature and evidence regarding switching between factor concentrates provides a challenge for both the patient as well as the prescriber. While many of the reasons why patients switch FVIII concentrates is not due to the efficacy of the drug, patients and physicians may be hesitant to change medications. Adherence to treatment may also be compromised in these situations; a study by Ragni et al. suggests that adherence to prophylaxis may vary depending on the severity of bleed and infusion difficulty. [36] However, no correlation was made regarding adherence and switching between dosing regimens. [36]

1.6 The WAPPS-Hemo Program

In order to assess if knowledge of PK on a prior concentrate is beneficial prior to switching between hemophilia treatments, PopPK models are required. However, this can be challenging given the considerable amount of data required to develop a robust PopPK model. In addition, the collection of data may be particularly challenging for a rare disease such as hemophilia. The WAPPS-Hemo is a database to aid clinicians in facilitating hemophilia treatment by obtaining individual PK assessments such as half-life and time-to-threshold concentrations. Clinicians input post-infusion factor VIII/IX plasma levels using as few as 3-4 patient samples as well as patient characteristics, and in return receive individual PK estimates. Brand-specific PopPK models have been created using patient data gifted from the industry. Once individual data containing specific patient information is submitted to the WAPPS-Hemo website (www.wapps-hemo.org), a report containing individual PK estimates will be generated after expert validation, including time in which the factor level reaches a specific threshold (5%, 2%, or 1%). Each report generated for patients is vetted by a PK expert before returning to the user. As of 2023, there are over 700 centres with access to WAPPS-Hemo. Over 11000 patients and 67000 infusions have been recorded in the WAPPS-Hemo database (Figure 3).

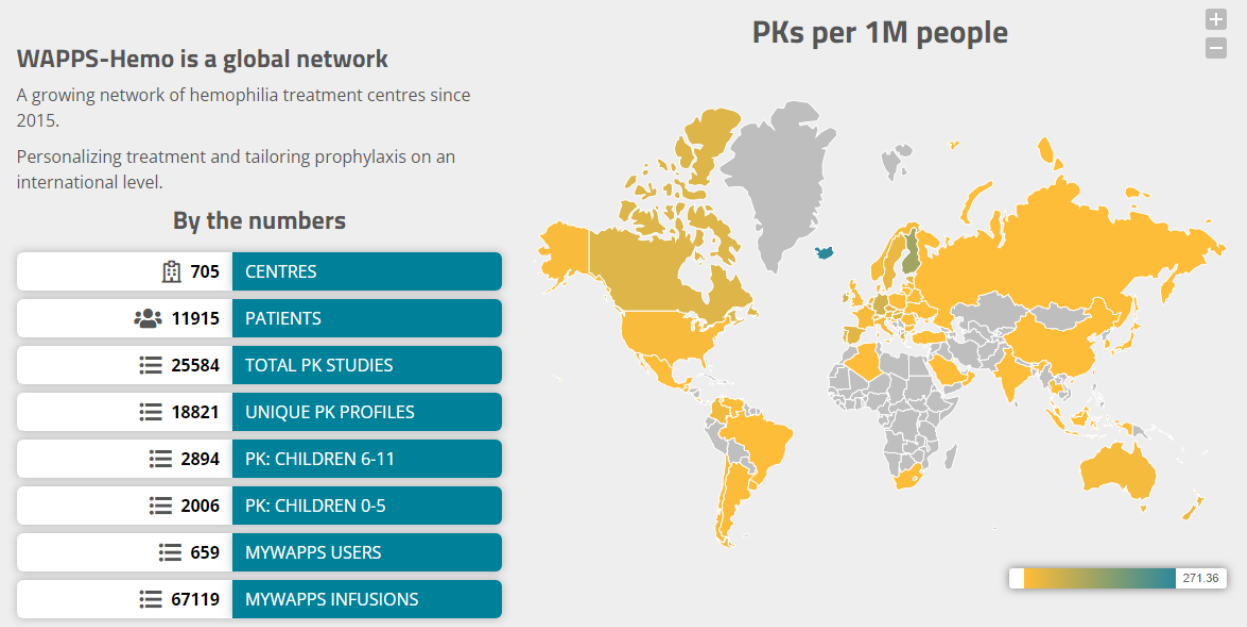

Figure 3. The WAPPS-Hemo network; The colour of each country indicates the number of registered centres (obtained from http://www.wapps-hemo.org, January 9, 2023).

1.7 Pharmacoeconomics of Hemophilia A

With high treatment costs and the approval of emicizumab, understanding the pharmacoeconomics of hemophilia is imperative for healthcare systems for reimbursement approval and contributing to commercial success and decision making as to whether emicizumab should be covered or not. [37] In Canada, in order to determine which medication is covered by the Canadian healthcare system, a tender process for medications in hemophilia is conducted every two to three years. The Canadian Blood Services (CBS) and Héma-Québec (HQ) conduct periodic requests for proposals for different blood products, including FVIII products. All manufacturers with products in Canada submit bids and are reviewed by a committee which assigns a score for each product based on an agreed-upon criteria and weighting. The criteria include items such as the product description and monograph, pharmacokinetic profile, and safety information. A large component in deciding which FVIII will be chosen to be covered by the government will depend on the cost of the product.

Conducting economic evaluations in the hemophilia space is integral to the Canadian healthcare system, as it is publicly funded by the taxpayer's money. The cost of drug therapy in hemophilia can be several hundred thousand dollars per year or even higher for those with complications such as inhibitor development. Hemophilia is also a lifelong disease, meaning that comparing that the chosen treatment option for individuals may lead to significant long-term impact. Due to the tender process in Canada, CBS and HQ are able to utilize economic evaluations in a Canadian healthcare system perspective to assist in their decisions in choosing which drug therapy to reimburse for patients with hemophilia.

Conducting a literature search regarding economic evaluations in hemophilia show that the comparison between life-long prophylaxis between standard half-life (SHL) FVIII, extended

half-life (EHL) FVIII, and emicizumab products are limited. Most of the cost-effectiveness analysis and cost-utility analysis include comparing prophylactic treatment versus on-demand treatment in hemophilia, the use of bypassing agents used to treat hemophilia with inhibitors, and other alternative strategies for treating inhibitor patients such as the use of low- and high-dose immune tolerance induction. There has only been one cost-utility analysis in the Canadian context published in 2008, focusing on prophylaxis versus on-demand treatment therapy of FVIII products. [38] The economic evaluations conducted in the hemophilia field are also prone to methodological deficiencies due to several reasons, including the lack of clinical trial data due to the rare nature of the disease, as well as the lack of clarity of the doses used in practice or the relative efficacy of treatments. [39] Given the lifelong burden of the disease, the high cost of treatment in hemophilia, and the approval of emicizumab, a drug that may change the landscape of how hemophilia is treated, an economic evaluation studying the cost and effectiveness of different prophylactic treatment regimens would be beneficial.

1.8 Objectives and Hypotheses

1. Assess if the knowledge of prior PK parameters is more predictive of individual PK parameters when switching between FVIII concentrates in the same hemophilia A patient.

Hypothesis: The knowledge of individual PK from one factor concentrate will provide predictable PK when switching FVIII concentrates in the same hemophilia A patient.

2. Use PopPK to illustrate the changes in time-to-trough levels when increasing emicizumab dose to the nearest vial size, and explore the implications of changing a patient's dose to the nearest vial to save on medication costs.

Hypothesis: Increasing emicizumab dose to the nearest vial size will decrease dosing frequency while maintain similar trough levels, thereby reducing the number of vials used. Reducing emicizumab dose to the nearest vial size may save on medication costs without a significant drop in trough concentrations.

3. Estimate the health and economic effects of using prophylactic EHL FVIII, SHL FVIII, and emicizumab in severe hemophilia A patients in Canada.

Hypothesis: Prophylactic emicizumab reduces bleeds more effectively than factor concentrates and is the most cost-saving option for treatment of hemophilia A in Canada.

Chapter 2: Using pharmacokinetics for tailoring prophylaxis in people with hemophilia switching between clotting factor products

This chapter is reflective of an original manuscript published by the Ph.D. candidate (Jacky Ka-Hei Yu) in Research and Practice in Thrombosis and Haemostasis. All pertinent dialogue in this chapter was written by the Ph.D. candidate.

Yu JK, Iorio A, Edginton AN, WAPPS-Hemo co-investigators. Using pharmacokinetics for tailoring prophylaxis in people with hemophilia switching between clotting factor products: A scoping review. Res Pract Thromb Haemost. 2019; 3(3):528-541. DOI: 10.1002/rth2.12204.

2.1 Introduction

The mainstay treatment of hemophilia involves administration of factor concentrates. In the past, FVIII and FIX infusions were given during or soon after an acute bleed. This "on-demand" treatment decreased the number of patients with joint deformities, but also significantly lowered their morbidity and mortality, ultimately increasing their quality of life. [5] This practice was soon to be found suboptimal and a study by Aledort et al. demonstrated that severe hemophilia patients without inhibitors undergoing an on-demand treatment regimen still experienced reduced orthopedic outcomes and increased deteriorated joints compared to those treated prophylactically. [5, 13] Prophylactic FVIII or FIX infusion has now been accepted as the standard for treating hemophilia patients well before joint damage is apparent. [13-17]

Prophylaxis was conceived as repeatedly dosing the patient so as to obtain a measurable factor activity at all times. The challenge is that appropriate dosing regimens vary by patient and factor concentrate and should be individualized from a therapeutic and economic standpoint. [17-19] A "trial and error" approach is usually adopted, which involves using a typical prophylactic dosing regimen of 20-50 international units per kilogram of body weight (IU/kg), a dose which should provide the average hemophilia patient with enough clotting factor to achieve the goal of a trough activity at or above 0.01 IU/mL at 48 hours. However, this "trial and error" approach fails to account for individual PK variability and, as per Iorio et al., may lead to suboptimal results. [21]

The "trial and error" approach is used again when switching between factor concentrates. Common practice in this scenario is that either the dose is initially kept the same as before the switch and frequency is adjusted proportionally to the relative expected change in terminal half-life, or the dose and frequency tested in the pivotal studies are used in a first instance. Current

guidelines suggest initiating EHL products at the same dose as standard half-life [40] concentrates but reducing the infusion frequency from three to two times weekly, and subsequently adjusting the dose based on a PopPK approach. [41, 42] When a person with hemophilia switches between factor concentrates, the person is switching from a product with known PK, or at least with known outcomes (e.g. dose required to reduce bleeding events), to one with unknown PK. Dosing a factor concentrate with unknown PK introduces the risk of under-dosing or resource wastage, leading to increased risk of bleeds or unnecessary use of factor concentrate, respectively.

The decision to switch between factor concentrates depends on a variety of factors, and shared decision making while assessing the product's safety, efficacy, cost, and convenience is essential before introducing a new product. The availability of newer and safer FVIII concentrates has resulted in switching between different plasma-derived or recombinant FVIII concentrates throughout the course of hemophilia treatment. [35] Newer FVIII products report to have better PK in terms of longer half-life and thus may provide the advantage of fewer infusions. [35] Other reasons for switching FVIII products may include cost savings, via a tender-based national plan coverage or otherwise, side effects, drug shortages, or hypersensitivity to the formulation. [35]

The optimal approach to dose selection when switching between factor concentrates remains unknown. In order to answer the question of what is known about the current use of PK for tailoring prophylaxis in people with hemophilia switching between factor concentrates, we conducted: a) a scoping literature review, searching for empirical evidence regarding optimal switching practice, and b) a review of the WAPPS-Hemo database available to explore the practice of switching as recorded in the real world. WAPPS-Hemo is a globally-accessible online

tool allowing hemophilia treaters to estimate individual PK using a population PK approach based on a limited set of 2-3 plasma factor activity measurements and patient covariates (e.g. age, weight, height). Patient covariates and PK profiles gathered by WAPPS-Hemo are de-identified and stored in a database. This database is available for research purposes to the members of the WAPPS-Hemo research network. [31] The WAPPS-Hemo database provides information on current practices regarding product switching, as patients who have had more than one infusion recorded and have used more than one factor concentrate can be tracked within the system.

2.2 Methods

2.2.1 Scoping Review

The scoping review process followed these steps: 1) Identify possible eligible studies; 2) Select relevant studies; 3) Chart the data; and 4) Collate, summarize and report the results, as proposed by Arksey and O'Malley. [43] Following the PCC mnemonic [44], studies included hemophilia A or B patients (Population) switching between different factor concentrates and including appropriate PK assessments (Concept) and without any limitation as to reasons for switching, socio-economical setting and underlying health care system characteristics (Context). Relevant studies were prospective in nature. A search strategy was developed using medical subject headings [45]. The literature search was independently performed in PUBMED (MEDLINE) in September 2018 by both JKY and ANE. Search terms included:

- ("Hemophilia A"[Mesh] OR "Hemophilia B"[Mesh] OR "Factor IX"[Mesh] OR "Factor VIII"[Mesh]) AND switch*
- ("Hemophilia A"[Mesh] OR "Hemophilia B"[Mesh]) AND "Cross-Over Studies"[Mesh].
- ("Hemophilia A"[Mesh] OR "Hemophilia B"[Mesh]) AND "Pharmacokinetics"
- ("Hemophilia A"[Mesh] OR "Hemophilia B"[Mesh]) AND "Bioequivalence"

2.2.2 WAPPS-Hemo Data Review

For this review, all patients within the WAPPS-Hemo database were eligible for inclusion unless they had only one infusion, or had only one type of factor concentrate recorded on multiple occasions (Figure 4). The WAPPS user agreement allows reuse of the data for modelling and other research purposes, as described in the WAPPS study protocols, approved by the ethics boards at McMaster University and the University of Waterloo and registered in clinicaltrial.gov (NCT02061072, NCT03533504).

2.3 Results

2.3.1 Study Selection

There were no research articles that specifically addressed the optimal approach to switching between factor concentrates. However, there were 39 peer-reviewed scientific articles that fell within our inclusion criteria (Figure 5). Reviewer 1 identified 39 and reviewer 2 identified 38 that were identical to those selected by reviewer 1. Upon discussion of the missing article, the reviewers decided to include it as it met the inclusion criteria. The 39 articles were the only studies that could provide treaters with methods for evidence-based switching using PK and were thus sorted based on their primary objective and appraised. Studies included bioequivalence or comparative PK studies, as well as inhibitor development studies during switching. All 39 studies are outlined in Table 1 (FVIII) and Table 2 (FIX).

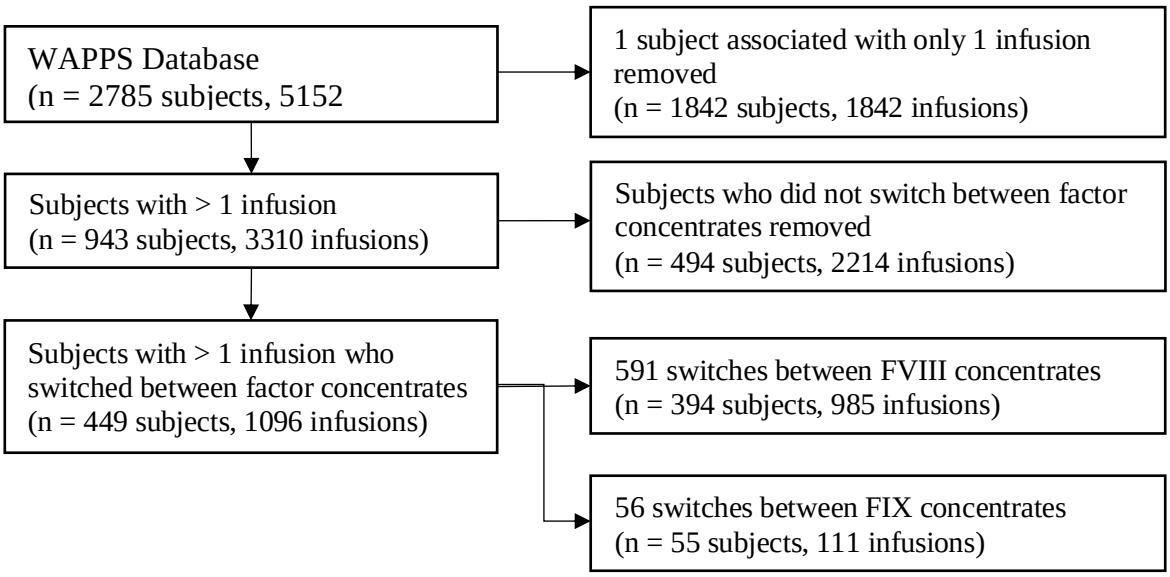

Figure 4. Study flow diagram of WAPPS data.

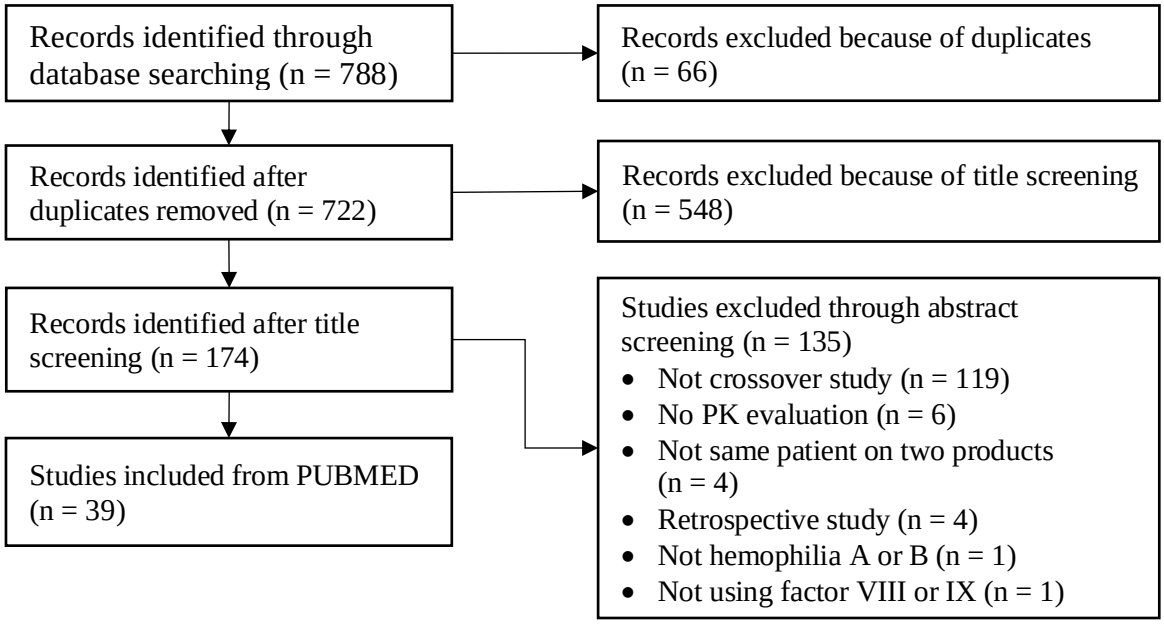

Figure 5. Study flow diagram of PUBMED search.

2.3.2 Biosimilarity/Bioequivalence or Comparative PK studies

Strictly speaking, the term "bioequivalence" should not be used for drugs produced by biotechnology; the term biosimilarity is more appropriate [46]. However, bioequivalence was the terminology used in many of the studies as many were published prior to the 2014 European Medicines Agency's guidance [46]. Irrespective of the term used, studies assessing biosimilarity/bioequivalence did not usually enhance a switching protocol as a primary objective; however, their standardized dosing protocol allowed for comparison of individual PK profiles between the two brands under study. Thus, this section focuses on biosimilarity and comparative PK studies as both types compared population PK.

There were a limited number of studies that were biosimilarity or comparative PK studies (n = 34) (Table 1 and 2). Biosimilarity refers to a lack of statistically significant differences in drug exposure between two drug products. In multiple crossover studies, biosimilarity was assessed by using a PK analysis to derive the maximum plasma factor activity (C_{max}) following

infusion and the area under the plasma concentration vs. time curve (AUC). [47-49] In order to establish biosimilarity, the ratio of the logarithmic geometric mean values of C_{max} and AUC must fall within the interval of 80%-125% based on a 90% CI. [47, 48]

All of the studies looking at comparing PK between two brands used PK endpoints, as suggested by the International Society of Thrombosis and Haemostasis and American and European regulatory bodies. [31, 35, 43] The test dose before and after the switch was almost always identical, usually with a weight-based dosing of 50 IU/kg of the factor concentrates. Using the same dose for different concentrates is a requisite for biosimilarity studies. All trials studied included a washout period of between 2 to 7 days before starting the trial and between different factor concentrates (Table 1 and 2).

Table 1. Summary of studies of hemophilia patients switching between factor VIII concentrates.

Author	Products	Dose (IU/kg)	# of Subjects Screened for PK	Age Range (Mean) [Median]	Minimum Washout Period (days)	Primary Objective
Biosimilarity or comparative PK studies						
Di Paola [47]	1) Advate 2) Refacto	50 ± 5	21	19 - 72 (35.8) [30]	3	Compare PK of ReFacto and Advate to establish bioequivalence
Dmoszynska [50]	1) Prior FVIII product 2) Optivate	50	15	12 - 65	3	Investigate the PK of Optivate against other FVIII products
Fijnvandraat [51]	1) rFVIII SQ 2) Octonativ M	50	12	17 - 64 (34)	4	Compare PK of rFVIII SQ and Octonativ M
Kessler [48]	1) Refacto (Two formulations) 2) Hemofil M	50	19	18 - 44 (26.3)	5	Compare PK of the two formulations of ReFacto with Hemofil M to establish bioequivalence
Klamroth [52]	1) Advate 2) rFVIII-Singlechain	50	27	19 - 60 (35.4)	4	Compare PK parameters of rFVIII-Singlechain with full length rFVIII
Martinowitz [53]	1) Advate 2) N8	50	25	13 - 54 (24)	4	Compare PK profiles of N8 and Advate to establish bioequivalence
Morfini [54]	1) pd-FVIII 2) rFVIII	25 - 56 25 - 45	17	15 - 51 (27.7) [24.9]	7	Compare PK profiles of two different classes of FVIII concentrates
Morfini [55]	1) Recombinate 2) Hemofil M	50	47	6 - 62 (26.4)	7	Compare PK profiles of Recombinate and Hemofil M
Morfini [56]	1) Hemofil M 2) Monoclate HT 3) Monoclate P	25	10	-	7	Compare in vivo behaviour between the three products
Recht [57]	1) Advate 2) Xyntha	50	24	12 - 60 [24]	3	Demonstrate PK equivalence of Advate
Shah [49]	1) Advate 2) Kovaltry	50	18	19 - 64 (37.3)	3	Compare PK profile of Advate and Kovaltry

				[36]		
Shirahata [58]	1) BAY14-2222 2) Kogenate	50	5	15 - 43 (32) [35]	5	Compare PK profile of BAY14-2222 and Kogenate
Biosimilarity or comparative PK, and inhibitor development studies						
Abshire [59]	1) Kogenate 2) rFVIII-FS	50	35	-	4	Compare PK and safety of Kogenate and rFVIII-FS
Coyle [60]	1) rFVIII-FS 2) BAY 94-9027	25/50 25/60	14	21 - 58 (36.1)	3	Assess PK and safety of BAY 94-9027
Kulkarni [61]	1) Prior FVIII product 2) Turoctocog alfa	- 25-60	69	1 - 11 (6.1)	3	Investigate safety, efficacy, and PK properties of turoctocog alfa
Mahlangu [62]	1) Advate 2) rFVIIIFc	50	30	12 - 65 [29]	-	Evaluate safety, efficacy, and PK of rFVIIIFc
Meunier [63]	1) Prior FVIII product 2) N8-GP	- 60	24	0 - 11 (6.0)	-	Assess safety, efficacy, and PK of N8-GP
Mullins [64]	1) Advate 2) BAX855	60 ± 5	31	1 - 11 (6) [6]	-	Determine immunogenicity, PK, efficacy, safety, and quality of life using BAX855
Powell [65]	1) Kogenate 2) Kogenate with pegylated liposome carrier (13 or 22 mg/kg)	35	26	12 - 60	2	Investigate the safety, tolerability, bioavailability, pharmacokinetics, and pharmacodynamics of Kogenate with pegylated liposome barrier compared with standard Kogenate
Schwartz [66]	1) Koate-HS 2) Recombinant FVIII	50 20 - 40	17	-	7	Compare PK of plasma-derived and recombinant FVIII, assess efficacy of recombinant FVIII for home therapy, and assess efficacy for major surgical procedures and hemorrhage
Skotnicki [67]	1) Vocento 2) Biostate-RP	50	17	18 - 57 (36.5) [37]	4	Evaluate efficacy, safety, and PK of Voncento
Tiede [68]	1) Prior FVIII product 2) N8-GP	- 25/50/75	26	20 - 60 [36.5]	4	Evaluate safety and PK of N8-GP in comparison with previous FVIII products

Young [69]	1) Prior FVIII product 2) rFVIIIFc	50	60	1 - 11 [5]	3	Evaluate safety, efficacy, and PK of rFVIIIFc
Inhibitor development studies						
Hsu [70]	1) Kogenate 2) Koate-HS	50 -	12	23 - 53 (37.8)	7	Evaluate safety and efficacy of Kogenate
Powell [71]	1) Advate 2) rFVIIIFc	25/65 25/65	19	23 - 61 (34.6)	3	Evaluate safety and treatment-emergent adverse events, development of antibodies, and laboratory monitoring

- : Not specified

Table 2. Summary of studies of hemophilia patients switching between factor IX concentrates.

Author	Products	Dose (IU/kg)	# of Subjects Screened for PK	Age Range (Mean) [Median]	Minimum Washout Period (days)	Primary Objective
Biosimilarity or comparative PK studies						
Alamelu [72]	1) Alphanine 2) Benefix	50	9	15 - 73 (41.2) [42]	7	Compare PK and pharmacodynamics properties of rFIX and pdFIX
Aznar [73]	1) Immunine / Octanine 2) FIX Grifols	65 - 75	25	12 - 38 (23.1)	7	Compare pharmacokinetic profile of FIX Grifols to available Immunine or Octanine
Ewenstein [74]	1) Benefix 2) Mononine	50	43	7 - 75 [18.5]	7	Assess pharmacokinetic properties of the two products and address variables affect in vivo recovery and half-life
Goudemand [75]	1) FIX-SD-15 2) FIX-SD	60	11	-	10	Compare PK and coagulation activation markers of FIX-SD-15 and FIX-SD
Liebman [76]	1) Alphanine 2) Mononine	40	12	-	7	Evaluate kinetics of FIX activity and protein
Lissitchkov [77]	1) Benefix 2) Alphanine	65 - 75	22	15 - 45 (27)	7	Compare PK between Benefix and Alphanine
Martinowitz [78]	1) Benefix 2) IB1001	75 ± 5	32	15 - 64	5	Compare PK of IB1001 with those of Benefix and assess consistency of PK parameters
Thomas [79]	1) Conventional FIX 2) High-purity FIX	75	19	-	7	Compare PK of high purity FIX to conventional FIX
Windyga [80]	1) Benefix 2) BAX326	75 ± 5	86	12 - 65	5	Characterize PK profile of BAX326 and determine PK equivalence with Benefix
Biosimilarity or comparative PK, and inhibitor development studies						
Collins [81]	1) Benefix 2) IB1001	75 ± 5	32	14.8 - 64.5 (32.7) [29.9]	5	Establish PK non-inferiority of IB1001 to Benefix, safety, and efficacy
Kenet [82]	1) Prior FIX product 2) rFIX-FP	50	27	1 - 11 (5.9)	-	Evaluate PK, efficacy, and safety of rFIX-FP

Inhibitor development studies						
Negrier [83]	1) Prior FIX product 2) N9-GP	- 25/50/100	20	21 - 55 [30]	7	Determine safety by evaluating adverse events, antibody formation against FIX and N9-GP, physical examination, and clinical laboratory assessments
Powell [84]	1) Benefix 2) rFIXFc	50	22	-	5	Determine annualized bleeding rate and development of inhibitors
Solano Trujillo [85]	1) Immunine 2) BAX326	20 - 40 75 ± 5	44	1 - 55	-	Document exposure to Immunine and monitor for inhibitor development
- : Not specified						

Biosimilarity/bioequivalence testing employs various types of statistics that are dependent upon the trial design. Most trial designs for biosimilarity testing of clotting factors employed a 2x2x2 crossover design. All biosimilarity and comparative PK studies observed average biosimilarity or average mean PK parameter differences and did not examine individual differences. Average biosimilarity assesses the pharmacokinetic BSV but does not directly assess the differences within a subject over time. This may be reasonable given the a priori knowledge that clotting factor concentrates demonstrate a high pharmacokinetic BSV and low WSV within one brand [17] and therefore the assessment of individual biosimilarity may not be necessary. Individual biosimilarity assesses for both the mean and variability of PK metrics and also the ratio of the two drug products on an individual basis, and is recognized when both the average biosimilarity is established and the subject-by-formulation effect is insignificant. [86] Average biosimilarity is important to assess mean PK differences in a population but individual biosimilarity is highly impactful if the goal is to give prescribers confidence that biosimilarity will occur when a patient on one of the drug products is switched to the other.

In order for a drug to be therapeutically equivalent to another product, it requires the same active pharmaceutical ingredient, dosage form, strength, route of administration, and established bioequivalence. [87] Because clotting factors are not identical as they are biologics, the PK BSV and WSV of the two brands may not hold; this is not the case with small molecules, where the active pharmaceutical ingredient systemic disposition is exactly the same between two drug products. As a result, the individual concentration-time profile of one factor concentrate can be different as compared to another factor concentrate of the same dose and frequency. If individual biosimilarity for two factor concentrates is established, they can be used interchangeably and the PK of one factor concentrate is therefore predictive of the other.

However, no study confirming individual patient biosimilarity has been completed because it is difficult to achieve. In a study by Di Paola et al., patients who switched from Advate to ReFacto had very different individual PK parameters even though the average PK parameters were similar. [47] Similar findings were observed with Martinowitz et al. [53] and Klamroth et al. (Figure 6) [52] The conclusion that two factor concentrates are bioequivalent does not mean that individuals will achieve the same concentration-time profile if the same dose is given. Likewise, similar average half-life between two factor concentrates does not mean that the half-life between two factor concentrates in any given individual will be similar; some individuals in Figure 6 had drastic differences in their PK across factor concentrates.

No study involving switching between factor concentrates where PK was assessed used this information to predict a proper dosing regimen.

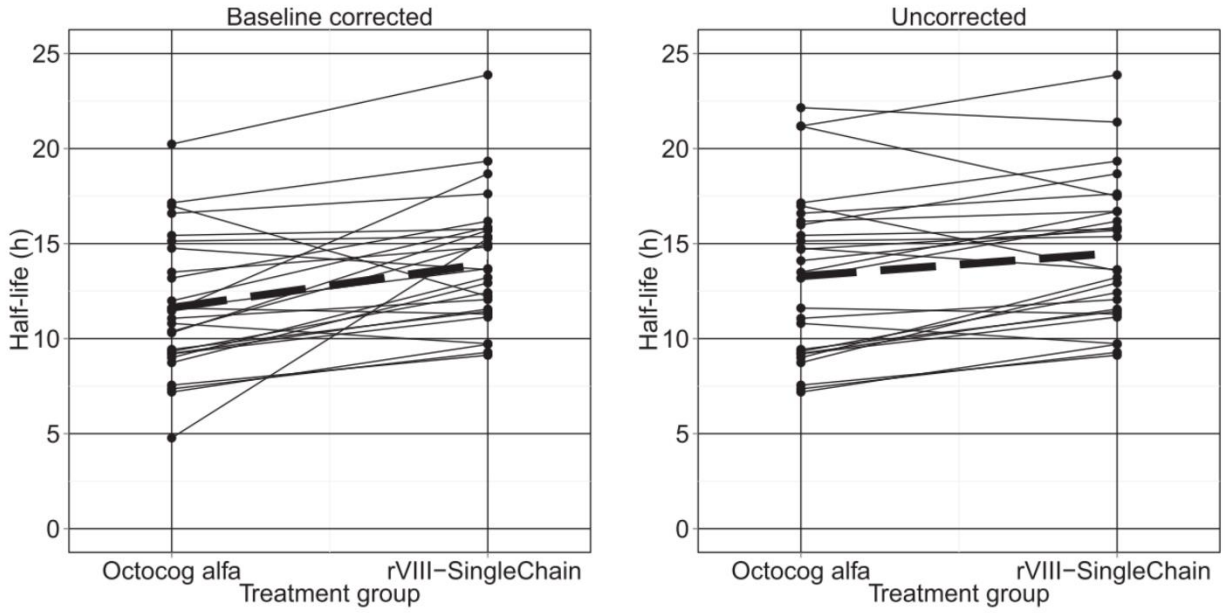

Figure 6. Example of individual PK parameters after switching.

2.3.3 Inhibitor Development Studies

The second type of study included patients serially taking at least two clotting factor concentrates and had the objective of examining inhibitor development. Inhibitors are antibodies that neutralize clotting factors. These inhibitors are generally measured using the Nijmegen modification of the Bethesda assay. [88, 89] Once inhibitors develop in a hemophilia patient, it becomes much more difficult to treat them, resulting in an increase in morbidity and mortality in the affected population. [88, 90]

Eighteen articles were identified where their primary outcome was focusing on inhibitor development after switching factor concentrate products (Table 1 and 2). It was previously thought that switching between factor concentrates was associated with an increased risk of inhibitor development [91], but recent studies have not shown consistent results. [91, 92] Although PK data may have been used in their statistical analysis, dosing regimens of each factor concentrate were not tailored based on PK. It was unclear whether or not the dose provided to the patient post-switch was the optimal dosing regimen. Without knowledge of the dosing regimen in hemophilia subjects, it was also unclear whether the overdosing or under-dosing of factor concentrate had an effect on inhibitor risk.

No inhibitor study that incorporated PK into its assessment was usable to inform methods for PK-tailored dosing.

2.3.4 WAPPS-Hemo Data

As of September 15, 2018, there were over 250 centres enrolled worldwide with over 3000 patients and over 6300 infusions recorded. Infusion data was gathered for the purposes of determining the incidence of switching between factor concentrates.

A total of 2785 patients were taken from the WAPPS data platform. The methodology is presented in Figure 5. Out of the 2785 subjects, 449 (16%) had infusions on two or more concentrates with a total of 647 switches. A summary of patient demographics is presented in Table 3.

Table 3. Demographics from WAPPS patients who have switched between factor concentrates.

Parameter	**Whole cohort**	**FVIII**	**FIX**
Subjects (n)	449	394	55
Switches (n)	647	591	56
Age (y)	1 – 78	1 – 78	2 – 68
Body weight (kg)	10 – 150	10 – 150	13 – 117
As of September 2018.			

In terms of FVIII products, there were a total of 394 patients and 591 switches, accounting for 91% of total switches on WAPPS-Hemo. FVIII products, classified based on their molecular structure, are presented in Table 4. Out of the 591 switches, the majority of the switches (n = 293) occurred from 2nd- and 3rd-generation recombinant full-length products (50%). Two-hundred and eight switches (35%) occurred to extended half-life products, 73 switches (12%) occurred to B-domain-deleted products, 229 switches (39%) occurred to another recombinant full-length product, and 81 switches (14%) occurred to plasma-derived products.

In terms of FIX products, there were a total of 55 patients and 56 switches, accounting for 9% of total switches on WAPPS-Hemo. FIX products, classified based on their molecular structure, are presented in Table 5. Out of the 56 switches, the majority of switches in

WAPPS-Hemo occurred when switching from any FIX product to a recombinant Fc-fusion protein FIX product (n = 34), accounting for 61% of all FIX switches.

Table 4. Number of hemophilia A patients from WAPPS-Hemo switching between FVIII concentrates.

	FVIII Products	SWITCH TO											Total
		Plasma-derived	Plasma-derived with vWF	1st-gen rec. full-length	2nd-gen rec. full-length	3rd-gen rec. full-length	2nd-gen rec. BDD	3rd-gen rec. BDD	4th-gen rec. BDD	3rd-gen EHL rec. BDD-PEGylated	4th-gen EHL rec. Fc-Fusion	3rd-gen EHL rec. single-chain	
SWITCH FROM	Plasma-derived	2	8	6	9	2	3	1	0	0	6	0	**37**
	Plasma-derived with vWF	4	26	6	20	5	2	0	0	2	10	1	**76**
	1st-Gen rec. full-length	4	11	0	15	18	7	6	1	0	2	0	**64**
	2nd-Gen rec. full-length	5	16	16	24	57	6	2	4	2	56	3	**191**
	3rd-Gen rec. full-length	0	0	8	5	6	3	13	4	12	50	1	**102**
	2nd-Gen rec. BDD	1	2	5	7	0	0	1	0	0	1	0	**17**
	3rd-Gen rec. BDD	0	0	0	0	2	1	5	2	2	19	1	**32**
	4th-Gen rec. BDD	0	1	0	0	0	0	0	0	0	4	0	**5**
	3rd-Gen EHL rec. BDD-PEGyl	0	0	0	1	3	0	0	0	0	0	0	**4**
	4th-Gen EHL rec. Fc-Fusion	0	1	0	4	9	0	6	6	30	0	0	**56**
	3rd-Gen EHL rec. single-chain	0	0	0	1	0	0	0	0	1	5	0	**7**
	Total	**16**	**65**	**41**	**86**	**102**	**22**	**34**	**17**	**49**	**153**	**6**	**591**

Table 5. Number of hemophilia B patients from WAPPS-Hemo switching between FIX concentrates.

FIX Products		SWITCH TO					Total
		Plasma-derived	Recombinant	Recombinant glycoPEGylated	Recombinant Fc-fusion protein	Recombinant albumin fusion protein	
SWITCH FROM	Plasma-derived	4	1	0	11	1	**17**
	Recombinant	0	1	1	22	7	**31**
	Recombinant glycoPEGylated	0	0	0	0	0	**0**
	Recombinant Fc-fusion protein	1	0	1	0	5	**7**
	Recombinant albumin fusion protein	0	0	0	1	0	**1**
	Total	**5**	**2**	**2**	**34**	**13**	**56**

2.4 Discussion

While literature states the average of PK parameters (e.g. half-life) when switching between factor concentrates, the range of such PK parameters can be highly variable. A study by Mahlangu et al. compared the terminal half-life of the recombinant FVIII Fc fusion protein, Eloctate, with a standard-acting factor VIII concentrate (Advate) in a phase 3 study to determine the safety, efficacy, and PK. [62] On average, the half-life of Eloctate was 1.5 times that of Advate at a dose of 50 IU/kg. [62, 69] This provides valuable information about the population, although it is clear from the breadth of factor concentrate brands being switched to and from as identified in the WAPPS-Hemo database that this type of study cannot be completed for all scenarios. A study by Young et al. demonstrated that the individual half-life ratios of FVIII and Eloctate ranged from 0.79 to 2.98. [69] Such high half-life variability within an individual across FVIII products makes the application of the mean population difference irrelevant for use in individual dosing recommendations.

Of particular note was there was a lack of evidence that standard-acting factor concentrates have shorter half-lives than long-acting factor concentrates at the individual level. In the study by Klamroth et al., the majority of patients had increased half-life when switching from octocog alfa to a rFVIII-SingleChain concentrate, however this was not the case for 4 out of 27 subjects. [52] The potential risk of assuming an increase in half-life when switching from a standard-acting to a long-acting concentrate may lead to increased risk of bleeds due to under dosing. Without assessing individual PK parameters, the current approach of using population level information to switch between factor concentrates may not yield expected results.

It would be desirable to estimate dosing regimens across a switch using an individualized approach. In an ideal scenario, where population PK tailored prophylaxis was widely adopted,

patients planning on switching to a different factor concentrate would have information regarding their own PK estimates on their current factor concentrate. In theory, combining the knowledge of the individual's PK of a factor concentrate prior to the switch (origin concentrate) with the knowledge of the population PK characteristics of the concentrate after the switch (destination concentrate) may potentially lead to the ability to predict individual PK estimates of the destination concentrate. The accuracy and precision of such an approach have not yet been studied and empirical demonstration of the feasibility of the process is first required. However, the perspective of enabling better estimation of individual PK on the destination concentrate is undoubtedly appealing. This is an example of a research project that could be performed with the rich WAPPS-Hemo database that contains many hemophilia subjects who have switched between different factor concentrates.

2.5 Study Limitations

The volume of literature we expected to find in this specific field was limited. As such we have not registered the protocol or used the PRESS checklist when conducting our search strategy. We cast a wide net with regards to our search terms but we are aware that this will limit the internal and external validity of our results.

2.6 Conclusion

Hemophilia treatment requires accurate and individualized dosing regimens in order to provide safe, effective, and cost-effective medication use. Although studies looking at bioequivalence/biosimilarity or assessing PK between two factor concentrates have led to PK comparisons, these studies lack the information required to predict an optimal dosing regimen for hemophilia patients starting on a new product. Studies that have examined the development of inhibitors did not mention the use PK parameters to optimize a dosing regimen. As such, there exists no literature on the role or use of PK in optimizing factor concentrate dosing during product switching.

Given these limitations, further research is required to utilize PK parameters from the origin product to predict the PK of the destination product in hemophilia patients. Due to similarity in PK parameters, especially across FVIII products [17], dose regimen predictability may be feasible using population PK methods and Bayesian forecasting. For example, standard-acting FVIII concentrates may be compared with other standard-acting FVIII concentrates and, in the same way, with newer long-acting FVIII concentrates.

With the introduction of newer and longer-acting concentrates, the use of population PK methods will be an integral part in determining and predicting accurate dosing regimens for patients. The use of population PK can change the current “trial and error” approach into a safer dosing regimen that makes use of prior PK knowledge to ensure patient safety and mindful resource consumption.

Chapter 3: A comparison of methods for prediction of pharmacokinetics across factor concentrate switching in hemophilia patients

This chapter is reflective of an original manuscript published by the Ph.D. candidate (Jacky Ka-Hei Yu) in Thrombosis Research. All pertinent dialogue in this chapter was written by the Ph.D. candidate.

Yu JK, Iorio A, Chelle P, Edginton AN. A comparison of methods for prediction of pharmacokinetics across factor concentrate switching in hemophilia patients. Thromb Res. 2019; 184:31-37. DOI: 10.1016/j.thrombres.2019.10.023.

3.1 Introduction

Hemophilia A is a genetic disorder caused by a deficiency in clotting factor VIII production. People with untreated hemophilia have significantly lower life expectancy [93] and may develop hemophilic arthropathy, which impairs mobility and quality of life. [5] The severity of hemophilia is dependent on the endogenous levels of FVIII activity (severe defined as < 1 IU/dL or < 1%, moderate as 1-5%, and mild as equal or greater than 5%). [5] Historically, FVIII infusions were administered to treat an acute bleed (on-demand), but this treatment modality was found to be suboptimal when compared to prophylactic treatment in terms of reducing the number of bleeds and minimizing joint damage. [94] People with severe hemophilia A are now often treated with prophylactic factor concentrate infusions in order to decrease the risk of joint deterioration and bleeds. [5, 13]

When initiating hemophilia A prophylaxis, FVIII concentrates are generally used at 20-40 international units per kg of body weight (e.g. 20-40 IU/kg), but this one-size-fits-all dosing method fails to account for the large inter-individual PK variability observed within the hemophilia population. [95] In order to optimize treatment, individual PK-tailored dosing may be a more effective method for ensuring that factor concentrate activities are maintained above target levels. [21] Back in 2001, the ISTH recommendations for PK studies of factor concentrates did not allow for adequate uptake of individual PK profiling as part of routine clinical practice. [28, 29] Building on the innovative application to hemophilia [21] of PopPK with subsequent Bayesian estimation (leveraging prior knowledge available from a patient population and thus requires only a few blood samples from a single patient to derive individual PK), [30, 32] the ISTH issued new guidelines [96] in 2017, which suggests using only a few blood samples from a single patient to derive individual PK.

The main focus of PopPK modeling is to quantify and describe the variability of a drug's PK in a population. [27] Variability can be explained by incorporating covariates such as demographic (age, sex, body weight, race), genetic (blood group or other phenotypes), or physiological (medical conditions, pregnancy) characteristics into our model. [27] Although covariates may explain a large portion of the observed BSV, there is still a remaining amount of unexplained variability. [97] This residual variability accounts for the difference between an individual's PK parameter value, such as CL, and the average value in the population after accounting for the covariates, and is typically represented by using an eta-value (η). [33] When inputting the specific values of the covariates for the patient, estimation of η can be performed using Bayesian methods, leading to stable PK parameter estimates in limited sampling cases. [96]

The use of PopPK models and Bayesian forecasting provides the optimal way to estimate individual PK profiles in order to design appropriate treatment regimens for people with hemophilia treated with factor concentrates. [42] Since the practical adoption of PopPK is beyond the technical capacity of most individual clinicians, the WAPPS-Hemo has been implemented as an online platform to facilitate hemophilia treatment optimization using individual PK profiling. Clinicians input patient characteristics and 2 to 3 post-infusion factor VIII/IX plasma levels, receive an expert-reviewed individual PK estimate report, use a simple clinical calculator module to tailor a treatment regimen, and have the option to activate a mobile app (myWAPPS) for the patient to provide him with real-time estimated factor activity levels.

As it is rare for people with hemophilia to use the same FVIII product throughout their life, [88] clinicians acquire new individual PK and re-design a dosing regimen for their patients when they switch factor concentrates. Factor concentrate switches may be prompted by the

availability of new, improved concentrates [98] by termination of national contracts resulting in a discontinuation of drug coverage, hypersensitivity to their current drug formulation, or adverse drug reactions. [35] Hemophilia A patients will likely switch between FVIII concentrates at some point or at multiple points in their life, but current recommendations do not formally take into account what was learned on a current concentrate when switching to a new one. [42] Clinically, a patient switching from one concentrate to a new one is either maintained on the same dose and frequency, or is prescribed the average dose and frequency indicated in the drug label or package insert. Indeed, patients may be switching from a regimen tailored on individually documented PK parameters to one based on average PK parameters.

The lack of PK-tailored guidance when switching from one product to another may result in a period of time where treatment may increase the risk of inappropriate dosing, leading to either an increased risk of bleeds or waste of expensive factor concentrate. While the PopPK models in WAPPS-Hemo can determine individual PK for each factor concentrate, extrapolating PK from one product to another has not yet been explored. Knowledge of an individual's PK on one brand and how their PK parameters differ from the population (e.g. by using their η-values) may be useful knowledge that can be applied to predict their PK for the switched brand. We hypothesize that the knowledge of η-values of the current factor concentrate will help predict PK of a new factor concentrate.

3.2 Methods

3.2.1 Study Population

3.2.1.1 Patient switching between two different standard half-life FVIII concentrates

Pharmacokinetic data from people with severe hemophilia A (n = 15, mean age = 23.3 years) with a baseline FVIII activity level of < 0.01 IU/mL was obtained from an open-label, sequential dosing study (NCT00837356) by Novo Nordisk. [53] The study aimed to compare PK properties of two serum-free FVIII products, octocog alfa (Advate; Baxter, Deerfield, IL) and turoctocog alfa (Novoeight; NovoNordisk, Copenhagen, Denmark). Subjects received a single intravenous dose of 50 IU/kg of Advate followed 4 days later by a single intravenous dose of 50 IU/kg of Novoeight. Blood samples were taken prior to and 0.25, 0.5, 1, 4, 8, 12, 24, and 48 hours after dose administration (average number of samples = 8). [53] Factor activity levels of < 0.0125 IU/mL were considered to be below the limit of quantification (BLQ).

3.2.1.2 Patient switching from standard to extended half-life FVIII concentrates

Pharmacokinetic data from people with hemophilia A was obtained from a phase III study (NCT01181128) by Bioverativ Therapeutics Inc. [62] This study was an open-labeled, multicenter, partially randomized study of recombinant FVIII Fc fusion protein (rFVIIIFc), Eloctate (Bioverativ, Waltham, MA) enrolling 165 male patients aged ≥ 12 years with severe hemophilia A. [62] A subgroup of these patients (n = 29, mean age = 31 years) had sequential PK evaluations using Advate for comparison. An injection of Advate 50 IU/kg was administered and samples were taken over 72 hours (average number of samples = 8). After a washout period, an injection of Eloctate 50 IU/kg was administered, and samples were taken over 120 hours (average number of samples = 7). Factor activity levels of < 0.005 IU/mL were considered to be BLQ. [62]

3.2.2 PK Analysis

Three concentrate-specific (Advate, Novoeight, Eloctate) PopPK models were used as prior information in the Bayesian estimation of this study. The PopPK models were developed for WAPPS-Hemo and the details are published elsewhere. [99, 100] All three PK models were two-compartment models including CL, intercompartmental clearance (Q), central volume (V_1), and peripheral volume (V_2), with BSV on CL and V_1. With respect to covariates, CL, V_1, and V_2 are a function of fat-free mass (FFM) [101] and CL is a function of age. [102] The three PopPK models were built on dense PK data from pivotal studies, including the data used in this study (Table S1).

Ultimately, Bayesian forecasting is estimating BSV terms within their distributions as assumed in the PopPK models. As an illustration of using a PopPK modelling approach [102], a patient *i* with known FFM (FFM_i) and age (Age_i), and who is infused with Advate, will have a Bayesian estimate for CL (CL_i) of:

$$CL_i[L/h] = CL_{pop}\left(\frac{FFM_i}{median\ FFM}\right)^{\theta_{FFM}}\left(1 + \theta_{AGE} \times \frac{\max\left(0, Age_i - median\ Age\right)}{median\ Age}\right)e^{\eta_i}$$

where CL_{pop} is the typical clearance value for the population, θ_{FFM} is the effect of fat-free mass on CL, θ_{AGE} is the effect of age on CL, η_i is the estimated deviation of CL of patient *i* from a typical individual with same FFM and age. For each BSV term of each PopPK model, the distributions of η were assumed normal with a standard deviation (SD) σ (e.g. CL and V_1 were assumed log normally distributed).

To ensure that the estimated PK parameters did not bring any bias in the predictions of the trial, the Bayesian method was compared to a non-compartmental analysis (NCA). The NCA was performed using the MATLAB® *sbionca* function. The regression was performed following the recommendation from the Pharmaceuticals Users Software Exchange [103] with a minimum

of 4 points per individual. Individuals who did not meet the requirements from the recommendation were excluded from the comparison with Bayesian forecast.

3.2.3 Experimental Design

Three methods were used to assess PK prediction accuracy during switching from a first product (Advate or Novoeight) to a second product (Novoeight or Eloctate when the first product was Advate, Advate when the first product was Novoeight). Table 6 presents the three methods used to predict the individual PK parameters (CL, V_1, Q, and V_2) on the second product.

- Method 1 used the typical population value of CL, V_1, Q, and V_2 of the second product from its PopPK model. This method assumes that all individuals have the same PK parameters.
- Method 2 used the calculated values of CL, V_1, Q, and V_2 for the second product based on the individual with a given set of covariates and the PopPK model of the second product. This method assumes that all individuals with identical fat-free mass and age will have the same PK parameters.
- Method 3 used the values of CL, V_1, Q, and V_2 for the second product based on an individual with a given set of covariates and the PopPK model of the second product, along with the predicted η-values of CL and V_1 from the first product and its PopPK model. This method takes into account what had happened on the first product in addition to Method 2.

Table 6. Three methods and the information gathered from PopPK models of the two products to estimate PK of the second product.

	PopPK model of first product	PopPK model of second product
Method 1	-	$\begin{Bmatrix} CL = CL_{pop} \\ V_1 = V_{1_{pop}} \\ Q = Q_{pop} \\ V_2 = V_{2_{pop}} \end{Bmatrix}$
Method 2	-	$\begin{Bmatrix} CL = CL_{pop} \times f_{CL}(FFM, AGE) \\ V_1 = V_{1_{pop}} \times f_{V1}(FFM) \\ Q = Q_{pop} \\ V_2 = V_{2_{pop}} \times f_{V2}(FFM) \end{Bmatrix}$
Method 3	η_{CL} and η_{V1} calculated from first product	$\begin{Bmatrix} CL = CL_{pop} \times f_{CL}(FFM, AGE) \times e^{\eta_{CL}} \\ V_1 = V_{1_{pop}} \times f_{V1}(FFM) \times e^{\eta_{V1}} \\ Q = Q_{pop} \\ V_2 = V_{2_{pop}} \times f_{V2}(FFM) \end{Bmatrix}$

Age is in years, fat-free mass (FFM) is in kg. CL, clearance; CL_{pop}, population clearance; Q, intercompartmental clearance; Q_{pop}, population intercompartmental clearance; V_1, central volume; V_{1pop}, population central volume; V_2, peripheral volume; V_{2pop}, population peripheral volume; $\theta_{AGE\text{-}CL}$, age effect on clearance; $\theta_{FFM\text{-}CL}$, fat-free mass effect on clearance; $\theta_{FFM\text{-}V1}$, fat-free mass effect on central volume; $\theta_{FFM\text{-}V2}$, fat-free mass effect on peripheral volume; η_{CL}, Unaccounted between-subject variability on clearance; η_{V1}, Unaccounted between-subject variability on central volume.

Method 3 assumes that percentiles of deviation are equivalent between PopPK models. Using the first product PopPK model, Bayesian forecasting was performed for each individual in the trial to obtain the individual η-values for CL and V_1 (η_1). Corresponding individual η-values for the second product (η_2) were calculated from η-values of the first product (η_1) assuming that the percentiles of deviation were equivalent between the two PopPK models. Operationally, η_2 was obtained by multiplying η_1 by the ratio between the standard deviations of the BSV of the PK parameters of the first (σ_1) and second (σ_2) products as shown:

$$\eta_2 = \eta_1 \times \frac{\sigma_2}{\sigma_1}$$

An example of the scaling algorithm is provided in **Figure 7**. The individual predicted η-value for CL and V_1 of the second product was then used in addition to individual covariates to estimate individual values of CL and V_1. Once all PK parameters were predicted for an

individual, the predicted values of half-life, time-to-0.05, -0.02, -0.01 IU/mL and plasma factor activity at 24h, 48h, and 72h were derived using the PK parameters and dose administered.

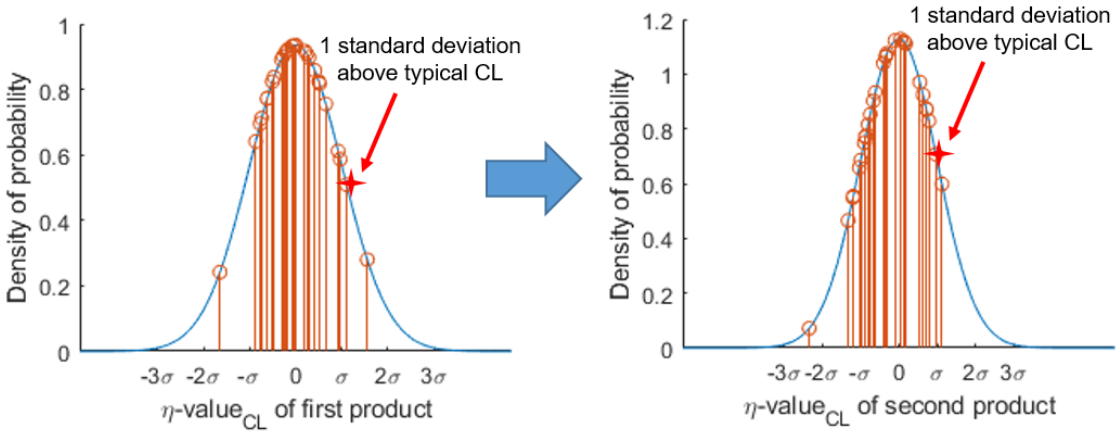

Figure 7. Converting η-values of e.g. Advate CL to Eloctate CL. The observed η-values of Advate CL have a mean of 0 and a standard deviation of σ_{ADV}. The distribution is divided by σ_{ADV} to obtain an η-distribution with a mean of 0 and standard deviation of 1. The normalized η-distribution of Advate is assumed to be equivalent to the predicted η-distribution of Eloctate. Lastly, the η-values used to predict Eloctate PK parameters are multiplied by the standard deviation of σ_{ELO} to obtain the predicted η-values of Eloctate. η, individual deviation of a PK parameter from the population; σ_{ADV}, standard deviation of Advate η-values; σ_{ELO}, standard deviation of Eloctate η-values.

3.2.4 Comparison of the different methods

To determine the most accurate method for predicting PK of the second product, absolute relative errors were calculated for each individual with regards to CL, V_1, half-life, time-to-0.05, -0.02, -0.01 IU/mL and plasma factor activity at 24h, 48h, and 72h. Absolute relative errors were calculated using the following equation:

$$Absolute\ relative\ error_{PK} = \left|\frac{PK_{pred} - PK_{est}}{PK_{est}}\right|$$

where PK_{pred} is the individual parameter prediction obtained using one of the three methods and PK_{est} is the actual PK value estimated with Bayesian forecasting using the second product PopPK model, individual covariates, and measured factor activity levels from the clinical studies. The method with the lowest mean and range of the absolute relative errors was considered to be the most accurate method. In addition, individual CL, V_1, half-life, time-to-0.05, -0.02, -0.01 IU/mL and plasma factor activity at 24h, 48h, and 72h were estimated with each of the three methods (PK_{pred}) and were regressed against the observed values (PK_{est}). Any regression line (PK_{pred} vs. PK_{est}) with a 95% CI that included the line of identity (slope of 1) indicated that the method was considered to be able to accurately predict the estimated PK.

3.2.5 Software

Bayesian forecasting and PK predictions were performed using non-linear mixed effects modelling as implemented in NONMEM (version 7.3, ICON, Hanover, MD) [104]. Graphics for model evaluation and statistical analysis were created using MATLAB® (version 2017b, The MathWorks, Natick, MA).

3.3 Results

3.3.1 NCA versus Bayesian method

The typical NCA and Bayesian half-life estimates are found in Table S2. NCA was flagged as unreliable for 1 instance (Advate from the Advate to Eloctate dataset) according to the relevant guidelines. [103] The remaining instances showed an average difference in half-life estimates for NCA as compared to the Bayesian method of 0.37h (Advate), 0.23h (Eloctate), 0.42h (Advate), and 0.70h (Novoeight) (Figure 8).

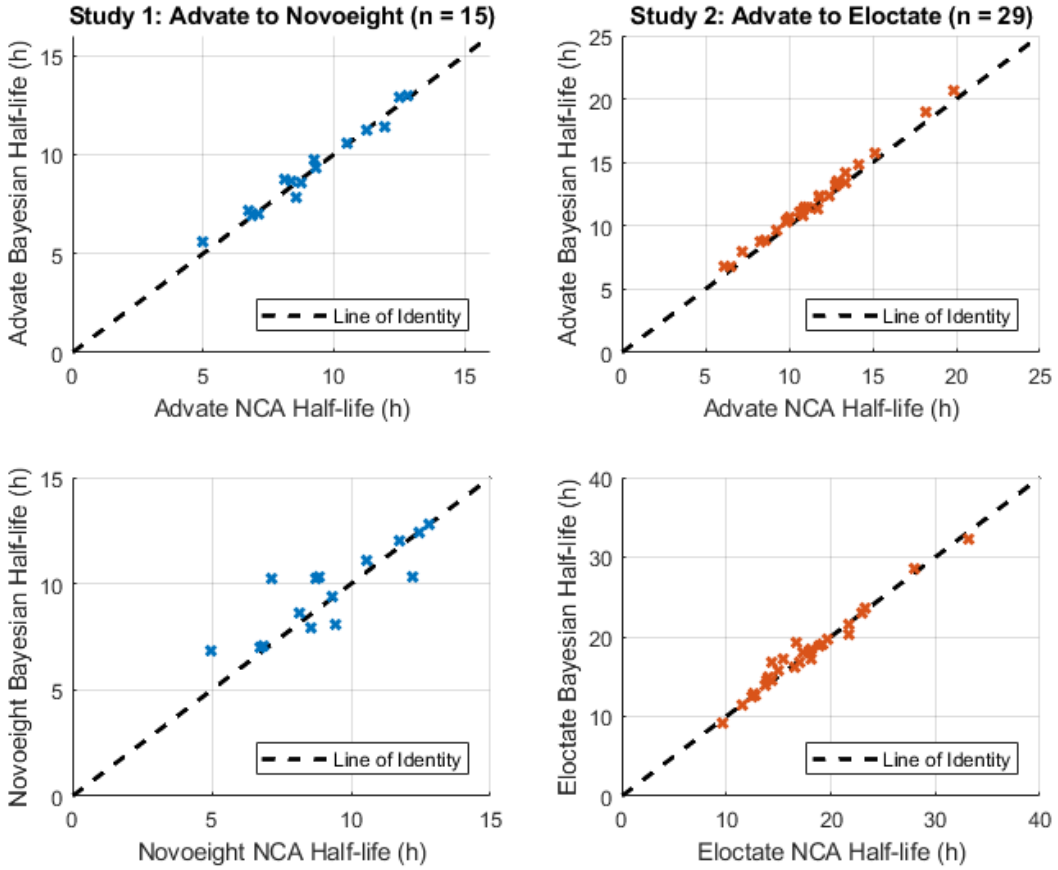

Figure 8. Non-compartmental analysis vs. Bayesian forecasting half-life predictions.

3.3.2 Comparative performance of the three prediction methods

The mean and range of absolute relative errors were lowest for method 3 across all studies and all PK outcomes (Table 7). The regression lines for each of the PK outcomes using method 1 and method 2 were significantly different from the line of identity, while only some were different using method 3 (Table 8). The slope for method 3 was closer to the line of identity than the other two methods for all PK outcomes (examples shown in Figure 9, Figure 10, and Figure 11).

Individual predicted half-lives are reported in Table S3. Method 3 produced predicted half-lives closest to the observed half-life 66.7%, 66.7%, and 48.3% of the time for Advate to Novoeight, Novoeight to Advate, and Advate to Eloctate respectively.

Table 7. Mean absolute relative errors of subjects' predicted PK outcomes switching between FVIII products.

PK outcomes (units)	Mean Absolute Relative Error in % [range]								
	Advate to Novoeight			Novoeight to Advate			Advate to Eloctate		
	Method 1	Method 2	Method 3	Method 1	Method 2	Method 3	Method 1	Method 2	Method 3
Clearance (L/h)	30.3 [1-64]	28.9 [4-58]	19.8 [4-58]	35.7 [5-62]	33.6 [6-60]	16.7 [4-37]	31.5 [1-155]	29.1 [0-129]	27.3 [0-62]
Volume (L)	23.0 [2-47]	17.2 [4-50]	14.1 [1-32]	26.8 [10-45]	20.6 [3-38]	13.1 [1-26]	15.2 [1-37]	12.6 [0-29]	11.4 [0-27]
Half-life (h)	22.2 [3-58]	27.6 [0-63]	11.6 [0-33]	28.9 [2-93]	33.3 [5-96]	13.1 [0-48]	21.2 [2-68]	18.8 [3-66]	13.6 [0-34]
Time to 0.05 IU/mL (h)	33.5 [0-90]	35.3 [1-91]	13.0 [0-35]	39.9 [1-122]	41.5 [0-121]	14.9 [0-54]	21.6 [0-61]	19.7 [1-60]	15.2 [1-35]
Time to 0.02 IU/mL (h)	30.1 [1-79]	33.0 [1-83]	12.5 [1-34]	36.5 [2-114]	39.0 [2-114]	14.3 [1-52]	21.4 [1-63]	19.5 [1-62]	14.8 [1-35]
Time to 0.01 IU/mL (h)	28.0 [1-72]	31.5 [1-77]	12.2 [0-34]	34.4 [1-109]	37.4 [2-109]	13.9 [0-51]	21.3 [1-64]	19.3 [2-63]	14.5 [1-35]
Concentration at 24 h (IU/mL)	89.4 [4-290]	82.1 [1-253]	23.1 [0-56]	116.0 [1-455]	109.8 [1-431]	32.1 [0-129]	25.9 [1-82]	24.5 [0-82]	19.7 [1-49]
Concentration at 48 h (IU/mL)	126.8 [0-377]	134.8 [3-380]	30.2 [3-76]	161.7 [4-558]	167.4 [1-544]	43.8 [3-212]	46.4 [1-238]	43.3 [2-234]	28.1 [2-68]
Concentration at 72 h (IU/mL)	65.1 [2-143]	78.7 [3-184]	20.8 [0-69]	77.4 [6-163]	89.6 [6-184]	25.2 [0-88]	60.8 [1-321]	57.3 [1-312]	33.2 [4-66]

Table 8. Regression slope of predicted PK outcomes of each study.

PK	Slope (95% CI)								
	Advate to Novoeight			Novoeight to Advate			Advate to Eloctate		
	Method 1	Method 2	Method 3	Method 1	Method 2	Method 3	Method 1	Method 2	Method 3
Clearance	0	0.09 (0.02, 0.16)	0.81 (0.47, 1.14)	0	0.07 (-0.01, 0.15)	0.86 (0.50, 1.21)	0	0.16 (0.00, 0.32)	0.92 (0.68, 1.17)
Central volume	0	0.08 (-0.25, 0.41)	0.47 (0.04, 0.90)	0	0.32 (0.00, 0.64)	0.68 (0.08, 1.27)	0	0.59 (0.40, 0.77)	0.85 (0.69, 1.02)
Half-life	0	-0.12 (-0.30, 0.06)	0.84 (0.39, 1.28)	0	0.05 (-0.11, 0.22)	0.67 (0.31, 1.03)	0	0.15 (0.02, 0.29)	0.66 (0.51, 0.81)
Time to 5%	-0.08 (-0.23, 0.06)	-0.06 (-0.26, 0.13)	0.81 (0.42, 1.20)	0.05 (-0.10, 0.20)	0.12 (-0.08, 0.32)	0.73 (0.38, 1.09)	0.07 (0.00, 0.13)	0.18 (0.05, 0.31)	0.66 (0.52, 0.80)
Time to 2%	-0.07 (-0.17, 0.03)	-0.08 (-0.27, 0.11)	0.82 (0.42, 1.23)	0.03 (-0.08, 0.15)	0.10 (-0.09, 0.29)	0.71 (0.36, 1.07)	0.05 (0.00, 0.10)	0.17 (0.04, 0.30)	0.66 (0.52, 0.80)
Time to 1%	-0.06 (-0.14, 0.02)	-0.09 (-0.28, 0.10)	0.83 (0.42, 1.25)	0.03 (-0.06, 0.11)	0.09 (-0.09, 0.28)	0.70 (0.35, 1.06)	0.04 (0.00, 0.08)	0.17 (0.04, 0.30)	0.66 (0.52, 0.80)
Concentration at 24h	-0.15 (-0.45, 0.15)	-0.05 (-0.27, 0.18)	0.71 (0.35, 1.08)	0.14 (-0.22, 0.50)	0.20 (-0.05, 0.46)	0.80 (0.40, 1.19)	0.27 (0.07, 0.46)	0.26 (0.11, 0.40)	0.72 (0.58, 0.86)
Concentration at 48h	-0.12 (-0.31, 0.07)	-0.11 (-0.37, 0.15)	0.71 (0.35, 1.06)	0.06 (-0.18, 0.30)	0.15 (-0.17, 0.47)	0.81 (0.41, 1.22)	0.12 (0.02, 0.21)	0.20 (0.07, 0.33)	0.63 (0.50, 0.76)
Concentration at 72h	-0.08 (-0.23, 0.06)	-0.14 (-0.45, 0.17)	0.70 (0.35, 1.06)	0.03 (-0.15, 0.21)	0.12 (-0.26, 0.49)	0.81 (0.40, 1.21)	0.06 (0.01, 0.11)	0.16 (0.04, 0.27)	0.55 (0.43, 0.66)

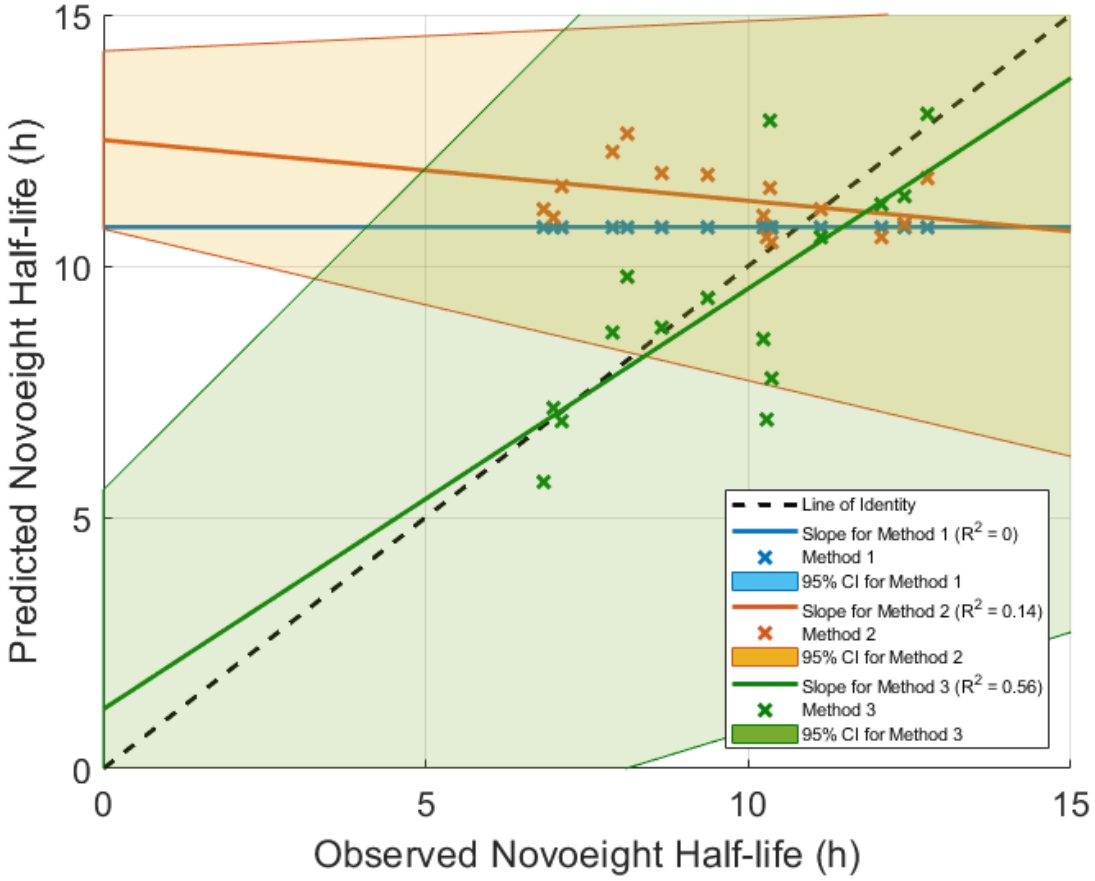

Figure 9. Comparison between regression lines using each method to estimate individual half-life on Novoeight for patients switching from Advate to Novoeight. Method 3 has the closest regression line compared to the line of identity (dashed line) and tends to better predict individuals with extreme half-life values. The coefficient of determination (R^2) refers to the fit to the line of identity. CI; confidence interval.

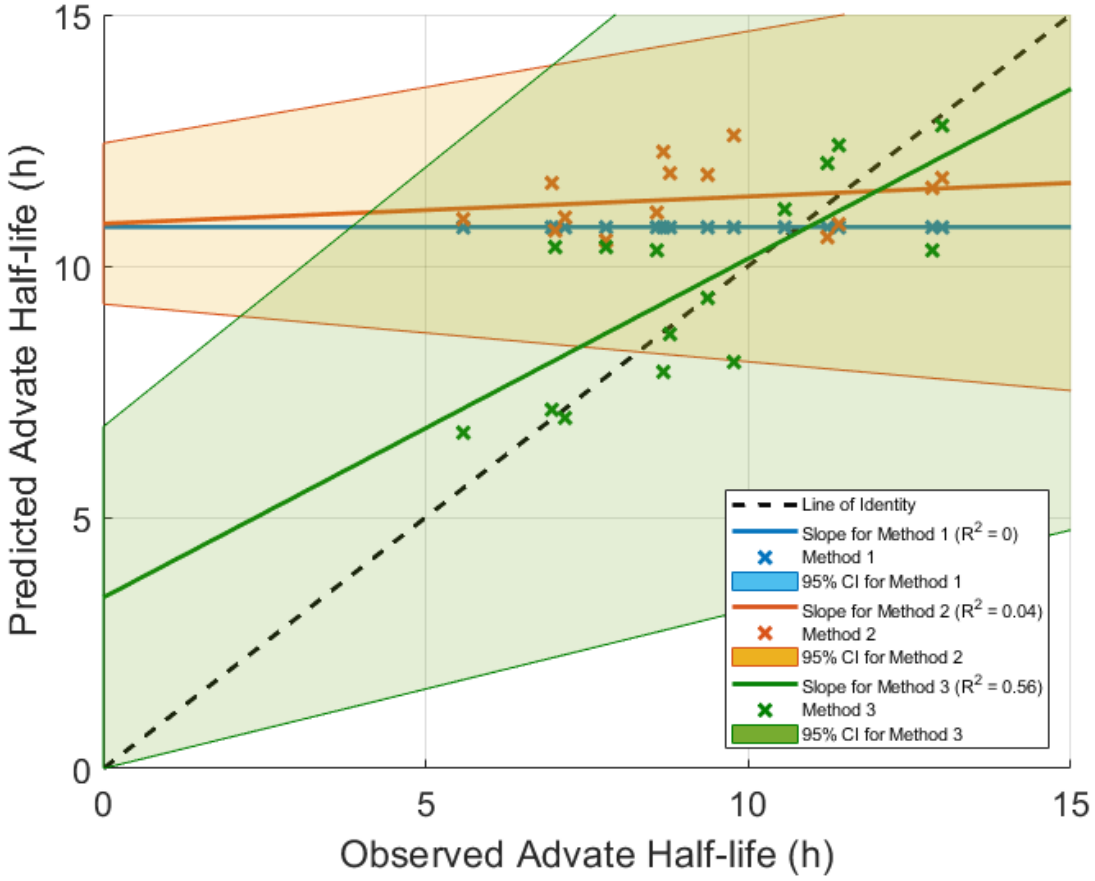

Figure 10. Comparison between regression lines using each method to estimate individual half-life on Advate for patients switching from Novoeight to Advate. Method 3 has the closest regression line compared to the line of identity (dashed line) and tends to better predict individuals with extreme half-life values. The R^2 refers to the fit to the line of identity. CI; confidence interval.

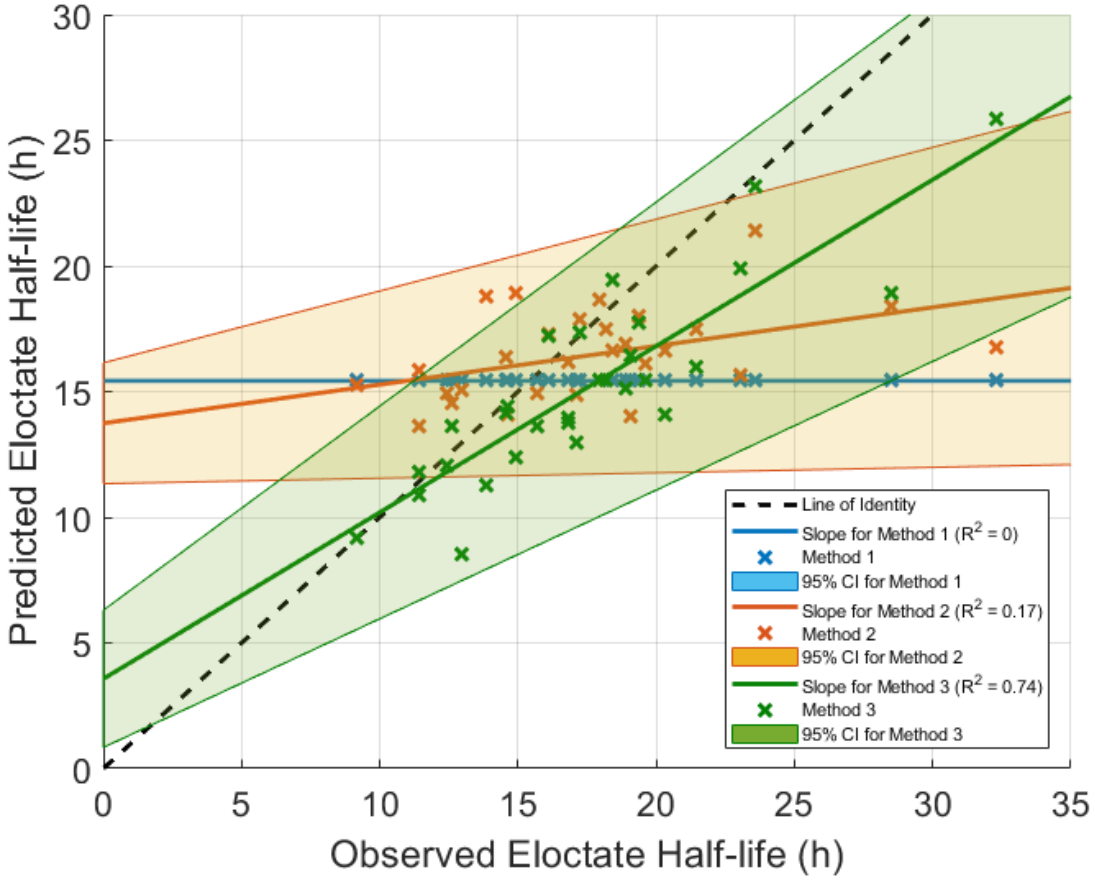

Figure 11. Comparison between regression lines using each method to estimate individual half-life on Eloctate for patients switching from Advate to Eloctate. Method 3 has the closest regression line compared to the line of identity (dashed line) and tends to better predict individuals with extreme half-life values. The R^2 refers to the fit to the line of identity. CI; confidence interval.

3.4 Discussion

We have established that the use of information from the PK profile on a current factor VIII concentrate can be used to predict the individual PK profile on a future concentrate, reducing the relative error in predicting half-life by 16.0%, 20.2%, and 5.2% (Advate to Novoeight, Novoeight to Advate, and Advate to Eloctate respectively) as compared to Method 2 for estimating half-life on the new concentrate. Adoption of Method 3 in clinical practice can reduce the likelihood of improperly dosing patients when switching among different factor concentrates.

Currently, hemophilia switching guidelines suggest initiating EHL FVIII products at the same dose as SHL FVIII products, reducing the frequency from three to two times weekly. [42, 96] This course of action, however, assumes all patients to have a similar half-life on the EHL FVIII product. On a population level, EHL products have been shown to have a longer half-life than SHL products, though this finding cannot be confirmed at an individual level. For instance, Young et al. have demonstrated that the individual SHL:EHL half-life ratio ranged from 0.79 to 2.98 concluding that some hemophilia patients exhibit a shorter half-life on an EHL product as compared to a SHL product while others have achieved near three-fold increase in half-life. [69]

As there is a high inter-individual variability and low within-subject variability in factor concentrate PK, this suggests that using PK-tailored individualized dosing may be appropriate for optimizing hemophilia treatment. [27, 33] The same variability comes into play when considering switching between different concentrates. We have shown that ignoring this variability (our Method 1), and dosing based on average population data is the least efficient approach, resulting in a high degree of imprecision when comparing estimated and measured PK outcomes. This is because there are individual factors that can influence the PK that are not taken

into account. The differences in the predicted to observed half-life ranged up to 17 hours, confirming that this approach is largely suboptimal for choosing a safe and effective dosing regimen for many individuals at the moment of switching.

The incorporation of covariates into the PopPK model that account for a portion of the BSV may lead to more precise estimated PK of individuals who are not represented by the typical patient in the population. Relevant covariates (such as age, body weight, blood type, and von Willebrand factor) have been shown to influence individual PK estimates and consequently factor concentrate activity levels. [17, 97, 105-109] Method 2 takes the covariate space into consideration when predicting individual PK across a switch. Some individuals were still not well represented from using this method, resulting in a mean relative error similar to that of Method 1 in terms of half-life (Table S3). For example, in the Advate to Eloctate study, the predicted half-life of one individual was 16 hours lower than observed; this difference would have a substantial clinical impact when deciding on a patient's dosing regimen, and this potential error could be due to some unexplained variability or other contributing factors not included in the PopPK model.

Using prior PK knowledge along with the PopPK model of the second product and individual covariates (Method 3) resulted in the lowest mean relative error compared to the prior two methods (Table S3). This method is more often better at predicting half-life in comparison to the other two methods, and particularly so for subjects with extreme values of half-life (Figure 9, Figure 10, and Figure 11). This suggests that using prior individual PK information (gathered on the first product) to predict the PK of the second product provides a reasonable starting point for dose determination. The predicted individual half-life can still differ from 0 up to 10 hours

compared to the estimated Bayesian values, which is significantly less compared to 17 hours for Method 1 and 16 hours for Method 2.

3.5 Study Limitations

Although using scaled η-values from the pre-switch concentrate in conjunction to the PopPK model of the second product and patient covariates has resulted in the lowest mean relative errors across all PK outcomes, none of the methods explored in this study was able to accurately predict PK outcomes to the extent where the observed vs. predicted regression line was equivalent to the line of identity. Since Method 3, thought to be the most precise, is not precise enough to be used in isolation, gathering blood samples and performing a new PK profile for the patient continues to be the recommended course of action for subjects switching factor concentrates. This method could be implemented into a platform such as WAPPS-Hemo and would provide valuable guidance around switching.

Another limitation is that this study only examined a limited number of hemophilia subjects. As hemophilia A is a rare disease, studies tend to be small and those that we used were no exception. Assessment of a higher number of patients across a wider breadth of factor concentrate products will be necessary to assess if method 3 would be useful in practice. Further, it is also unclear whether the normalized η-distribution of the current product could be assumed to be equivalent to the η-distribution of the future product. The η-values for CL or V_1 depend on which covariates are being taken into account for in the PopPK model. While in this study, the PopPK models used for switching incorporated the same covariates (fat-free mass and age) on the same parameters, other PopPK models that do not have the same covariate structure would produce η-values that describe different variabilities.

Further, the methods looked specifically at three factor concentrate products, Advate, Novoeight and Eloctate. The method should be continuously tested for switching between other products when the data become available.

3.6 Conclusion

This novel approach of using prior PK knowledge of individual η-values in order to predict PK of a new concentrate may aid in determining a safe and effective dosing regimen. Using this methodology may result in better outcomes compared to current guidelines as it uses prior individual PK knowledge to develop the regimen as opposed to arbitrarily giving the same dose with a different frequency as suggested in the guidelines. [96] This switching algorithm can be implemented on the WAPPS-Hemo platform to guide clinicians in estimating the individual impact of switching between FVIII concentrates and tailoring the initial regimen on the new concentrate while minimizing the time needed for dose optimization.

Chapter 4: A comparison of methods for prediction of pharmacokinetics when switching to extended half-life products in hemophilia A patients

This chapter is reflective of an original manuscript published by the Ph.D. candidate (Jacky Ka-Hei Yu) in Thrombosis Research. All pertinent dialogue in this chapter was written by the Ph.D. candidate.

Yu JK, Iorio A, Edginton AN. A comparison of methods for prediction of pharmacokinetics when switching to extended half-life products in hemophilia A patients. Thromb Res. 2020; 196:550-558. DOI: 10.1016/j.thrombres.2020.10.024.

4.1 Introduction

In hemophilia, it is rare for people to be treated using the same clotting factor concentrate for their entire lives. [88] Due to changes in national coverage or the development of extended half-life factor concentrates, people with hemophilia may switch to another factor concentrate that provides economical savings or a more convenient dosing regimen.

When switching to a new factor concentrate, it is currently recommended that an individual's PK profile should be generated upon the initial infusion and their dosing regimen be adjusted after their PK profile has been established. [42] Ideally, the individual would see some benefit (for example, decreasing the frequency when switching to an extended half-life product) from the switch. However, prior to switching, it is unknown whether the individual will benefit or not.

Most factor VIII concentrate regimens are started prophylactically based on international units per weight, but this "one-size-fits-all" approach does not account for the large PK variability between individuals. Dosing regimens should be individualized due to the high BSV and low inter-occasion variability (IOV) of factor VIII concentrates [17]. In 2017, the ISTH released recommendations [96] suggesting to use PopPK with subsequent Bayesian estimation in hemophilia in order to estimate individual PK parameters and ultimately tailor individual dosing regimens. The use of PopPK can help maintain an individual's factor activity level above a certain target threshold, typically between 1 to 5 IU/dL. [21]

PopPK models are used to describe observed drug exposure by quantifying typical PK parameters, such as CL and V_1, and their variability within a population based on physiological or clinical characteristics, otherwise known as covariates. [99, 110] The incorporation of covariates into a PopPK model can minimize unexplained BSV that is associated with PK

parameters. Each PopPK model is specific to its factor concentrate because the PK of each product can vary in ways that may be clinically significant. [99]

In a typical PopPK model, a PK parameter (for example, CL) for an individual (CL_i) is defined as a typical population value (CL_{pop}) with BSV, described as follows:

$$CL_i = CL_{pop} \times e^{\eta_i}$$

where η_i represents the individual deviation from the population value of the PK parameter. The eta-values (η) are normally distributed with a mean of 0 and a variance of ω^2. [111] While covariates (such as fat-free mass and age) can be incorporated into a PopPK model to describe variability thus explaining a component of BSV, the η-values indicate the unexplained BSV. In other words, the η-value is the unexplained variability not taken into account by explanatory covariates. η-values can be obtained for a new individual using Bayesian forecasting where the PopPK model is used as prior information, while patient covariates along with plasma samples of factor concentration activity over time provide a means to update the model and generate an individual PK estimation.

The use of a PopPK model to define an individual's PK, prior to switching to a new factor concentrate, typically involves inputting patient covariates into a PopPK model and setting the individual's η-value to 0 in order to obtain individual PK parameter predictions ("PopPK method"). This method provides a PK prediction for an individual typical for those covariates. Alternatively, it was previously hypothesized [112] that using knowledge of an individual's unexplained BSV (η-values) from their current factor concentrate derived using Bayesian forecasting ("η-method") may be beneficial in predicting the PK of another product. The η-method functions under the assumption that the prior η-values obtained from the first PopPK model is comparable to the second product. In other words, if two PopPK models are both

described using the same covariates, the unexplained BSV encompasses the same elements across the two factor concentrates and thus extrapolating individual PK from one product to another may be possible.

This η-method, however, has several drawbacks. First off, it has only been studied in clinical trial data and has not yet been tested in real world scenarios. The prediction accuracy of this method was also stated at a population level, thus there is no understanding of which individuals may benefit from using this method to predict PK over using a PopPK model alone. Finally, the η-defined method was only studied when switching from Advate, a SHL, to Eloctate, an EHL product. Switching between EHL products has not yet been explored.

The aim of this study is to explore whether the η-method results in better predictions of individual PK outcomes compared to the PopPK method when (1) using sparse data acquired from the WAPPS-Hemo database and when (2) switching from an EHL to another EHL factor concentrate. In addition, we wanted to (3) explore if patient characteristics could be linked to improved precision of PK outcomes and (4) whether the η-method was able to better predict individuals who would have a more favourable PK on another factor concentrate. The overarching goal is to implement this into a switching protocol for use in the WAPPS-Hemo platform, which (if successful) may provide clinicians with better guidance for assessing if switching between factor concentrates is beneficial for individuals.

4.2 Methods

4.2.1 Study Population

PK data was collected from clinical trial data and from clinician inputted data through the WAPPS-Hemo platform on March 3, 2020. Infusion data was collected from individuals administered Eloctate, as well as either antihemophilic factor (recombinant) pegylated (Adynovate) (including data from [100]) or a SHL product (either a recombinant full-length FVIII (rFVIII) or a recombinant B-domain deleted (BDD) FVIII). Individual factor activity levels (reported using the one-stage assay), demographics including body weight, age and height, PK parameters (CL, V_1, half-life, time-to-0.05/0.02/0.01 IU/mL, and factor activity level at 24/48/72h), and η-values of CL and V_1 were obtained. The most informative occasion with the most data points per infusion, at a minimum of three, was used. In the event more than one occasion fit this criteria, the infusion kept for analysis, in priority order, was the following:

a) Occasion with the most data points per infusion
b) Infusion including the furthest time point from the time of infusion
c) Infusion containing a predose
d) Infusion containing the fewest number of BLQs
e) Infusion that is most recently inputted into the WAPPS-Hemo platform

SHL products from the WAPPS-Hemo database that had less than 10 individuals taking the factor concentrate and switching to Eloctate were excluded from the study. If an individual had taken Adynovate, Eloctate, and a SHL FVIII, the most informative infusion for each factor concentrate was kept and the individual was included in all three switching analyses. If an individual had taken multiple SHL FVIII products, the most informative rFVIII and BDD FVIII infusion was kept for analysis.

4.2.2 PK Analysis

Three PopPK models were used as prior knowledge for Bayesian forecasting in this study (Table 9). The PopPK models for Adynovate, Eloctate, and generic FVIII were developed for WAPPS-Hemo and have been described elsewhere [99, 100, 113] The Adynovate PopPK model is a two-compartment model including CL, V_1, Q, and V_2, with BSV on CL and V_1, a fat-free mass effect on CL and V_1, and an age effect on CL. The Eloctate and generic FVIII PopPK models are two-compartment models including CL, V_1, Q, and V_2, with BSV on CL and V_1, a fat-free mass effect on CL, V_1, and V_2, and an age effect on CL. Individual time points with factor VIII activity levels below 1 IU/dL were considered to be BLQ.

Table 9. Three PopPK models developed for the WAPPS-Hemo platform.

Drug	PopPK model
Eloctate	$\begin{cases} CL = CL_{pop} \times f_{CL}(FFM, AGE) \times e^{\eta_{CL}} \\ V_1 = V_{1_{pop}} \times f_{V1}(FFM) \times e^{\eta_{V_1}} \\ Q = Q_{pop} \\ V_2 = V_{2_{pop}} \times f_{V2}(FFM) \end{cases}$
Adynovate	$\begin{cases} CL = CL_{pop} \times f_{CL}(FFM, AGE) \times e^{\eta_{CL}} \\ V_1 = V_{1_{pop}} \times f_{V1}(FFM) \times e^{\eta_{V_1}} \\ Q = Q_{pop} \\ V_2 = V_{2_{pop}} \end{cases}$
SHL FVIII	$\begin{cases} CL = CL_{pop} \times f_{CL}(FFM, AGE) \times e^{\eta_{CL}} \\ V_1 = V_{1_{pop}} \times f_{V1}(FFM) \times e^{\eta_{V_1}} \\ Q = Q_{pop} \\ V_2 = V_{2_{pop}} \times f_{V2}(FFM) \end{cases}$

As fat-free mass is not a mandatory input to record infusions into the WAPPS-Hemo platform, fat-free mass was calculated using the method by Al-Sallami et al [101] as follows:

$$FFM\ (kg) = \left[0.88 + \left(\frac{(1-0.88)}{\left[1 + \left(\frac{Age}{13.4}\right)^{-12.7}\right]}\right)\right] \cdot \left[\frac{(9270 \cdot BW)}{6680 + (216 \cdot BMI)}\right]$$

Where fat-free mass (FFM) is in kilograms, AGE is in years, body weight (BW) is in kilograms, and body mass index (BMI) is in kg/m^2.

4.2.3 Experimental Design

Two methods were used to assess PK prediction accuracy for three switching protocols: 1) Adynovate to Eloctate, 2) Eloctate to Adynovate, and 3) SHL FVIII to Eloctate. Table 10 presents the two methods used to predict the individual PK parameters (CL, V_1, Q, and V_2) on the second product.

Table 10. Information used to estimate PK of the second product.

Switch	Method	First product	Second product
Adynovate to Eloctate	**PopPK method**	-	Eloctate PopPK model
	η-method	η_{CL} and η_{V1} calculated from Adynovate PopPK model	
Eloctate to Adynovate	**PopPK method**	-	Adynovate PopPK model
	η-method	η_{CL} and η_{V1} calculated from Eloctate PopPK model	
SHL FVIII to Eloctate	**PopPK method**	-	Eloctate PopPK model
	η-method	η_{CL} and η_{V1} calculated from generic FVIII PopPK model	

SHL, standard half-life; η_{CL}, Unaccounted between-subject variability on clearance; η_{V1}, Unaccounted between-subject variability on central volume.

The PopPK method uses the calculated values of CL, V_1, Q, and V_2 for the second product based on the individual with a given set of covariates and the PopPK model of the second product. This method assumes that all individuals with identical fat-free mass and age will have the same PK parameters.

The η-method used the values of CL, V_1, Q, and V_2 for the second product based on an individual with a given set of covariates and the PopPK model of the second product, along with

the predicted η-values of CL and V_1 from the first product and its PopPK model. This method takes into account what had happened on the first product in addition to the PopPK method.

To illustrate incorporating η-values into a PopPK model to estimate PK parameters of a patient *i* on the second product (η-method), a patient may have a predicted individual clearance (CL_i) as follows:

$$CL_i = CL_{pop} \times (Cov)^{\theta_{Cov}} \times e^{\eta_i}$$

Where CL_{pop} represents the typical value of clearance, Cov represents a covariate, θ_{Cov} represents the covariate effect, and η_i is the estimated deviation in CL of patient *i* derived from the observed η-value of the first product. The η-value from the first product (η_1) is scaled for use by multiplying η_1 by the ratio between the standard deviations of the BSV of the PK parameters (CL and V_1) as shown:

$$\eta_2 = \eta_1 \times \frac{\sigma_2}{\sigma_1}$$

where the η-value of the second product (η_2) is used in the PopPK model of the second product, as performed in a previous study. [112] This ensures that if the CL of the individual was in the 80th percentile on the first product, they will be in the 80th percentile on the second product.

4.2.4 Comparing method performance in predicting PK outcomes

One of the primary outcomes of this study is the relative reduction in mean absolute percent difference of PK parameters (CL and V_1) and PK endpoints (half-life, time-to-5%, -2%, -1%, and factor activity at 24h) when comparing between the η-method and the PopPK method. Absolute percent differences are calculated using the following equation:

$$Absolute\ percent\ difference_{PK} = \left|\frac{PK_{pred} - PK_{ref}}{PK_{ref}}\right| \times 100\%$$

where PK_{pred} is the individual parameter prediction obtained using the PopPK method or the η-method, and PK_{ref} is the actual PK value obtained with Bayesian forecasting using the PopPK model, individual covariates, and measured factor activity levels on the second product. The absolute percent differences of all individuals were calculated to determine the arithmetic mean absolute percent difference. The method with the lowest arithmetic mean absolute percent difference was considered to be the method with the highest accuracy. The relative difference in mean absolute percent difference using the η-method compared to the PopPK method was calculated using the following equation:

$$Relative\ difference_{\eta-method} = \frac{Mean\ absolute\ percent\ difference_{PopPK\ method}}{Mean\ absolute\ percent\ difference_{\eta-method}} - 100\%$$

In addition, individual predicted (PK_{pred}) PK parameters and outcomes were regressed against the estimated values (PK_{ref}). Any regression line (PK_{pred} vs. PK_{ref}) with a 95% CI that included the line of identity (slope of 1) indicated that the method accurately predicted the estimated PK.

4.2.5 Comparing method performance in parsed individuals

The next objective was to identify groups of individuals who obtains a lower absolute percent difference from one method over the other. For each switching protocol (Table 10), individuals were split based on their η-values of CL and V_1 percentiles of the first factor concentrate into five subgroups (0-20th percentile, 20-40th percentile, 40-60th percentile, 60-80th percentile, and 80-100th percentile). The median between each subgroup's mean absolute percent difference on half-life and time-to-0.02 IU/mL using the two methods were compared for statistical significance using the Wilcoxon signed rank test. The infusions of patients with a baseline factor activity level above time-to-0.02 IU/mL were not taken into account for time-to-0.02 IU/mL analysis.

4.2.6 Predicting an increase or decrease in half-life

For all three switching protocols (Adynovate to Eloctate, Eloctate to Adynovate, and SHL FVIII to Eloctate), individual patient half-lives were determined using Bayesian forecasting for both products. Individuals who had at least a 12h increase in time-to-2% and time-to-1% after the switch were considered to have favourable PK on the second factor concentrate. The two methods were assessed to identify the proportion of correct predictions for individuals who had a 12h increase in time-to-2% and time-to-1% after the switch and if individuals were estimated to have an increase or decrease in half-life on the new product.

4.2.7 Software

The dataset was formatted for non-linear mixed effects modeling to perform Bayesian post hoc estimations in NONMEM (v7.3; ICON Development Systems, Ellicott City, MD, US), as described in McEneny-King et al. [114]

4.3 Results

A total of 231 Eloctate infusions, 200 SHL FVIII infusions, and 39 Adynovate infusions were included in this study. The SHL FVIII products which met the inclusion criteria were Advate, Kogenate, Kogenate FS, Kovaltry, Nuwiq, and ReFacto AF.

4.3.1 Data analysis and Bayesian methods

Subject demographics are summarized in Table 11. Thirty-nine infusions were measured on both Adynovate (mean age = 21.1, n = 39) and Eloctate (mean age = 20.3, n = 39). The mean (SD) half-life calculated using Bayesian forecasting for individuals on Adynovate and Eloctate were 15.3 (3.9) and 15.8 (5.2) hours, respectively. The mean predicted half-life for individuals on Adynovate was 15.0 (2.3) using the PopPK method and 16.7 (4.2) using the η-method when switching from Eloctate. The mean predicted half-life for individuals on Eloctate was 13.9 (2.6) hours using the PopPK method and 14.3 (4.5) hours using the η-method when switching from Adynovate.

Two hundred SHL FVIII infusions (mean age = 24.4, n = 195), and 195 Eloctate infusions (mean age = 25.3, 195 individuals) were included. The mean (SD) half-life calculated using Bayesian forecasting for individuals on Eloctate was 14.6 (5.5) hours. The average predicted half-life for individuals on Eloctate was 14.3 (3.4) hours using the PopPK method and 13.0 (4.5) hours using the η-method when switching from a SHL FVIII product.

Table 11. Demographic characteristics and half-life of subjects.

	n	Mean (SD)	[Min-Max]
WAPPS-Hemo dataset (Adynovate and Eloctate)			
Age, years	39		
Adynovate		21.1 (13.9)	[3-63]
Eloctate		20.3 (13.5)	[1-61]
Half-life, h	39		
Eloctate, Bayesian forecasting		15.8 (5.2)	[7-29]
Eloctate, PopPK method		13.9 (2.6)	[7-22]
Eloctate, η-method, switching from Adynovate		14.3 (4.5)	[5-25]
Adynovate, Bayesian forecasting		15.3 (3.9)	[9-25]
Adynovate, PopPK method		15.0 (2.3)	[13-23]
Adynovate, η-method, switching from Eloctate		16.7 (4.2)	[10-27]
WAPPS-Hemo dataset (SHL FVIII and Eloctate)			
Age, years	195		
SHL FVIII		24.4 (16.7)	[1-74]
Eloctate		25.3 (16.6)	[1-74]
Half-life, h	200		
SHL, Bayesian forecasting	200	10.1 (3.4)	[4-23]
Eloctate, Bayesian forecasting	195	14.6 (5.5)	[5-34]
Eloctate, PopPK method	195	14.3 (3.4)	[7-22]
Eloctate, η-method, switching from a SHL FVIII	200	13.0 (4.5)	[4-28]

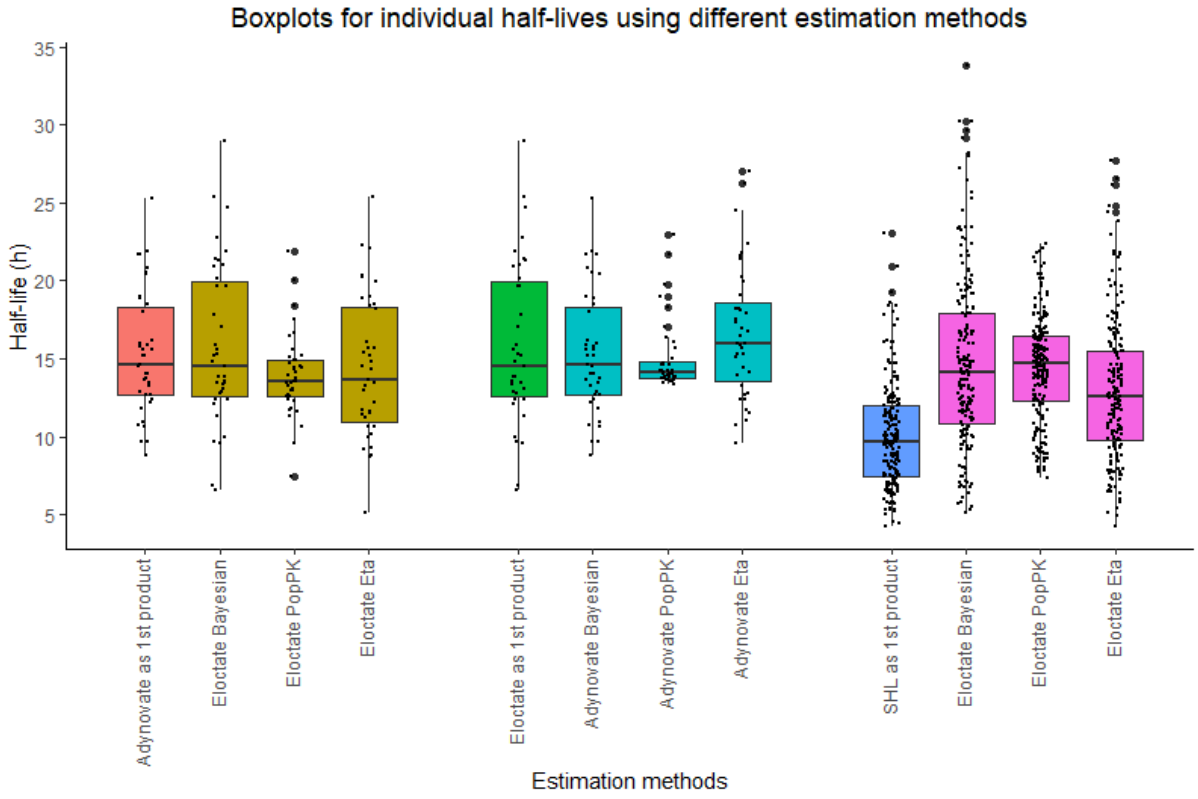

Figure 12. Boxplot for individual half-lives using different estimation methods.

4.3.2 Comparing method performance in predicting PK outcomes

Mean absolute percent difference and range of all PK parameters are reported in Table 12. In general, with the exception of V_1, the η-method produced slightly lower mean absolute percent differences compared to the PopPK method. For the three switching protocols (Adynovate to Eloctate, Eloctate to Adynovate, and SHL FVIII to Eloctate), the η-method resulted in a relative difference reduction in mean absolute percent difference of 27.8%, 4.9%, and 18.0% in half-life compared to the PopPK method respectively (Figure 12).

Table 12. Arithmetic mean absolute percent difference (%) for all switching protocols on the two methods for each PK outcome, grouped based on switching protocol.

PK outcomes (units)	Mean absolute percent difference in % [range]					
	Adynovate to Eloctate		Eloctate to Adynovate		SHL FVIII to Eloctate	
	PopPK method (N = 39)	η-method (N = 39)	PopPK method (N = 39)	η-method (N = 39)	PopPK method (N = 195)	η-method (N = 200)
Clearance (L/h)	25.7 [1-86]	21.0 [0-88]	21.6 [0-69]	15.0 [0-42]	28.0 [1-131]	30.8 [0-210]
Volume (L)	11.8 [1-74]	14.5 [1-90]	9.7 [0-39]	16.8 [1-59]	16.0 [0-127]	16.1 [0-154]
Half-life (h)	21.6 [0-51]	15.6 [1-59]	18.5 [0-57]	17.6 [0-129]	24.5 [0-136]	20.1 [0-79]
Time to 0.05 IU/mL (h)	22.1 [2-69]	14.7 [1-53]	19.5 [1-59]	16.2 [0-113]	26.1 [0-152]	20.9 [0-109]
Time to 0.02 IU/mL (h)	21.7 [1-63]	14.5 [2-56]	19.9 [1-58]	16.4 [1-118]	25.7 [0-147]	20.4 [0-100]
Time to 0.01 IU/mL (h)	21.4 [1-58]	14.5 [2-56]	20.1 [1-58]	16.6 [0-121]	25.5 [1-145]	20.3 [0-95]
Concentration at 24 h (IU/mL)	26.6 [0-104]	19.7 [0-71]	25.4 [1-86]	19.9 [1-97]	42.3 [1-403]	30.8 [0-224]

The results for all regression lines are summarized in Table 13. With the exception of concentration at 72h when switching from SHL FVIII to Eloctate, the slope for the η-method was closer to the line of identity (slope of 1) than the PopPK method across all PK outcomes.

Most of the regression slopes for both methods were significantly different from the line of identity (example shown in Figure 13).

Table 13. Regression slope (95% CI) for all switching protocols on the two methods for each PK outcome.

PK outcomes (units)	Slope (95% CI)					
	Adynovate to Eloctate (N = 39)		Eloctate to Adynovate (N = 39)		SHL FVIII to Eloctate (N = 200)	
	PopPK method	η-method	PopPK method	η-method	PopPK method	η-method
Clearance (L/h)	0.27 (0.11, 0.44)	0.93 (0.65, 1.20)	0.43 (0.29, 0.57)	0.67 (0.51, 0.82)	0.23 (0.18, 0.29)	0.62 (0.52, 0.71)
Volume (L)	0.66 (0.53, 0.80)	0.73 (0.55, 0.91)	0.69 (0.54, 0.83)	0.85 (0.60, 1.10)	0.71 (0.65, 0.77)	0.73 (0.67, 0.80)
Half-life (h)	0.34 (0.21, 0.47)	0.66 (0.47, 0.86)	0.29 (0.12, 0.46)	0.73 (0.47, 0.99)	0.39 (0.33, 0.46)	0.62 (0.54, 0.69)
Time to 0.05 IU/mL (h)	0.42 (0.31, 0.54)	0.78 (0.63, 0.94)	0.47 (0.30, 0.64)	0.90 (0.71, 1.10)	0.45 (0.39, 0.52)	0.66 (0.58, 0.73)
Time to 0.02 IU/mL (h)	0.42 (0.30, 0.54)	0.78 (0.61, 0.94)	0.44 (0.27, 0.62)	0.87 (0.66, 1.08)	0.42 (0.35, 0.49)	0.63 (0.55, 0.71)
Time to 0.01 IU/mL (h)	0.37 (0.23, 0.50)	0.78 (0.59, 0.98)	0.34 (0.15, 0.52)	0.75 (0.52, 0.97)	0.40 (0.32, 0.47)	0.63 (0.55, 0.71)
Concentration at 24 h (IU/mL)	0.56 (0.45, 0.67)	0.82 (0.69, 0.94)	0.70 (0.55, 0.86)	0.99 (0.84, 1.14)	0.62 (0.53, 0.71)	0.74 (0.65, 0.83)

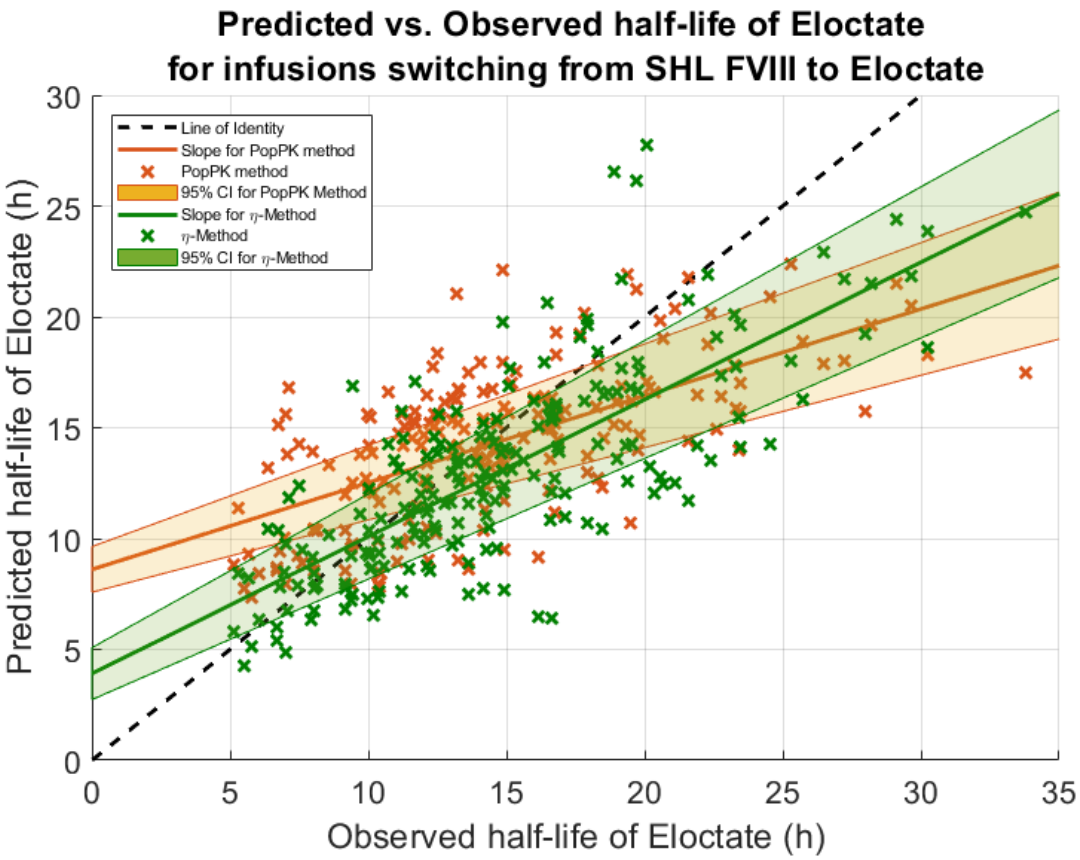

Figure 13. Subjects switching from SHL FVIII to Eloctate. The η-method has a better regression line fit to the line of identity (dashed line) compared to the PopPK method.

4.3.3 Comparing method performance in parsed individuals

A summary of the method performance comparison can be found in Table 14, Table 15, and Table 16. Parsing the data based on the number of observations per infusion did not bring about any predictable pattern. When individuals were parsed based on their η-values (for either CL or V_1), inconsistent results were obtained across the percentile ranges. The difference in mean absolute percent differences were largest for individuals with a high (> 80th percentile) or low (< 20th percentile) η_{CL} or η_{V1} on the first product. The η-method produced more precise half-life and time to 0.02 IU/mL predictions compared to the PopPK method for individuals at the

extreme percentile ranges, however only some of the subgroups were statistically different (p-value < 0.05) (example shown in Figure 14).

Table 14. Relative difference in arithmetic mean absolute percent difference (%) for the three switching protocols for half-life and time to 0.02 IU/mL parsed by the number of observations per infusion on the first product.

Switch	PK outcome	Number of observations per infusion on first product[a]		
		Less than 5	5	More than 5
Relative difference in arithmetic mean absolute percent difference (%) (N, number of subjects)				
Adynovate to Eloctate (N = 39)	Half-life	+14.3 (6)	-39.1 (27)[b]	-18.5 (6)
	Time to 0.02 IU/mL	+7.7 (5)	-43.9 (26)[b]	-18.8 (6)
Eloctate to Adynovate (N = 39)	Half-life	+27.1 (17)	-24.6 (22)	-
	Time to 0.02 IU/mL	+5.6 (15)	-32.0 (22)	-
SHL FVIII to Eloctate (N = 200)	Half-life	-18.7 (93)	-25.5 (58)	-7.3 (49)
	Time to 0.02 IU/mL	-20.8 (86)	-27.3 (52)	-11.1 (46)

[a]Negative values indicate that the η-method resulted in a lower arithmetic mean absolute percent difference compared to the PopPK method
[b]Statistically significant (p-value < 0.05)

Table 15. Relative difference in arithmetic mean absolute percent difference (%) for the three switching protocols for half-life and time to 0.02 IU/mL parsed by using η_{CL} percentiles on the first product.

Switch	PK outcome	η_{CL} percentile range				
		0 to 20	20 to 40	40 to 60	60 to 80	80 to 100
Relative difference in arithmetic mean absolute percent difference (%) (N, number of subjects)[a]						
Adynovate to Eloctate (N = 39)	Half-life	-64.3 (7)[b]	-30.1 (7)	-13.2 (12)	-8.5 (4)	+0.5 (9)
	Time to 0.02 IU/mL	-62.4 (7)[b]	-53.0 (7)[b]	-8.8 (11)	+208.2 (3)	-38.3 (9)
Eloctate to Adynovate (N = 39)	Half-life	-60.4 (7)[b]	+64.5 (12)	+77.6 (11)	-50.6 (4)	-61.2 (5)
	Time to 0.02 IU/mL	-61.9 (7)[b]	+37.4 (11)	+49.2 (11)	-60.6 (3)	-70.2 (5)
SHL FVIII to Eloctate (N = 200)	Half-life	-1.8 (19)	-23.8 (30)[b]	-8.9 (40)	-22.6 (52)[b]	-21.4 (59)
	Time to 0.02 IU/mL	-5.9 (17)	-28.8 (25)[b]	-24.1 (38)	-19.7 (50)	-27.2 (54)

[a]Negative values indicate that the η-method resulted in a lower arithmetic mean absolute percent difference compared to the PopPK method
[b]Statistically significant (p-value < 0.05)

Table 16. Relative difference in arithmetic mean absolute percent difference (%) for the three switching protocols for half-life and time to 0.02 IU/mL parsed by using η_{V1} percentiles on the first product.

Switch	PK outcome	η_{V1} percentile range				
		0 to 20	20 to 40	40 to 60	60 to 80	80 to 100
Relative difference in arithmetic mean absolute percent difference (%) (N, number of subjects)[a]						
Adynovate to Eloctate (N = 39)	Half-life	+18.7 (5)	+13.9 (7)	+18.5 (15)	-33.3 (10)	+46.8 (2)
	Time to 0.02 IU/mL	-29.0 (4)	-77.6 (7)[b]	-11.3 (15)	-27.5 (9)	+140.7 (2)
Eloctate to Adynovate (N = 39)	Half-life	-53.5 (4)	-24.1 (7)	-41.4 (12)	-3.1 (8)	+70.4 (8)
	Time to 0.02 IU/mL	-62.7 (4)	-19.3 (7)	-41.6 (11)	-28.1 (7)	+37.6 (8)
SHL FVIII to Eloctate (N = 200)	Half-life	+15.3 (33)	-31.7 (46)[b]	-29.6 (55)[b]	-27.7 (33)[b]	+1.3 (33)
	Time to 0.02 IU/mL	+5.4 (29)	-30.6 (42)	-28.3 (53)	-35.4 (28)[b]	-15.2 (32)

[a]Negative values indicate that the η-method resulted in a lower arithmetic mean absolute percent difference compared to the PopPK method
[b]Statistically significant (p-value < 0.05)

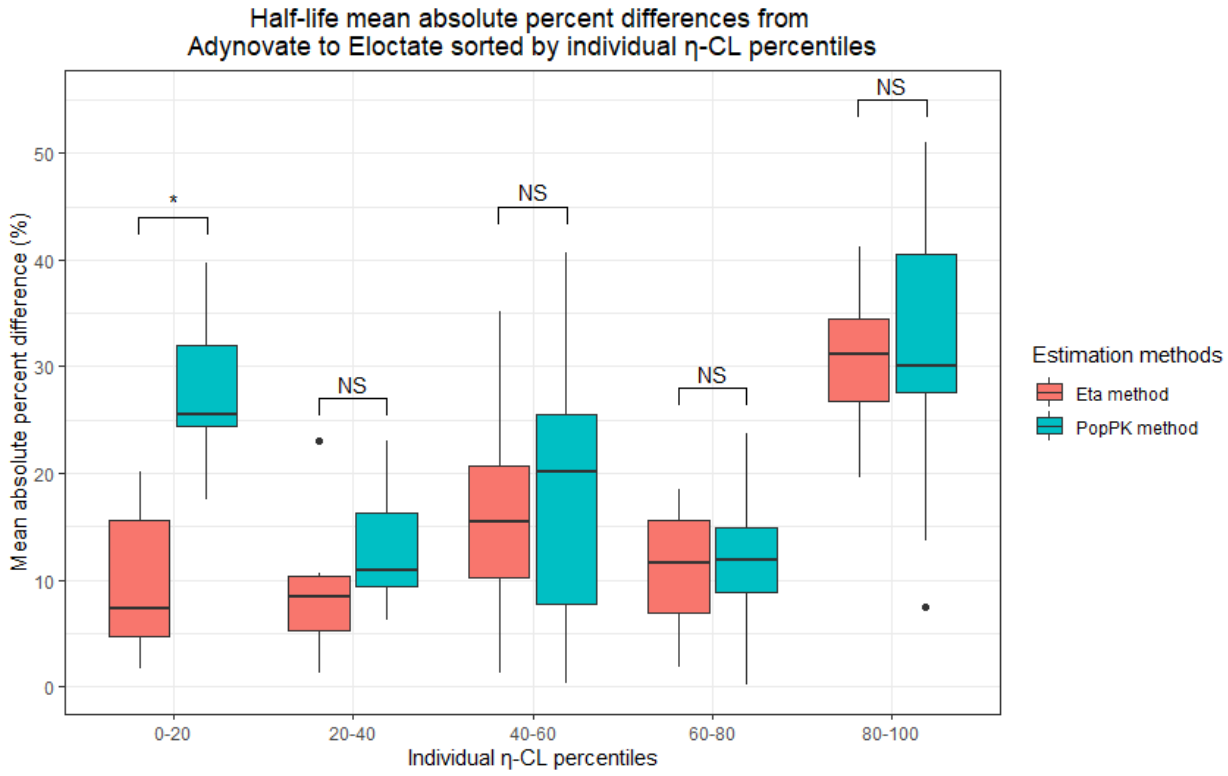

Figure 14. Comparison of the η-method vs. Bayesian estimates (red) and the PopPK method vs. Bayesian estimates (blue) to obtain individual half-life absolute percentage differences when

switching from Adynovate to Eloctate, parsed based on individual Adynovate η_{CL} percentiles. NS; not significant.

4.3.4 Predicting the trend of half-life on two methods

For each of the two methods, a total of 278 switches were compared to half-life trends obtained using Bayesian forecast (39 infusions from Adynovate to Eloctate, 39 infusions switching from Eloctate to Adynovate, and 200 infusions from SHL FVIII to Eloctate). Table 17 presents the proportion of individuals whose increase in half-life, time-to-2%, and time-to-1% by at least 12h was correctly predicted using the two methods.

Table 17. Correctly predicted half-life, time-to-2% and time-to-1% trend of individuals on the second FVIII product.

		N, number of subjects (%)				
Switch	**N**	**Bayesian estimation**	**PopPK method predictions**	**η-method predictions**	**PopPK method # of correct predictions**	**η-method # of correct predictions**
		Increase in half-life				
Adynovate to Eloctate	39	22 (56)	15 (38)	13 (33)	22 (56)	20 (51)
Eloctate to Adynovate	39	17 (44)	18 (46)	23 (59)	28 (72)	27 (69)
SHL FVIII to Eloctate	200	185 (93)	181 (91)	196 (98)	172 (86)	183 (92)
		Increase in time-to-2% by at least 12h				
Adynovate to Eloctate	37	8 (22)	6 (16)	1 (3)	25 (68)	30 (81)
Eloctate to Adynovate	37	10 (27)	7 (19)	12 (32)	28 (76)	29 (78)
SHL FVIII to Eloctate	184	137 (74)	139 (76)	124 (67)	124 (67)	131 (71)
		Increase in time-to-1% by at least 12h				
Adynovate to Eloctate	36	9 (25)	7 (19)	1 (3)	26 (72)	28 (78)
Eloctate to Adynovate	36	10 (28)	11 (31)	12 (33)	27 (75)	30 (83)
SHL FVIII to Eloctate	175	139 (79)	139 (79)	133 (76)	125 (71)	133 (76)

4.4 Discussion

The PK outcomes of two different methods were compared to the PK outcomes obtained using Bayesian forecasting when switching between two factor concentrates. Previously, the study showed incorporating η-values of the prior factor concentrate (η-method) resulted in closer PK estimates compared to solely using the PopPK model of the new factor concentrate (PopPK method) for switching between Advate to Novoeight, Novoeight to Advate, and Advate to Eloctate. [112] However, it was uncertain whether or not this method worked for other factor concentrates as well as with non-clinical trial data. The η-method resulted in a relative difference reduction in mean absolute percent difference of 27.8%, 4.9%, and 18.0% in half-life compared to the three switches explored (Adynovate to Eloctate, Eloctate to Adynovate, and SHL FVIII to Eloctate), respectively, compared to the PopPK method. On average, this demonstrated the η-method was slightly better than the PopPK method.

It is stated that factor concentrates exhibit high BSV and low IOV within a brand [17, 33], which is reflected by the large range of half-lives of Adynovate and Eloctate in this study (Table 11). When BSV is high, the chances of targeting and achieving a certain factor activity level at a certain time point decreases when the variability is unaccounted for, which may result in bleeding episodes (due to under-dosing) or wastage of valuable resources (due to overdosing).

When switching between FVIII products within the same class (e.g. SHL to SHL, or EHL to EHL), literature suggests that weight-based dosing and frequency before and after the switch for the individual were similar if not identical. [115] This approach assumes that factor concentrates have almost identical PK parameters. While this may be true for Adynovate and Eloctate [100] at the population level, the values reported are the population mean and do not describe the change in PK at the individual level. Individual variability across different factor

concentrates is significant enough to drastically change a patient's factor activity level response; while the population average half-lives of the two factor concentrates (15.3h and 15.8h in the Adynovate and Eloctate dataset) are similar, the observed difference in half-lives for one of the individuals in this study switching from Adynovate to Eloctate was 14 hours (11 hours vs. 25 hours). Using the same weight-based dosing and frequency for an individual switching to another factor concentrate does not guarantee the same response. This issue was addressed for some individuals using the η-method, more notably the individuals predicted to have extremely low or high half-life values. For individuals without extreme half-life predictions, the η-method performed similarly to the PopPK method.

Taking a closer look into the EHL FVIII switching data, each infusion from WAPPS-Hemo included 3 to 8 observations per infusion. It has been previously demonstrated that infusions with many sampling time points would better calculate Bayesian estimates. [116] This also infers that infusions with more sampling points would increase our confidence in acquiring reasonable η-values. It was thus hypothesized that individuals with more observations on the first product would predict more accurate PK outcomes using the η-method. Table 14 shows that on average, infusions with 5 or more sampling points was associated with a closer prediction in PK outcomes compared to using the PopPK method. There is a possibility that observations at certain time points that were included in the dataset were more informative when calculating η-values for using the η-method. Making use of optimal sampling time points may be required to obtain better PK estimates, including η-values. [116]

When switching from SHL to EHL FVIII products, literature suggests to initiate the individual with the same weight-based dosing, however reducing the frequency of the infusion. [42, 96] While at a population level, EHL products have a longer half-life than SHL products,

this does not necessarily hold at the individual level. [69] Individual half-life ratios between Eloctate and SHL FVIII ranged from 0.63 to 3.90 in our study, which is consistent with literature (0.79 to 2.98 as per Young et al [69]). This study explored whether we can predict an increase or decrease in half-life on the switched product. Both the PopPK method and the η-method were able to predict the half-life trend in most individuals switching from a SHL FVIII to Eloctate, and less so when switching between EHL FVIII products (Table 17).

The magnitude of the unexplained variability can be estimated by integrating relevant covariates (fat-free mass and age) into the PopPK model, which helps in describing the BSV of individuals on a factor concentrate, resulting in more precise PK estimations. Fat-free mass and age are covariates that have been shown to influence the PK of factor concentrates [97, 113] and consequently help describe PK variability in a population. Fat-free mass has been demonstrated to describe a significant portion of the BSV on CL and V_1 [99], and age acts as a surrogate for vWF levels, since vWF is known to decrease clearance of factor concentrates [117] and vWF levels increase with age [118]. The PopPK method predicts PK outcomes generally well, with mean absolute percent difference < 28% for clearance, volume, half-life, and time-to-5%, -2%, and 1% (Table 12). However, when switching to a new factor concentrate, the PopPK method does not take into account additional information that may be beneficial for PK estimation from the first product, notably η-values.

η-values account for any BSV that hasn't been explained by the PopPK model, and can encompass all causes of individual variability (such as organ perfusion or transport mechanisms) that may be challenging to quantify. Multiplying individual η-values using a scaling factor assumes that individuals with a CL or V_1 value at a certain percentile on the first product will also exhibit a CL or V_1 value at the same percentile on the second product. The η-method

resulted in only slightly lower mean absolute percent difference in all PK outcomes as compared to the PopPK method except for volume. In addition, the regression slopes for some PK outcomes using the η-method included the line of identity (slope of 1).

Another method was explored by using a regression equation, where the x-axis is the η-value of a PK parameter (e.g. CL or V_1) of individuals on the first product, and on the y-axis is the η-value of the same PK parameter of individuals on the second product. A regression line is formed to determine the relationship between two η-values. However, the linear regression equation relies on population information, and the drastic change in η-values from the first product to the second product in order to fit that line produced unreliable and unrealistic results.

A benefit of switching to another factor concentrate with a higher half-life or longer time-to-trough level is the fewer infusions required. The reduction in frequency can improve an individual's quality of life and decrease infusion burden. With this in mind, groups of individuals were assessed to see who may benefit from one method over the other. When individuals were parsed based on the percentile of η-values on the first product, Table 15 and Table 16 show that parsing by η_{CL} resulted in a more consistent trend than parsing by η_{V1}, suggesting that individuals are more likely to be different from CL than from V_1. Individuals at lower η_{CL} percentiles were sometimes statistically better predicted on the η-method compared to the PopPK method. However, the η-method does not seem to better predict an increase or decrease in half-life of a future product compared to the PopPK method, nor can it predict an extension in time-to-2% or time-to-1% of at least 12h on the new factor concentrate. Most individuals would benefit from acquiring PK estimates using either method.

The use of the η-method can be implemented into the WAPPS-Hemo tool for predicting PK in individuals with hemophilia A switching from one FVIII product to another. However, the

implementation of the η-method poses several limitations. PopPK models with different relevant covariate structures would produce η-values that describe different variabilities and could not use this method to predict PK outcomes. The η-method was also only studied in FVIII concentrates. It is unclear whether the method would produce similar results for FIX concentrates for patients with hemophilia B, and therefore the η-method should be tested for switching between other factor concentrates when there is sufficient switching data. Although the η-method was the more precise method by a small margin, it is still recommended that blood samples are gathered when performing a PK profile for a patient on a new factor concentrate. Another limitation of using the η-method is that the η-distribution of factor concentrates was assumed to be normally distributed, and that the distribution can be scaled to be equivalent to the η-distribution of another product.

4.5 Conclusion

The use of prior knowledge by implementing η-values into PopPK models may provide clinicians with a safer and more effective method to choose a dosing regimen for patients with hemophilia A switching from one factor concentrate to another. The η-method was found to perform similarly to the PopPK method in predicting PK parameters for three switches explored (Adynovate to Eloctate, Eloctate to Adynovate, and SHL FVIII to Eloctate) when using sparse data. On average, higher number of observations (5 or more) used during Bayesian estimation to acquire η-values led to better precision of PK parameter estimates obtained when using the η-method. Individuals with extreme η_{CL} values on the prior concentrate had predictions closer to the truth using the η-method compared to the PopPK method, suggesting that the η-method may result in less biased predictions in such individuals. However, it does not better predict the extension in half-life or time-to-trough levels compared to the PopPK method. For those that are not in the extremes with respect to PK, either method would suffice. The η-method can be implemented into the WAPPS-Hemo database for predicting PK when switching from one factor concentrate to another.

Chapter 5: Pharmacokinetic implications of dosing emicizumab based on vial size: A simulation study

This chapter is reflective of an original manuscript published by the Ph.D. candidate (Jacky Ka-Hei Yu) in Haemophilia. All pertinent dialogue in this chapter was written by the Ph.D. candidate.

Yu JK, Iorio A, Chelle P, Edginton AN. Pharmacokinetic implications of dosing emicizumab based on vial size: A simulation study. Haemophilia. 2021; 00:1-8. DOI: 10.1111/hae.14292.

5.1 Introduction

Hemophilia A is a bleeding disorder due to low plasma levels of clotting FVIII resulting in bleeding tendency if left untreated. Even when adopting prophylactic treatment with intravenous FVIII concentrates with any of the numerous FVIII concentrates commercially available, patients experience bleeding events [62], and approximately 30% of severe hemophilia A patients develop inhibitors [40, 119] which impedes further FVIII replacement therapy.

Emicizumab (HEMLIBRA®; Chugai Pharmaceutical Co., Ltd.) is a recombinant bispecific monoclonal antibody that restores the function of activated clotting FVIII in people with hemophilia A. [120-122] Emicizumab is dosed based on body weight (BW) at 1.5 mg/kg weekly (QW), 3 mg/kg every 2 weeks (Q2W), or 6 mg/kg every 4 weeks (Q4W). The relationship between plasma emicizumab concentration and annualized bleeding rate (ABR) was previously investigated, showing that the target trough concentration required to achieve zero ABR in ≥ 50% of patients is 45 μg/mL. [123] Currently, the manufacturer provides guidance on vial size selection through a website (https://www.hemlibra.com/hcp/dosing-administration/dosing.html). Depending on the patients' weight, the number of vials and their sizes are calculated to provide the required volume to be administered. According to the label, any unused solution from a vial must be discarded, thereby wasting expensive resources.

There have been previously published articles relating the pharmacokinetics to the structural characteristics of monoclonal antibodies. [26] Monoclonal antibodies exhibit similar clearances, ranging from 1.4 to 14.1 mL/kg/day. [124] Emicizumab follows the general trends in the pharmacokinetics of monoclonal antibodies, with a clearance of 3.4 mL/kg/day. [124] Emicizumab's long half-life of approximately 4 weeks in adults [24] allows for flexibility in dose and injection frequency selection to achieve efficacious concentrations. The approval of

three different yet equivalent dosing regimens for emicizumab in which clinical efficacy has been proven lends itself the opportunity to explore the impact of further dosing and frequency combinations.

It has not yet been explored how modifying the emicizumab dose to a full vial size and correspondingly extending or reducing the injection frequency would pan out when targeting the same steady state concentration to maintain the efficacy and safety shown in clinical trials. The aim of this study was to use PopPK to illustrate the changes in time-to-trough levels when modifying the dose to the nearest vial size, across the age continuum. In addition, the implications of changing a patient's dose to the nearest vial to save on medication cost remains to be determined.

5.2 Methods

An emicizumab PopPK model was developed by Chugai Pharmaceutical Co., Ltd, a subsidiary of Hoffman-La Roche Ltd, using data from healthy volunteers (n = 42, BW = 55-87 kg) in clinical trial #JapicCTI-121934 [24] plus hemophilia A patients (n = 18, BW = 41-82 kg) participating in a Phase 1 study [125, 126]. This PopPK model, reported by Yoneyama et al. [123], is a one-compartment model with first-order absorption and elimination, with BSV terms on CL/F, volume V_1/F, and absorption rate constant (ka). A combined additive-plus-proportional model was employed for describing residual unexplained variability. BW effects were fixed on allometric exponents of 0.75 on CL/F and 1 on V_1/F. [123]

5.2.1 Evaluation of the performance of the Yoneyama model in children

A model evaluation was required in order to use the PopPK model for PK predictions in children outside of the model's covariate space (< 41 kg). Two studies were used for this purpose:

- A phase 3 study of emicizumab prophylaxis in children with hemophilia A with inhibitors by Young et al. [127] Eighty-eight participants received emicizumab loading dose (3.0 mg/kg QW) for 4 weeks and were treated with emicizumab at either 1.5 mg/kg QW (n = 68, age range 1-15, weight > 3 kg), 3.0mg/kg Q2W (n = 10, age range 2-10, weight >3 kg) or 6.0 mg/kg Q4W (n = 10, age range 2-11, weight >3 kg) regimen. Trough emicizumab concentrations were recorded over 81 weeks.
- An open-label study of emicizumab in children with severe hemophilia A without inhibitors by Shima et al. [119] Thirteen Japanese participants received emicizumab loading dose (3.0 mg/kg QW) for 4 weeks and were treated with emicizumab at either 3.0 mg/kg Q2W (n = 6, age range 1.5-10.7, weight range 10.9-35.6 kg) or 6.0 mg/kg Q4W (n

= 7, age range 0.3-8.1, weight range 6.6-25.6 kg). At least 24 weeks of emicizumab was administered. Trough emicizumab concentrations were recorded over 40 weeks.

A population of 1600 individuals was simulated, consisting of 100 individuals per year between 0-15 years of age. BWs were derived from the distribution provided by the National Health and Nutrition Examination Survey database. [128] BSV terms for CL/F, V_1/F, ka, and covariance for CL/F and V_1/F were taken from the respective distributions in the model. [123] Individual PK estimates were obtained using the model. A loading dose of 3.0 mg/kg QW was given for 4 weeks, followed by 3 dosing regimens (1.5 mg/kg QW, 3.0 mg/kg Q2W, 6.0 mg/kg Q4W) for 81 weeks, and the concentration-time profiles were simulated for each dosing regimen. Mean and standard deviation of the simulated population were calculated by bootstrapping. One thousand populations of n subjects within the age and BW range of the corresponding clinical study were generated (Table 18). For each population, mean and SD of the time profiles were calculated. The median, 5th, and 95th percentiles of the trough concentrations were used to summarize the results obtained in the 1000 populations. For observed troughs and simulated time profiles, variability in the population was plotted as 95% range of the population derived from SD as mean-1.96*SD and mean+1.96*SD. The simulated and observed mean tendency and variability in plasma concentrations were visually compared to assess the model's ability, originally built for adults, to capture emicizumab pharmacokinetics in children.

Table 18. Number of individuals with demographics used for PopPK model evaluation.

Regimen and source (n = number of individuals)	Median age (range) in years and body weight (range) in kg
QW regimen from Young et al. [127] (n = 68)	Age: 6.0 (1-15) BW: >3
Q2W regimen from Young et al. [127] (n = 10)	Age: 8.0 (2-10) BW: >3
Q4W regimen from Young et al. [127] (n = 10)	Age: 9.0 (2-11) BW: >3
Q2W regimen from Shima et al. [119] (n = 6)	Age: 6.6 (1.5-10.7) BW: 19.5 (10.9-35.6)
Q4W regimen from Shima et al. [119] (n = 7)	Age: 4.1 (0.3-8.1) BW: 15.7 (6.6-25.6)

5.2.2 Simulation study on labelled dosing regimens

One-thousand individuals with identical BWs were simulated (for all BWs between 10-100 kg in 1 kg increments) and PK parameters were calculated, incorporating BSV values based on the model. Individual PK estimates of CL/F, V_1/F and ka were derived. Individual concentration-time profiles were simulated on three dosing regimens (1.5 mg/kg/week, 3.0 mg/kg every 2 weeks, 6.0 mg/kg every 4 weeks). The individual trough concentration ($TROUGH_{ind}$) at steady state was obtained for each dosing regimen.

5.2.3 Evaluation of dosing regimens when rounding to the nearest vial size

Four emicizumab vial sizes are available: 30 mg/mL, 60 mg/0.4mL, 105 mg/0.7 mL, and 150 mg/mL. The manufacturer has recommended that the 30 mg/mL vial size should not be mixed with the other 3 vial sizes, due to different drug concentrations in the vial. In addition, doses requiring more than 2 mL should be separated into multiple injections. However, for the purposes of this study, each day's worth of injection is considered to be only one administration, even if multiple syringes would be used.

The individual rounded-up dose ($DOSE_{up}$) was obtained by rounding the labeled dose up to the nearest vial size. The time to $TROUGH_{ind}$ ($INTERVAL_{up}$) was calculated using individual

PK parameters and $DOSE_{up}$. The extension of the interval ($INTERVAL_{extension}$) was calculated by subtracting either 7, 14, or 28 days, depending on dosing regimen, from $INTERVAL_{up}$, and rounded to the nearest day. All BWs in which 95% of the population have an $INTERVAL_{extension}$ of at least 1 day were recorded.

This process was repeated for assessing the implications when rounding down, replacing $DOSE_{up}$ with the rounded-down dose ($DOSE_{down}$) and $INTERVAL_{up}$ with the interval time of the rounded-down dose. In addition, a 4-week loading dose of 3 mg/kg weekly followed by $DOSE_{down}$ were simulated for all individuals. Trough concentrations at steady state were obtained, and the percent reduction in trough concentration between the rounded-down dose and $TROUGH_{ind}$ was calculated.

5.2.4 Number of units, injections and cost saved per annum

The total units of emicizumab administered annually per individual on the labeled doses was calculated by multiplying the number of units per administration and the number of administrations per year. The same formula was used to calculate the total units of emicizumab administered annually when rounding up, however the number of administrations per year is calculated by dividing 365 days by $INTERVAL_{extension}$. The number of units saved per year is defined as the difference between the total units of emicizumab administered annually on the labeled doses and on the rounded-up or rounded-down doses. The amount saved annually is determined by using prices (in Euro) found on the Roche website (https://www.roche.fr/fr/pharma/traitements-medicaux-innovants/nos_produits/hemlibra.html) and from Lexicomp (in USD), a collection of drug information databases.

5.2.5 Software

PK predictions were performed using non-linear mixed effects modelling in NONMEM (version 7.4, ICON, Hanover, MD). [104] Graphical figures were created using MATLAB® (version 2017b, TheMathWorks, Natick, MA).

5.3 Results

5.3.1 Evaluation of the Yoneyama model for children

Table 18 presents the number of children and the covariate space of the simulated individuals for each study and dosing regimen. The concentration-time profiles for each dosing regimen are presented in Figure 15 and Figure 16, plotted alongside the observed mean and 95% CI emicizumab trough concentrations obtained from Young et al. [127] and Shima et al. [119], respectively. The central tendency of the simulated trough concentrations well represented the observed data. Variability was reasonably captured through comparison of the simulated vs. observed 95% CI for Shima et al. and Young et al.

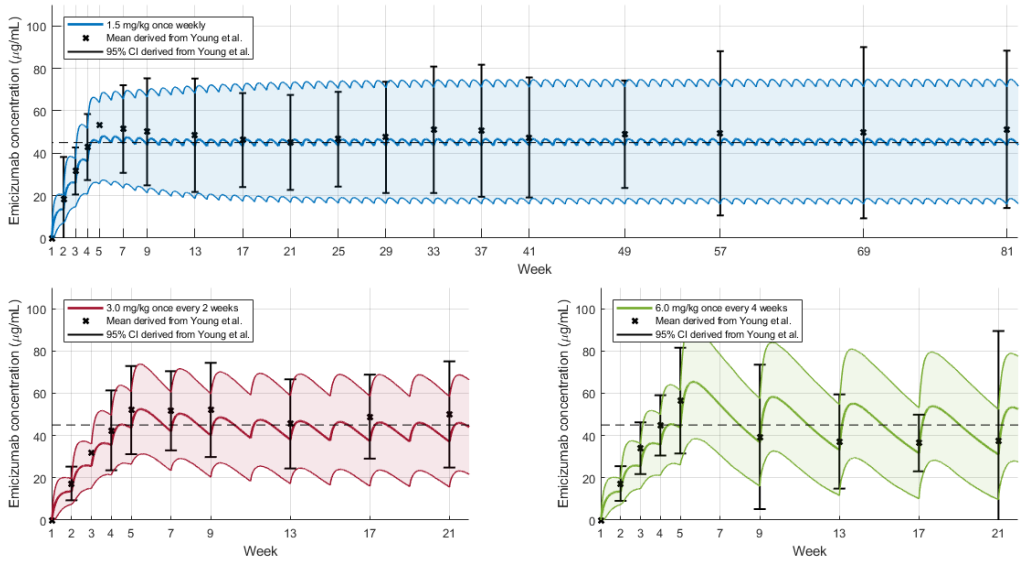

Figure 15. Population concentration-time profile of simulated individuals (mean and 95% CI) plotted alongside data from Young et al (originally reported with mean and SE). Dashed line represents the target trough level of 45 µg/mL.

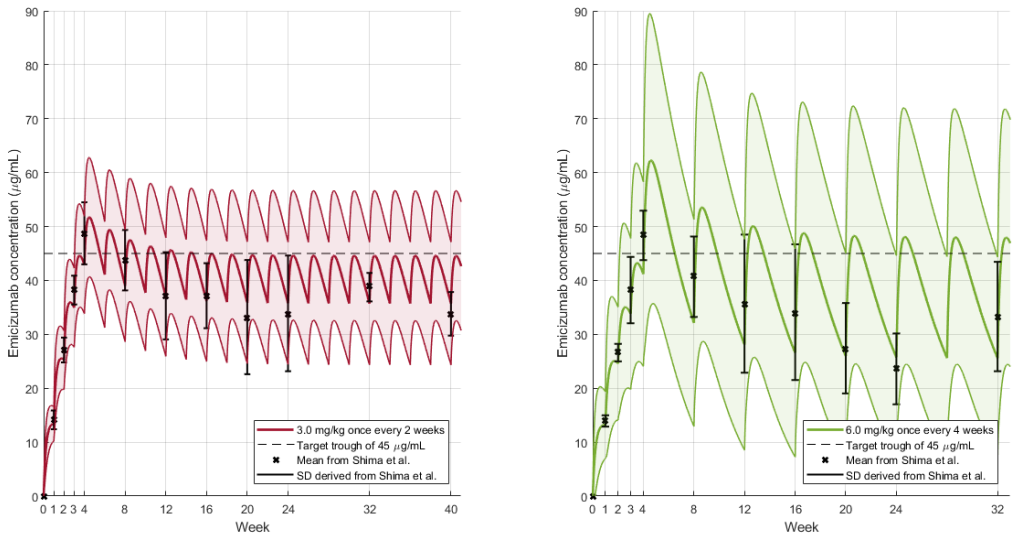

Figure 16. Population concentration-time profile of simulated individuals (mean and 95% CI) plotted alongside data from Shima et al.

5.3.2 Simulation study

The time-to-trough difference was simulated in Figure 17 and Figure 18. When rounding up on a QW, Q2W, and Q4W regimen, the average individual below 53 kg, 47 kg, and 39 kg have a time-to-trough increase of up to a median of 5.7, 7.9, and 5.8 days respectively. When rounding down on the QW, Q2W, and Q4W regimen, the average individual above 60 kg, 45 kg, and 38 kg have a time-to-trough decrease by less than 1 day respectively. The percent reduction in trough concentration when maintaining the QW, Q2W, and Q4W administration frequency is depicted in Figure 19.

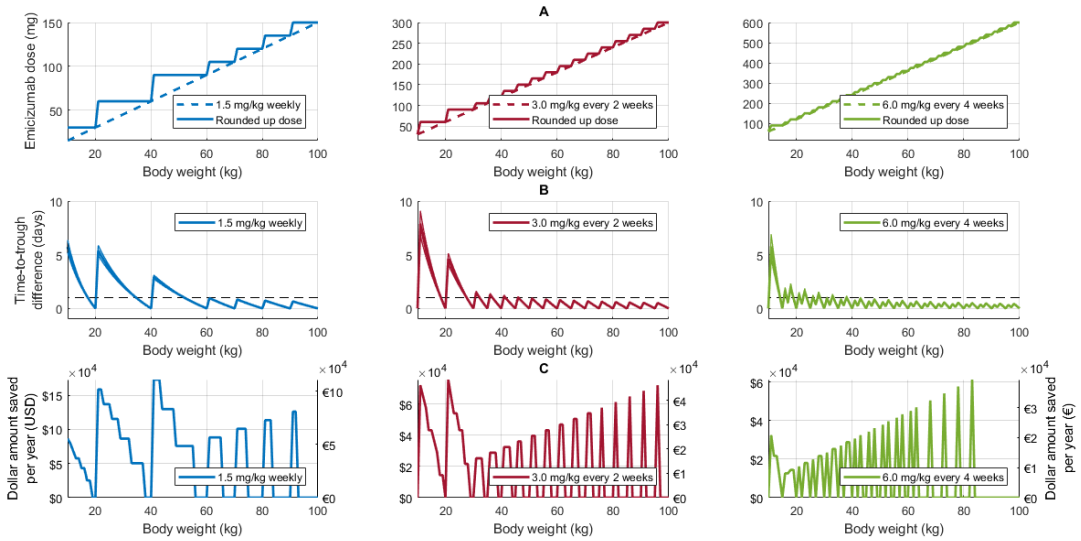

Figure 17. (A) Comparison between labeled and rounded-up dose. **(B)** Time-to-trough difference (median, 5th, and 95th percentile) compared to labeled dose when rounding up to the nearest vial. Dashed line signifies time-to-trough increase by 1 day. **(C)** Mean yearly reduction in emicizumab cost (in USD and Euro respectively) due to reduced frequency when rounding dose up to the nearest vial.

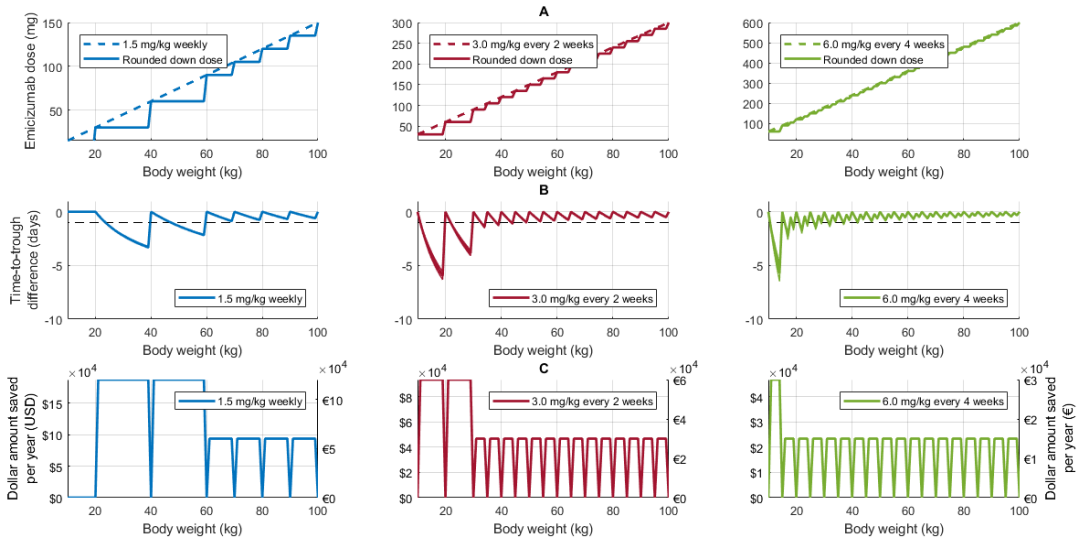

Figure 18. (A) Comparison between labeled and rounded-down dose. **(B)** Time-to-trough difference (mean, 5th and 95th percentile) compared to labeled dose when rounding dose down to the nearest vial. Dashed line signifies a time-to-trough decrease by 1 day. **(C)** Mean yearly reduction in emicizumab cost (in USD and Euro respectively) due to maintaining frequency when rounding dose down to the nearest vial.

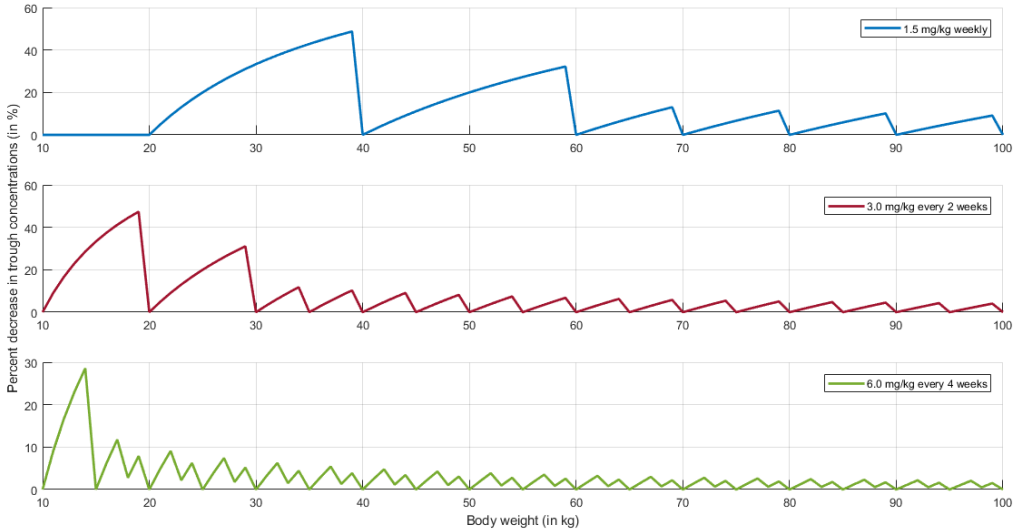

Figure 19. Percent decrease in emicizumab trough concentrations when rounding down to the nearest vial.

5.3.3 Number of units saved per annum

There was an annual reduction in emicizumab cost of up to $173,136, $75,747, and $61,319 USD (111,067, 48,592, and 39,336 Euro) per patient when rounding dose up and reducing the frequency of administration by the extension in time-to-trough concentrations rounded to the nearest day, respectively. On the QW, Q2W, and Q4W regimen, there was a percentage annual reduction in emicizumab dose of up to 46%, 38%, and 23% respectively, shown in Figure 20.

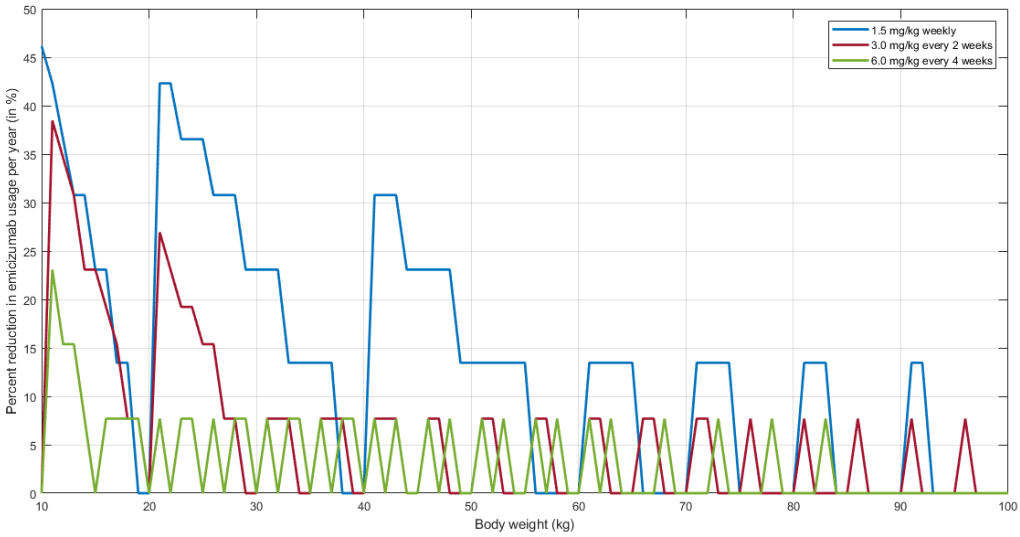

Figure 20. Annual percent reduction in emicizumab usage due to reduced frequency when rounding dose up to the nearest vial.

5.4 Discussion

We externally evaluated the Yoneyama model for emicizumab, and extended its applicability to a pediatric population. The model is robust and confirms the highly predictable PK of emicizumab. We proved the robustness of our hypothesis that emicizumab regimens can be built to obtain the same steady state plasma levels as those tested in clinical trials by adjusting injection intervals to use full vials, thus avoiding wastage of drug and resources. We have found that the savings are more evident for individuals with BW below 39-53 kg (depending on infusion frequency) and require extending the infusion interval by up to 6-8 days (depending on the dose). Individuals with a higher BW may benefit from maintaining their dosing frequency and rounding dose down without a significant drop in emicizumab trough concentrations. Corresponding savings may achieve over $100,000 US dollars per year per patient. We have not explored changing the infusion dose to minimize the number of reconstituted vials, or to infuse a maximum of 2 mL (i.e. performing a single injection), but we have created an online calculator allowing to do so with potential benefits to patients of any weight and age.

When rounding dose up, the time-to-trough extension was higher for individuals who have a higher percentage dose increase. Some individuals with lower BWs can decrease their frequency of administration while dosing up, resulting in less medication wasted. At higher BWs, due to the sizes of emicizumab vials available, rounding up the dose resulted in a relatively smaller increase in dose administered. The availability of four vial sizes shows that at higher BWs, the combination of vial sizes results in a dose difference of up to 15 mg per dose. This small increase in dose was not sufficient enough to extend the time-to-trough concentration by at least 24 hours. In contrast, individual recommended doses below 105 mg can only use the 30 mg/mL and 60 mg/0.4 mL vials, which can result in a dose difference of up to 30 mg.

For individuals with lower BWs that can benefit from reducing dose frequency and administering the entire vial, this may result on average in an annual reduction in emicizumab usage by up to 46%. The reduction in emicizumab usage is greater on the QW regimen as compared to the Q2W and Q4W regimens. a decrease in annual consumption of emicizumab can result in significant cost savings for the payer and may potentially improve quality of life because of decreased number of subcutaneous injections administered per year.

On the QW, Q2W, and Q4W dosing regimens, rounding down results in up to a 48.7%, 47.4%, and 28.6% decrease in trough concentrations, respectively particularly in the smaller BWs. However, trough levels for higher BWs decrease by no more than 13%. Since the target for emicizumab is to maintain a trough concentration ≥45 μg/mL to achieve zero ABR in ≥50% of patients [123], a decrease of up to 13% is most likely insignificant in maintaining the target. In addition, studies by Young et al. [127] and Shima et al. [119] demonstrate that the vast majority of children did not experience any spontaneous bleeding events while on emicizumab, with the exception of one individual in the Q2W cohort by Shima et al. who experienced a spontaneous bleed. Higher BWs may likely be able to reduce their dose while maintaining dosing frequency and achieve similar trough concentrations. At BWs above 60 kg, rounding emicizumab dose down while maintaining dosing frequency can result in cost savings of up to $93,781, $46,891, and $23,446 USD (or 60,161, 30,081, and 15,040 Euro) per patient respectively for the payer. Concentration-time profiles of the simulated population on emicizumab also reveal that individuals are more likely to maintain a trough concentration ≥45 μg/mL on a QW regimen as compared to the Q2W and Q4W regimens.

The PopPK model used in this simulation study was evaluated to predict concentration-time profiles outside of the covariate space for which it was developed. The PK in simulated

children was compared to observed PK data from Young et al. [127] and Shima et al. [119] After 4 weeks of loading dose, observed emicizumab troughs were approximately 15% higher than simulated. During the maintenance dose phase, observed troughs were within the model simulation although variability was larger for the simulation as compared to literature, potentially due to the limited number of individuals used for model evaluation. The allometric coefficient for the effect of BW on CL and V_1 was 0.75 and 1, respectively, which is comparable with other large molecules. [45, 129] Consequently, the PopPK model outcomes in the maintenance phase were deemed acceptable for its further use in children.

The limitations of this study includes assuming it is appropriate to dose by total body weight. For obese individuals treated with FVIII concentrates, the use of body weight dosing led to higher levels than those observed in patients with normal body weight [130-132]. Similarly, dosing emicizumab based on ideal body weight instead of total body weight may further reduce the amount of emicizumab needed to achieve therapeutic levels and avoid overdosing overweight patients. Another limitation includes the rationale in which vial sizes are determined when rounding. The rounded doses used for determining time-to-trough changes were calculated presuming that all vial sizes could be used. Presuming that some vial sizes were unavailable, or one wanted to use only one vial size or inject no more than 2 mL in one injection, the time-to-trough extension seen when rounding up will be different. Likewise, when rounding down, the percent decrease in emicizumab trough concentrations will also be different. To address this issue, an online resource connected to the WAPPS-Hemo portal and research network (Calibra, http://calibra.app) is available to help find the most effective combination of emicizumab vials and suggests an optimum combination of dose and frequency to achieve the same plasma concentrations seen in clinical trials. Once the clinician has provided the patient weight and

reference dosing regimen, Calibra can determine the time-to-trough extension when using the entirety of any desired combination of available vial sizes.

5.5 Conclusion

The study shows that individuals with a lower BW may benefit from reducing dosing frequency and rounding up dose. Administering the entire vial and reducing the frequency may result in a reduction of vials used annually and consequently potential cost-savings. Individuals with a higher BW may benefit from maintaining dose frequency and rounding down dose without a significant drop in trough concentrations. The Calibra software is made available for clinicians to optimize emicizumab dosing and find the most effective combination of vial sizes to reduce unnecessary wastage of the drug.

Chapter 6: Relationship between estimated FVIII trough levels and bleeding rates for the treatment of severe hemophilia A patients in Canada

This chapter consists of unpublished works by the Ph.D. candidate (Jacky Ka-Hei Yu). All pertinent dialogue in this chapter, including analyses, tables, and figures were written by the Ph.D. candidate.

6.1 Introduction

Pharmacokinetic-based factor VIII prophylaxis have been increasing more common for individualized dosing in hemophilia A. The goal of prophylactic factor VIII was to keep the FVIII activity level above 1% to prevent spontaneous bleeding episodes. [4] However, there have been publications that have considered maintaining FVIII activity level >15%, particularly with extended half-life recombinant FVIII therapies. [133] In order to achieve a higher FVIII trough level, it is likely that a higher dose of FVIII concentrate is required and, therefore, will also be more costly for the healthcare system.

Currently, there are no trials that demonstrate that maintaining a higher FVIII trough level may be a more cost-effective option. Hypothetically, targeting a higher FVIII trough would result in less spontaneous bleeding, however characterizing this relationship requires a significant number of patients and may be difficult since hemophilia is a rare disorder. The Canadian Hemophilia Bleeding Disorders Registry (CBDR) is a clinical database for patients in Canada with bleeding disorders which allows for recording of bleeding events, and prophylactic FVIII usage. [134] In addition, the CBDR is integrated with the WAPPS-Hemo, a globally-accessible online tool that collects plasma factor activity measurements with patient covariates and PK profiles and is stored in a database. The WAPPS-Hemo database contains PopPK models that allow hemophilia treaters to estimate individual PK through Bayesian methods using plasma factor activity measurements and patient covariates, and provides trough FVIII levels accordingly to the individual factor VIII product, dose, and frequency. Both the CBDR and WAPPS-Hemo databases can be utilized together to provide better insight on the relationship between bleeding rates and estimated FVIII trough levels.

The objective of this chapter was to present the preliminary results, using real world data, of the relationship between estimated FVIII activity levels, annualized bleeding rates, and the type of FVIII (SHL or EHL FVIII). A sensitivity analysis comparing the results by including patients with a minimum of 90 vs. 365 days of treatment was also explored to determine if including only longer FVIII treatment periods make a difference in ABR results.

6.2 Methods

6.2.1 Canadian Bleeding Disorders Registry

Ethics approval by the Office of Research Ethics at the University of Waterloo was received to retrieve severe hemophilia A data from the Canadian Bleeding Disorders Registry (CBDR) (Protocol #43528). Data and variables extracted from CBDR on September 15, 2022 include patient demographics, and prophylactic dosing regimen.

The eligibility criteria and information retrieved from CBDR was included in Table 19. Dosing regimens were recorded in CBDR by the number of infusions per week. For the purposes of simulating trough FVIII concentrations, it is assumed that the infusions were given at regular intervals; a dosing record of 3 infusions per week would be assumed to be given every 2.33 days, as opposed to every Monday, Wednesday and Friday.

Table 19. Eligibility criteria and information gathered from CBDR.

Eligibility criteria for information gathered from CBDR
• Patients must be diagnosed with severe hemophilia A (baseline FVIII level <1%) • A minimum of 70% of infusions recorded in CBDR (for SHL FVIII, a minimum of 109 infusions in a year; for EHL FVIII, a minimum of 72 infusions in a year) • A minimum of 90 days on each recorded treatment plan
Variables obtained from CBDR
• Patient demographics (diagnosis, age, gender, and weight) • Prophylaxis treatment plan (includes specific FVIII concentrate, dose, and frequency) • Start and end date of treatment plan • Number of bleeding episodes while on prophylaxis

6.2.2 WAPPS-Hemo

The data collected from WAPPS-Hemo was extracted on September 15, 2022 and included individual PK parameters, prophylactic FVIII treatment, baseline factor levels, and various patient demographics such as age and body weight. PopPK models from WAPPS-Hemo were coded in RStudio (version 2022.07.2). Using individual PK parameters and the PopPK model of their associated FVIII brand, as well as the dosing information from CBDR,

concentration-time profiles were simulated to steady state. Trough FVIII level at steady state was estimated for each individual based on their PK, dosing regimen, and FVIII brand, and matched with the CBDR dataset by patient ID.

6.2.3 Data Analysis

Annualized bleeding rates were parsed by the type of factor VIII concentrate (standard half-life vs. extended half-life) and the following target FVIII trough levels and summarized by descriptive statistics:

- Target FVIII trough level <1%
- Target FVIII trough level 1-3%
- Target FVIII trough level 3-5%
- Target FVIII trough level >5%

ABR were calculated for individuals who had multiple treatment plans who received the same type of factor VIII concentrate and the same FVIII trough level group by taking the total number of bleeds and dividing by the total number of days on all treatments, normalized to 365 days. were calculated using the total number of bleeds during the timeframe as below:

$$ABR = \frac{Total\ number\ of\ bleeds}{Total\ years\ on\ prophylactic\ SHL\ FVIII}$$

The proportion of subjects with 0 ABR for individuals who received the same type of factor VIII concentrate and the same FVIII trough level group was also summarized and reported. The eligibility for information gathered from CBDR included a minimum of 90 days on each recorded treatment plan – the results were compared with an inclusion criterion of a minimum of 365 days.

6.3 Results

A total of 519 treatment records for SHL FVIII and 228 treatment records for EHL FVIII were included for this analysis for 242 unique patients. ABRs parsed by FVIII trough levels are reported in Table 20 (90-day inclusion criteria) and Table 21 (365-day inclusion criteria). When including subjects based on the inclusion criteria of minimum 90 days on treatment plan, ABRs were reported to be highest in the group where the estimated FVIII trough level was <1%. The proportion of individuals with 0 ABR ranged from 6-33% for SHL FVIII and 36-44% for EHL FVIII. Mean monthly FVIII consumption ranged from 220-380 IU/kg/month for SHL FVIII and 358-674 IU/kg/month for EHL FVIII.

When including subjects based on the inclusion criteria of minimum 365 days on treatment plan, ABRs were reported to be the highest in the group where the estimated FVIII trough level was <1%. The proportion of individuals with 0 ABR ranged from 6-31% for SHL FVIII and 43-50% for EHL FVIII. Mean monthly FVIII consumption ranged from 299-510 IU/kg/month for SHL FVIII and 365-444 IU/kg/month for EHL FVIII.

Table 20. Annualized bleeding rates parsed by FVIII trough levels based on inclusion criteria of a minimum of 90 days on treatment plan.

	Estimated Factor VIII Trough Level			
SHL FVIII	**<1% (n=30)**	**1-3% (n=85)**	**3-5% (n=35)**	**>5% (n=39)**
Age				
Mean (SD)	20.5 (15.3)	19.4 (15.8)	24.9 (16.4)	33.0 (17.3)
ABR				
Mean (SD)	6.9 (13.4)	3.2 (6.9)	1.7 (1.9)	3.6 (5.7)
Median (Q1 to Q3)	2.4 (1.3 – 6.2)	1.3 (0.3 – 3.2)	1.2 (0.0 – 2.6)	1.0 (0.0 – 5.2)
Subjects with 0 ABR				
Percentage (%)	6.7	18.8	28.6	33.3
Monthly factor concentrate usage (IU/kg/month)				
Mean (SD)	345.4 (169.6)	417.5 (201.0)	446.6 (159.6)	481.8 (198.5)
EHL FVIII	**<1% (n=12)**	**1-3% (n=48)**	**3-5% (n=39)**	**>5% (n=50)**
Age				
Mean (SD)	27.8 (21.6)	22.3 (16.2)	24.9 (15.0)	27.7 (15.4)
ABR				
Mean (SD)	4.0 (5.9)	2.0 (3.7)	1.8 (2.3)	2.0 (2.7)
Median (Q1 to Q3)	0.4 (0.0 – 5.6)	0.5 (0.0 – 1.9)	0.8 (0.0 – 3.2)	1.2 (0.0 – 2.7)
Subjects with 0 ABR				
Percentage (%)	41.7	43.8	41.0	36.0
Monthly factor concentrate usage (IU/kg/month)				
Mean (SD)	379.5 (364.1)	363.5 (153.1)	360.3 (89.8)	406.4 (177.0)

ABR=annualized bleeding rate; EHL=extended half-life; n=number of subjects; SD=standard deviation; SHL=standard half-life.

Table 21. Annualized bleeding rates parsed by estimated FVIII trough levels based on inclusion criteria of a minimum of 365 days on treatment plan.

365 Day Inclusion Criteria	Estimated Factor VIII Trough Level			
SHL FVIII	**<1% (n=16)**	**1-3% (n=45)**	**3-5% (n=21)**	**>5% (n=29)**
Age				
Mean (SD)	29.5 (14.1)	23.8 (15.6)	32.3 (15.4)	34.1 (15.0)
ABR				
Mean (SD)	7.4 (15.1)	1.9 (2.9)	2.2 (1.7)	4.5 (6.4)
Median (Q1 to Q3)	3.5 (1.3 – 6.3)	0.8 (0.2 – 2.6)	1.8 (1.0 – 3.8)	1.7 (0.0 – 7.0)
Subjects with 0 ABR				
Percentage (%)	6.3	24.4	9.5	31.0
Monthly factor concentrate usage (IU/kg/month)				
Mean (SD)	299.4 (124.8)	383.1 (176.6)	461.5 (176.0)	509.6 (249.1)
EHL FVIII	**<1% (n=8)**	**1-3% (n=31)**	**3-5% (n=23)**	**>5% (n=32)**
Age				
Mean (SD)	28.7 (24.6)	21.2 (16.1)	24.5 (14.7)	30.9 (15.7)
ABR				
Mean (SD)	3.1 (5.5)	1.4 (2.1)	1.7 (2.6)	2.0 (2.9)
Median (Q1 to Q3)	0.1 (0.0 – 3.2)	0.6 (0.0 – 2.0)	0.6 (0.0 – 2.4)	1.0 (0.0 – 2.7)
Subjects with 0 ABR				
Percentage (%)	50.0	41.9	43.5	37.5
Monthly factor concentrate usage (IU/kg/month)				
Mean (SD)	444.6 (435.9)	370.4 (108.4)	365.6 (87.6)	399.3 (179.8)

ABR=annualized bleeding rate; EHL=extended half-life; n=number of subjects; SD=standard deviation; SHL=standard half-life.

6.4 Discussion

The results of this study provide insights on the use of SHL FVIII and EHL FVIII and the assessment of bleeding rates based on FVIII trough levels. In general, higher monthly factor concentrate usage was seen with SHL FVIII compared to EHL FVIII, and while ABR was highest in individuals with a FVIII trough level of <1%, higher ABR was also reported in individuals with a FVIII trough level of >5%. The proportion of individuals with zero bleeds was similar to a clinical phase 3 study by Klamroth et al. [135] in which the proportion of patients with hemophilia A in the FVIII trough level of 1-3% was reported to be 42% for rurioctocog alfa pegol, an EHL FVIII (versus 43.8% in the CBDR and WAPPS-Hemo dataset).

A comparison between the 90-day vs. 365-day inclusion criteria was conducted because a single bleeding episode may drastically change the ABR of an individual on a FVIII treatment for a shorter period of time. For example, a single bleed for an individual on FVIII prophylaxis treatment for 90 days would increase their ABR from 0 to around 4, thus significantly altering the interpretation of ABR results. The comparison between 90-day and 365-day inclusion criteria showed ABR and proportion of subjects with 0 ABRs.

It was hypothesized that higher FVIII trough levels would result in lower ABR, and this was the case when comparing to FVIII trough level of <1%. However, when comparing between other FVIII trough levels, the results were inconclusive, particularly of note is higher ABR noted for estimated FVIII trough levels >5% as compared to 1-5%. There may be multiple reasons for targeting higher FVIII trough levels or administering higher doses. Patients with hemophilia A may be undergoing immune tolerance induction therapy due to the presence of inhibitors, which would result in high doses but low actual FVIII trough levels. The PopPK models developed in WAPPS-Hemo do not account for the faster clearance observed in people with hemophilia A

with inhibitors and would thus estimate a higher trough level than what may be actually observed. Lower FVIII trough levels for severe hemophilia patients may result in their FVIII levels to be <1%, resulting in spontaneous bleeding and consequently increasing their ABR. Another explanation may be that some patients had a higher number of bleeds at a prior lower target FVIII trough level, therefore their dose was increased to limit the number of bleeds for phenotypic high frequency bleeders. Phenotypic frequent bleeders are likely on a higher dose to lower their risk of bleed and thus are more likely to be in higher trough FVIII levels, however may have higher ABR similar to those at lower FVIII trough levels. ABR may also be increased for those with a higher bleeding risk (e.g. physical trauma from partaking in more strenuous physical activities), but this information was not reported in the dataset. In order to determine the FVIII trough level that is most cost-effective for the hemophilia population, using the value of ABR alone is insufficient without additional information regarding the numerous factors affecting bleeding risk. The usage of SHL FVIII was generally higher than in EHL FVIII, which may be due to less frequent dosing and a longer reported half-life of EHL FVIII at the population level. [69] Those taking EHL FVIII have lower ABRs compared to SHL FVIII at the same FVIII trough level.

Limitations identified in this chapter mainly pertain to the source of the dataset. As the dataset is collected from real-world data input by clinicians (in WAPPS-Hemo) and patients (in CBDR), there is potential for user input error when identifying various factors including patient covariates such as age and weight, as well as clinician-inputed concentration-time points. The CBDR and WAPPS-Hemo dataset do not have information on physical activity intensity, which may play a significant role in the ABR value. In addition, patient adherence in real world scenarios is likely lower compared to clinical trial data, resulting in lower confidence of doses

recorded and collection of bleeding history. Despite these challenges, the inclusion criteria aimed to minimize reporting unreliable data by only including treatment plans with >70% infusions recorded within CBDR.

6.5 Conclusion

In summary, this chapter summarizes the relationship between estimated FVIII trough levels, ABR, and FVIII usage. Higher FVIII trough levels tend to be correlated with higher FVIII usage. ABR was highest in the <1% FVIII trough group, however ABR did not decrease as the FVIII trough reached >5%, potentially due to immune tolerance induction therapy and social factors that may increase bleeding risk. In addition, phenotypic frequent bleeders are likely on a higher dose to lower their risk of bleed and thus are more likely to be in higher trough FVIII levels, however may have higher ABR similar to those at lower FVIII trough levels. The ABR results obtained from this real-world dataset is similar to what was seen in clinical trials. [135]

Chapter 7: Cost-utility analysis of emicizumab for the treatment of severe hemophilia A patients in Canada

This chapter is reflective of an original manuscript published by the Ph.D. candidate (Jacky Ka-Hei Yu) in Haemophilia. All pertinent dialogue in this chapter was written by the Ph.D. candidate.

Yu JK, Wong WWL, Keepanasseril A, Iorio A, Edginton AN. Cost-utility analysis of emicizumab for the treatment of severe hemophilia A patients in Canada. Haemophilia. 2022; 00:1-10. DOI: 10.1111/hae.14723.

7.1 Introduction

Hemophilia A is caused by a deficiency of clotting factor VIII, with the severe phenotype defined as < 1%. [5] There are still many challenges with prophylactic treatment, including the use of multiple clotting factor concentrates throughout treatment, including SHL FVIII and EHL FVIII. [88] FVIII administration is required generally three times weekly to maintain FVIII trough levels ≥ 1% to prevent spontaneous bleeding. [4, 20, 136] When switching an individual from SHL to EHL products, the dose of the EHL FVIII is initiated with the same weight-based dosing while reducing the frequency of infusion, [17, 42] suggesting that EHL products have a longer half-life than SHL products.

Emicizumab is a bispecific, recombinant, monoclonal antibody that bridges activated factor IX and factor X, thus mimicking and partially restoring the function of clotting FVIII in people with hemophilia A. [23] Emicizumab provides several advantages, including its subcutaneous route of administration, reduction of bleeding episodes and dosing frequency. These benefits may replace the use of prophylactic FVIII concentrates in hemophilia A.

In Canada, hemophilia products are provided to Canadian patients through HQ and the CBS through a Request for Proposals submission. [137] The Canadian tender process is conducted every 2-3 years, where the CBS and HQ conduct periodic requests for proposals for blood products. [138] All manufacturers with products in Canada submit bids and are reviewed by a committee. [138] A large component in deciding which FVIII concentrate will be chosen to be covered by the federal government depends on the cost of the product. [138]

Conducting a literature search regarding economic evaluations in hemophilia show that the comparison between prophylaxis between SHL, EHL FVIII, and emicizumab are limited. Most cost-effectiveness and cost-utility analysis are prone to methodological deficiencies due to

lack of clinical trial data, the rare nature of the disease, and lack of clarity of doses used in practice. [25, 38, 39, 139, 140]

With the approval of emicizumab in Canada, the Canadian Agency for Drugs and Technologies in Health (CADTH) has recently published its reimbursement recommendation, suggesting that emicizumab should be reimbursed for the treatment of patients with severe hemophilia without FVIII inhibitors if the public payer cost of emicizumab should not exceed the public payer cost of treatment with the least costly FVIII replacement that is being reimbursed. [141] Given the lifelong burden of the disease and the high cost of treatment, an economic evaluation comparing the cost and effectiveness of prophylactic FVIII and emicizumab would be beneficial. The objective of this study is to estimate the health and economic effects of using prophylactic EHL FVIII, SHL FVIII, and emicizumab in severe HA.

7.2 Methods

7.2.1 Overview

To determine the cost-effectiveness of prophylactic SHL FVIII, EHL FVIII, and emicizumab, a state-transition Markov model was used in the form of cost-utility analysis. A Canadian provincial ministry of health payer perspective was taken, with the focus being on direct medical costs of providing patient care. Effectiveness was measured using quality-adjusted life years (QALYs), the product of time spent in each health state and the quality-of-life utility values. An annual discount rate of 1.5% on cost and effectiveness was used. [142] The model was built using TreeAge Pro 2021 (TreeAge Software, Williamstown, MA).

7.2.2 Study Cohort

The study cohort in the state-transition model includes 2-year-old male patients with severe hemophilia A, because primary prophylaxis regimens are started at a very young age before joint disease has developed, and children less than 2 years of age are not usually included in licensure studies. [5, 143]

7.2.3 Treatment Strategies

Three prophylactic treatment strategies were compared:

- SHL FVIII (standard of practice)
- EHL FVIII (standard of practice)
- Emicizumab

7.2.4 Decision Model

Cohorts that were included in the model are assigned to prophylactic EHL FVIII, SHL FVIII, or emicizumab and cycled monthly through different health states over a lifetime horizon.

Patients remained or move to another health state based on transition probabilities. Patients accumulated costs and utilities, expressed as Canadian dollars and QALYs respectively.

In each treatment arm, the Markov model consisted of 4 main health states (Figure 21). In the FVIII prophylactic health state, patients were at risk of death from any cause, bleeding event, and joint damage. During the first 12 and 18 cycles (for SHL and EHL FVIII respectively), patients were at risk for inhibitor development, as the risk usually occurred within the first 150 exposure days (ED) [144]. Patients who experienced a bleeding event incur additional costs from additional FVIII consumption. Patients who experienced joint damage incur additional costs for an orthopedic procedure, assumed to be knee replacement surgery. For the remainder of the cycles, patients who have experienced joint damage incurred costs associated with physiotherapy, consultations with healthcare providers, and laboratory tests.

In the inhibitor development health states, patients were assumed to undergo immune tolerance induction (ITI) therapy along with emicizumab prophylaxis for 12 cycles. If ITI therapy was successful, patients transitioned to FVIII prophylaxis with no risk of inhibitor, and if unsuccessful, patients transitioned to emicizumab prophylaxis. Finally, the death from any cause state was considered an absorbing state. A detailed Markov model decision tree for prophylactic SHL FVIII, EHL FVIII, and emicizumab can be found in Figure S1.

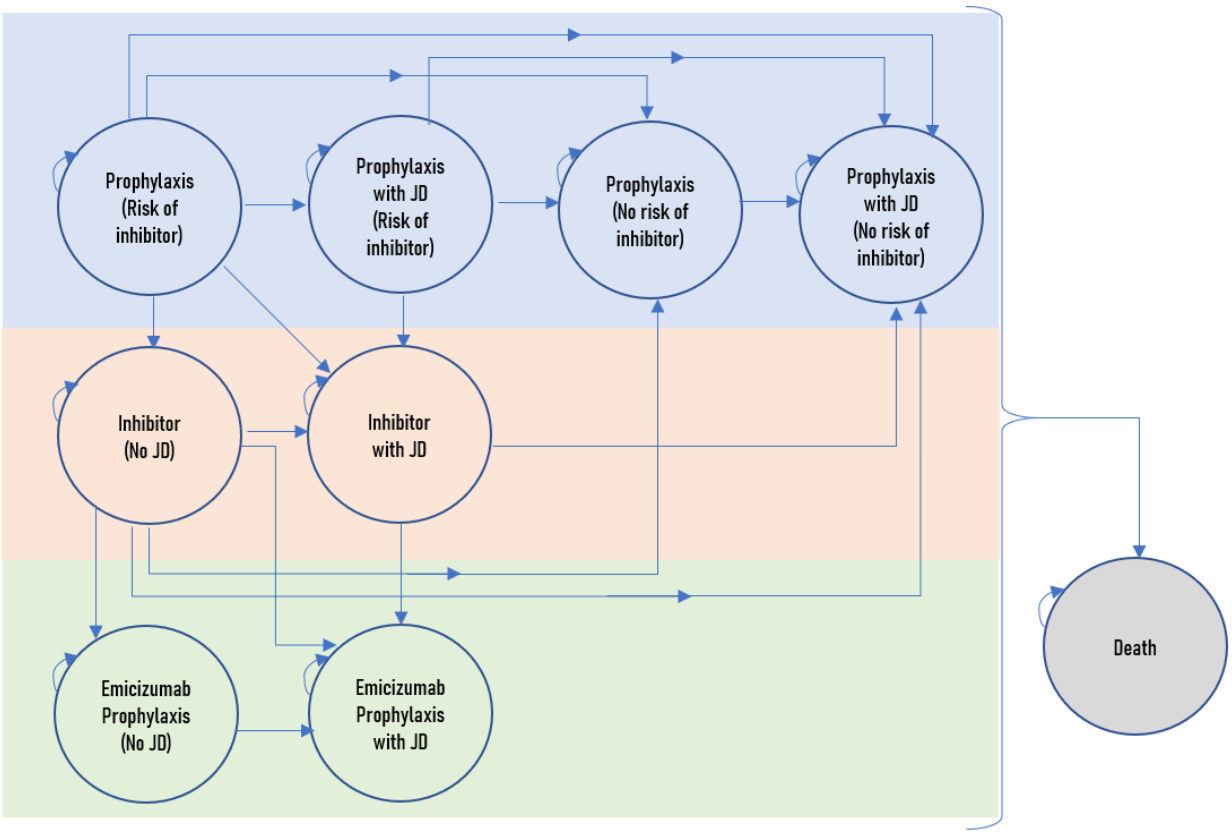

Figure 21. Markov model structure used in cost-utility analysis for SHL FVIII, EHL FVIII, and emicizumab prophylaxis. JD = Joint Damage. For additional implementation details on the prophylaxis health states, see Figure S1.

7.2.5 Model Parameters

The base-case estimates and ranges of all clinical probabilities, time courses, quality of life measures (utilities), and costs used in the model are presented in Table 22.

Table 22. Base-case estimates and ranges used in sensitivity analyses.

Variable	Base-case	Range	Distribution	Source
Clinical Probabilities (Annual)				
Probability of inhibitor development on SHL FVIII (across 12 months)	0.3	(0.225, 0.375)	Beta	[145]
Probability of inhibitor development on EHL FVIII (across 18 months)	0.3	(0.225, 0.375)	Beta	[145]
Probability of inhibitor development on emicizumab	0			Assumption
Probability of bleed on SHL FVIII	0.639	(0.411, 0.778)	Beta	CBDR
Probability of bleed on EHL FVIII	0.509	(0, 0.774)	Beta	CBDR
Probability of bleed on emicizumab	0.292	(0.178, 0.391)	Beta	[146]
Probability of joint damage on SHL FVIII (over lifetime horizon)	0.6	(0.45, 0.75)	Beta	Based on clinical opinion
Probability of joint damage on EHL FVIII (over lifetime horizon)	0.6	(0.45, 0.75)	Beta	Based on clinical opinion
Probability of joint damage on emicizumab (over lifetime horizon)	0.6	(0.45, 0.75)	Beta	Assumption: Same as SHL and EHL FVIII
Probability of successful ITI therapy on SHL FVIII	0.7	(0.53, 0.88)	Beta	[145]
Probability of successful ITI therapy on EHL FVIII	0.7	(0.53, 0.88)	Beta	[145]
Probability of death from any cause	Age specific			
Health Utilities				
Utility on prophylactic SHL FVIII	Table S5		Beta	CBDR (n = 136)
Utility on prophylactic EHL FVIII	Table S5		Beta	CBDR (n = 40)
Utility on prophylactic emicizumab	Table S5		Beta	Assumption: Same as SHL and EHL FVIII [147]
Utility on immune tolerance induction therapy	0.66	(0.50, 0.83)	Beta	[140]
Disutility for bleeding event (per event) on SHL FVIII	-0.12	(-0.15, -0.09)	Beta	[148]
Disutility for bleeding event (per event) on EHL FVIII	-0.12	(-0.15, -0.09)	Beta	[148]

Disutility for bleeding event (per day) on emicizumab	-0.12	(-0.15, -0.09)	Beta	Assumption
Disutility for arthroplasty procedure	-0.39	(-0.49, -0.29)	Beta	[148]
Disutility for joint damage	-0.06	(-0.08, -0.05)	Beta	[149]
Costs (in Canadian dollars, $)				
SHL FVIII concentrate (per IU)	2.77		Gamma	[150]
EHL FVIII concentrate (per IU)	3.68		Gamma	[151]
Emicizumab (per mg)	162.57		Gamma	[152]
Recombinant FVIIa (per µg)	3.83		Gamma	[153]
Knee replacement therapy	9527.40	(7145.55, 11909.25)	Gamma	[154]
Other hemophilia costs (per year) (e.g. doctor consultations, healthcare professionals consultations, laboratory tests, and other diagnostic tests)	698.50	(523.87, 873.12)	Gamma	[155]
Joint damage related costs (per year) (e.g. physiotherapy)	312	(234, 390)	Gamma	OMHLTC
Other variables				
Discount rate for costs	0.015			
Discount rate for effects	0.015			
Dosage of SHL FVIII (IU/kg) per month, prophylaxis	365.15	(343.5, 386.8)	Normal	CBDR
Dosage of EHL FVIII (IU/kg) per month, prophylaxis	384.86	(346.4, 423.4)	Normal	CBDR
Dosage of emicizumab (mg/kg) per month, prophylaxis dose (loading)	12	(9, 15)		
Dosage of emicizumab (mg/kg) per month, prophylaxis dose (maintenance)	6	(4.5, 7.5)		
Dosage of SHL FVIII (IU/kg) per bleeding episode while on prophylaxis	49.7	(48.2, 51.3)	Normal	CBDR
Dosage of EHL FVIII (IU/kg) per bleeding episode while on prophylaxis	49.1	(47.1, 51.4)	Normal	CBDR
Dosage of FVIIa (mcg/kg) per bleeding episode while on emicizumab	270	(202.5, 337.5)	Normal	

Dosage of FVIII immune tolerance induction therapy (IU/kg) per day	100	(75, 125)	Normal
Duration of bleeding event (days)	1		
Body weight (kg)	Age specific		

7.2.6 Canadian Bleeding Disorders Registry

This study protocol was reviewed by the Office of Research Ethics at the University of Waterloo and received ethics approval to retrieve severe hemophilia A data from the Canadian Bleeding Disorders Registry (CBDR) (Protocol #43108). Data and variables extracted from CBDR on July 9, 2021 include patient demographics, prophylactic and bleeding treatment plans, ABR, and EQ-5D global quality-of-life scores. The eligibility criteria and information retrieved from CBDR was included in Table S4.

For this analysis, the weight-based dosing values of FVIII (median and 95% CI) were obtained from CBDR. The prophylactic doses of FVIII were increased to 100 IU/kg if patients developed inhibitors and underwent ITI therapy. Patients taking prophylactic emicizumab would be administering a loading dose of 3 mg/kg weekly in the first cycle, followed by a maintenance dose of 6 mg/kg in subsequent cycles.

The recommended doses in case of bleeding episodes were derived using the dose recorded for a severe traumatic bleeding episode. ABRs were derived using the total number of bleeds during the timeframe. If a bleeding event occurred while on prophylactic emicizumab, a dose of 270 µg/kg recombinant FVIIa (rFVIIa) would be administered.

Utility scores were based on the EQ-5D-5L score, obtained from the Patient Reported Outcomes Burdens and Experiences (PROBE) questionnaire. The questionnaire is completed voluntarily by the patient during their hemophilia clinic visit. The prophylactic weight-normalized dose, ABRs, and quality-of-life scores for each individual were calculated from the CBDR dataset using the following equation:

$$Parameter = \frac{\sum_{i=1}^{n}(Parameter\ value_i \times Duration\ of\ treatment_i)}{\sum_{i=1}^{n} Duration\ of\ treatment_i}$$

For the calculated parameters, the median and the 95% CI for each parameter were used as the base-case and variability respectively.

7.2.6.1 Clinical Probabilities

Clinical probabilities of SHL and EHL FVIII were obtained from CBDR. The probability of bleed for emicizumab was reported to be more effective than FVIII prophylaxis at reducing the rate of bleeds by 36%. [146] The probability of bleeds is assumed to be constant, as there is a lack of evidence to describe the complex relationship between variables (e.g. age, weight, and location of bleed) as an input; the American Thrombosis and Hemostasis Network repeated time to event model (unpublished data) showed that once pharmacokinetics was taken into account, there were no significant variables on bleeding risk.

In regards to inhibitor development, the probability of successful ITI therapy was based on expert opinion, assumed to be 70% for FVIII. While there is potential for anti-drug antibodies to develop while on emicizumab, the frequency seen in clinical trials is very low [127] and was not included.

The probability of joint damage on SHL and EHL FVIII was calculated based on expert opinion, assuming that approximately 60% of patients would develop joint damage over their lifetime. Due to the lack of long-term data with the use of emicizumab, the probability of joint damage on emicizumab was assumed to be equivalent to FVIII.

Finally, the probability of death is assumed to be equal to an individual without hemophilia A. The standard life table for the years 2016-2018 for Canadian male individuals from Statistic Canada was used.

7.2.6.2 Costs

Foreign cost data was converted to Canadian dollars using the Purchasing Power Parity [156] and costs were inflated to 2022 Canadian dollars based on Consumer Price Index [157]. The price of octocog alfa, efmoroctocog alfa, and recombinant coagulation factor VIIa were used as the representative cost for SHL, EHL FVIII, and rFVIIa respectively [150-153]. The prophylactic FVIII dosing regimen per cycle is obtained using the median weekly dosage obtained from CBDR.

The cost per knee replacement was taken from the 2018-2019 Canadian Joint Replacement Registry. [154] Patients with joint damage incur physiotherapy costs in line with the fees set by the Ontario Ministry of Health and Long-Term Care for one Episode of Care [158].

7.2.6.3 Quality-of-life measures (utilities)

To evaluate quality-of-life, EQ-5D scores, developed by the EuroQol Group, of severe hemophilia A patients were obtained using the PROBE questionnaire. EQ-5D scores were obtained cross-sectionally and were recorded into CBDR. The EQ-5D values are converted to a quality-of-life score between 0 to 1, where 0 represents death, and 1 represents perfect health. [159] The median utility scores while on prophylactic SHL and EHL FVIII were obtained for various age groups from CBDR and reported in Table S5. The utility score of emicizumab was assumed to be equivalent to the combined median utility of FVIII.

When individuals experience a bleed, a disutility score of -0.12 was applied based on data obtained from the Institute for Clinical and Economic Review. [160] The disutility of a bleed is multiplied by the time course of the bleeding event. A disutility score of -0.06 was applied based

on data from 2000-2002 Medical Expenditure Panel Survey EQ-5D index scores for arthropathies. [149]

7.2.7 Analysis Plan

The mean cost and effectiveness values from the probabilistic sensitivity analysis (PSA) were used for the base case analysis to calculate incremental cost-effectiveness ratio (ICER) and to account for uncertainties of the model parameters. [147] The PSA was performed using a Monte-Carlo simulation of 10,000 iterations by sampling parameters from a probability distribution (See Table 22), resulting in a cost-effectiveness plane. A gamma distribution was applied to costs, beta distribution to probabilities and utilities, and normal distribution for all other distributions. A cost-effectiveness acceptability curve of each treatment was created based on the ICER in relation to a willingness-to-pay (WTP) threshold of $0 per QALY for cost-saving, as well as $50,000 for cost-effectiveness, similar to what is seen from other economic evaluations in hemophilia. [161]

A microsimulation of 10,000 individuals was conducted to compare the difference in the number of bleeds. In addition, one-way sensitivity analysis was used to evaluate the uncertainty in the base case model parameters on the ICER. The parameter ranges for the one-way sensitivity analysis were derived based on the calculated 95% CI from data obtained from CBDR and literature wherever possible, or alternatively, a default variation of 25% was used.

Scenario analyses were conducted for five scenarios:

a) Duration of bleeding event of 2 days.
b) Time horizon of 3 years; the CBS recommends to keep contracts for the tender process to 2 or 3 years. [162]
c) Length of ITI therapy for 18 months.

d) Use of emicizumab, and emicizumab with FVIII prophylaxis every 2 weeks for tolerance after successful treatment of ITI.

e) Reduction in cost of 5%, 10%, and 20% of SHL and EHL FVIII.

7.3 Results

7.3.1 Demographics

A total of 591 subjects were included from the CBDR dataset (Table 23). The average age of the prophylactic SHL and EHL FVIII cohorts were 21.6 (range 0-81 years) and 22.8 (range 0-68) respectively.

Table 23. FVIII Prophylactic and bleeding regimen characteristics (n = 691).

	Prophylactic SHL FVIII	**Prophylactic EHL FVIII**	**Bleeding SHL FVIII**	**Bleeding EHL FVIII**
Subjects, n	447	144	336	102
Regimens, n	447	237[a]	336	102
Mean age (SD) [min, max]	21.6 (16.8) [0, 81]	22.8 (17.0) [0, 68]	22.8 (17.1) [0, 81]	26.4 (17.3) [0, 68]

[a]In CBDR, there were subjects who were taking more than 1 EHL FVIII in different regimens

7.3.2 Base-case analysis

The base-case analysis resulted in a total cost per person for SHL FVIII of $39.8M and 41.10 QALYs, whereas EHL FVIII cost $54.3M and resulted in 41.37 QALYs, and emicizumab cost $38.8M and resulted in 41.59 QALYs (Table 24). Emicizumab was the cheapest and most effective option; treatment using emicizumab resulted on average in 46 and 25 less bleeds in a lifetime compared to SHL and EHL FVIII respectively (Table 25), based on a microsimulation of 10,000 individuals. Thus, emicizumab dominated the other two treatment options.

Table 24. Base-case analysis.

Treatment	**Cost, $**	**ΔCost, $**	**QALY**	**ΔQALY**	**ICER**	**WTP: $0**
Emicizumab	$38,808,764	N/A	41.59	N/A	-	100%
SHL FVIII	$39,844,055	$1,035,291	41.10	-0.49	Dominated	0%
EHL FVIII	$54,332,603	$15,523,839	41.37	-0.22	Dominated	0%

Note: All costs are in 2022 Canadian dollars. EHL FVIII, extended half-life factor VIII; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-years; SHL FVIII, standard half-life factor VIII.

Table 25. Mean number of bleeds during lifetime.

Treatment	Mean number of bleeding events; lifetime horizon[1]
SHL FVIII	72
EHL FVIII	51
Emicizumab	26

[1]A microsimulation of 10,000 subjects was conducted. Values reported were rounded to whole numbers.

7.3.3 Sensitivity analyses

In the 1-way sensitivity analyses, all parameters were varied over clinically plausible ranges (Figure 22-23). Parameters related to prophylactic hemophilia treatment, such as costs and utilities, had the largest effect. If the utility score of prophylactic emicizumab was worse than the prophylactic utilities for SHL and EHL, then FVIII prophylaxis would be the more cost-effective option. Following utility scores, drug unit costs were the next most sensitive parameter noted.

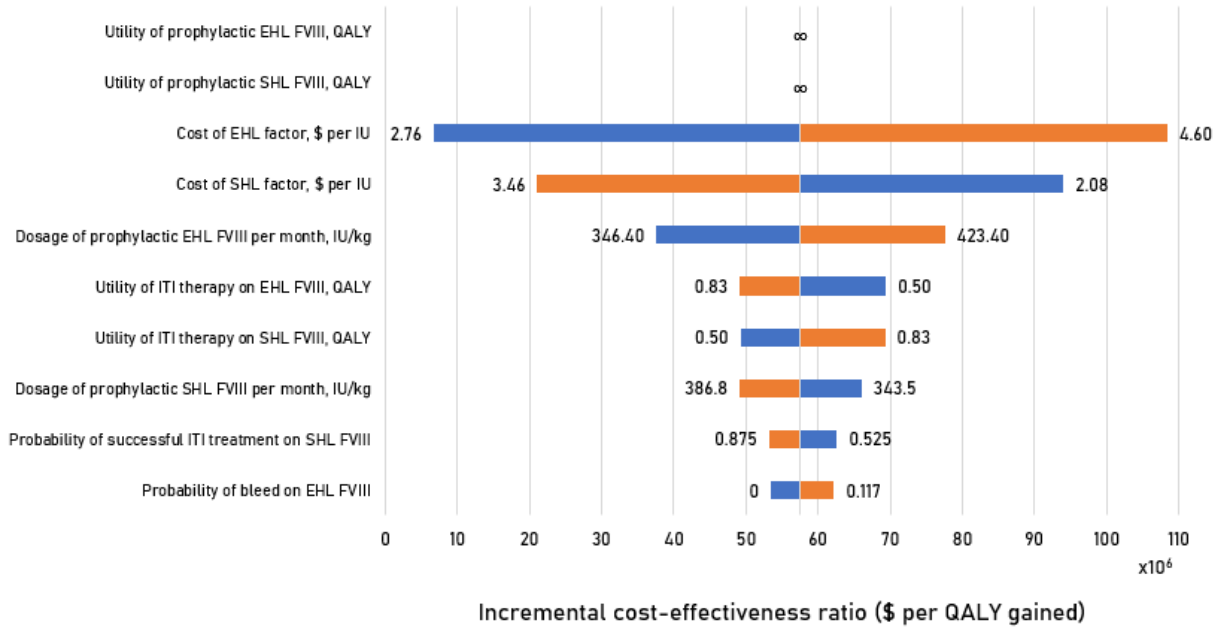

Figure 22. One-way sensitivity analysis between SHL FVIII and EHL FVIII (ICER = 57,561,888). The 10 variables whose variation caused the most significant change in ICER (x-axis) are shown. Ranges of the 1-way sensitivity analyses are shown beside the bar.

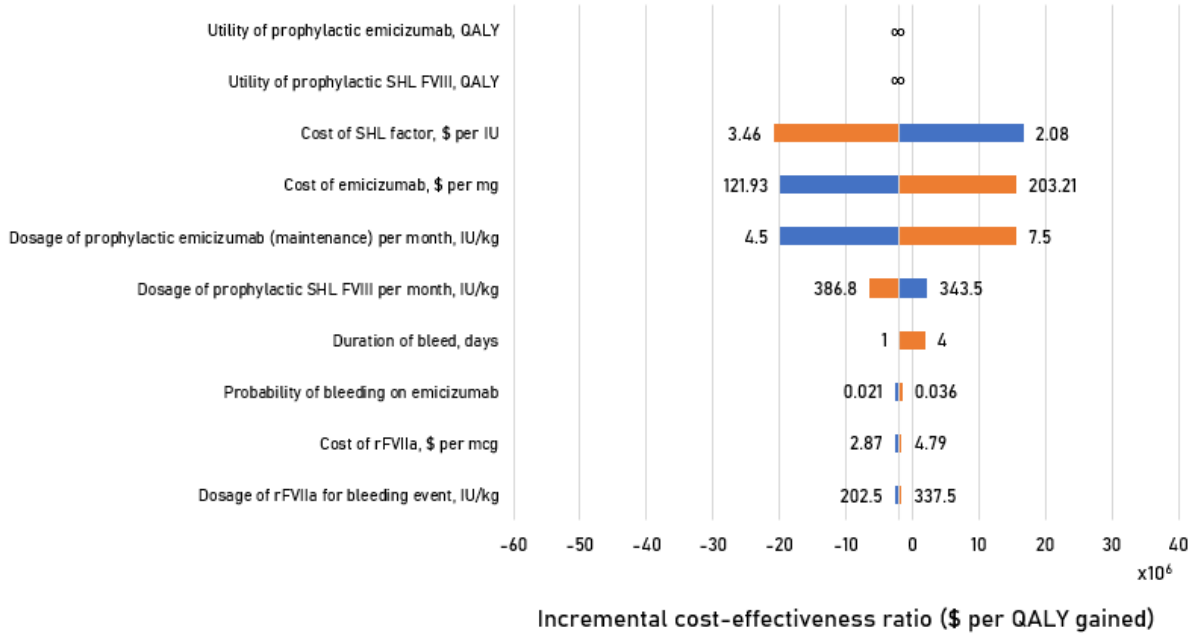

Figure 23. One-way sensitivity analysis between SHL FVIII and emicizumab (ICER = -2,122,287). The 10 variables whose variation caused the most significant change in ICER (x-axis) are shown. Ranges of the 1-way sensitivity analyses are shown beside the bar.

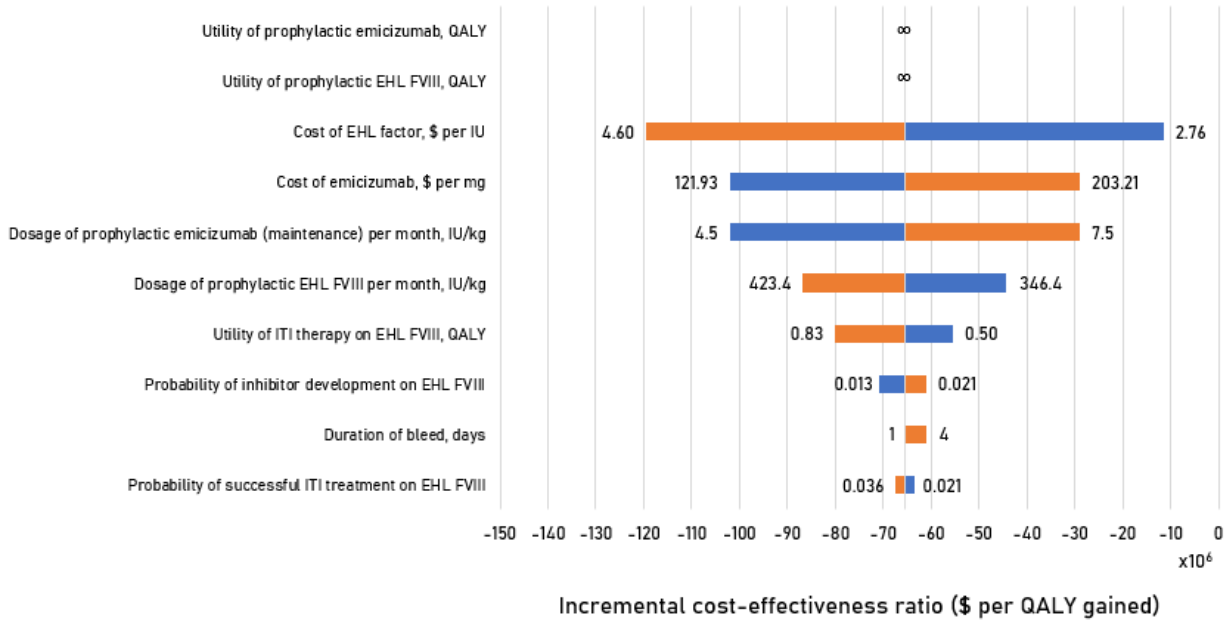

Figure 24. One-way sensitivity analysis between EHL FVIII and emicizumab (ICER = -65,489,114). The 10 variables whose variation caused the most significant change in ICER (x-axis) are shown. Ranges of the 1-way sensitivity analyses are shown beside the bar.

7.3.4 Probabilistic sensitivity analysis

In the PSA, uncertainties were assessed in all parameters. Assuming a cost-saving WTP threshold of $0 per QALY gained, emicizumab was considered the cost-saving option 100% of the 10,000 Monte Carlo simulations (Table 24).

7.3.5 Scenario analysis

The results of the scenario analysis are shown in Table 26. Emicizumab was cost-saving in 82.5% of the simulations and cost-effective at a WTP of $50,000 in 83.9% of the simulations, when the duration of bleeding events increased to 2 days. A decrease in 5% of cost of SHL resulted in emicizumab being cost-saving in 0% and cost-effective at a WTP of $50,000 in 0% of the simulations. Using emicizumab prophylaxis after successful ITI resulted in emicizumab being cost-saving in 100% and cost-effective at a WTP of $50,000 in 100% of the simulations.

Based on one-way sensitivity analysis, emicizumab no longer is a cost-savings option at a discount rate of 2.8% for SHL FVIII and 30.3% for EHL FVIII.

Table 26. Scenario analysis.

Scenario	Cost of emicizumab, $	QALY	SHL FVIII compared to emicizumab			EHL FVIII compared to emicizumab			WTP	
			ΔCost, $	ΔQALY	ICER	ΔCost, $	ΔQALY	ICER	$0	$50K
Base case	38,808,764	41.59	1,035,291	-0.49	Dom.	15,523,839	-0.22	Dom.	100%	100%
Duration of bleeding events = 2 days	39,924,155	41.60	403,324	-0.49	Dom.	14,867,179	-0.25	Dom.	82.5%	83.9%
Time horizon = 3 years	574,331	2.93	395,507	-0.08	Dom.	743,379	-0.18	Dom.	100%	100%
ITI therapy = 18 months	38,804,413	41.60	1,249,269	-0.54	Dom.	15,808,383	-0.28	Dom.	100%	100%
Emi prophylaxis after successful ITI	38,805,358	41.60	910,790	-0.42	Dom.	12,539,007	-0.23	Dom.	100%	100%
Emi prophylaxis + FVIII q2w after successful ITI	38,803,914	41.59	2,692,217	-0.41	Dom.	15,040,214	-0.21	Dom.	100%	100%
5% Discount on FVIII costs	38,804,288	41.59	-800,077	-0.49	1,632,811	12,965,803	-0.22	Dom.	0%	0%
10% Discount on FVIII costs	38,807,344	41.59	-2,637,615	-0.49	5,382,888	10,408,588	-0.22	Dom.	0%	0%
20% Discount on FVIII costs	38,806,111	41.59	-6,308,965	-0.48	13,143,677	5,287,333	-0.22	Dom.	0%	0%

7.4 Discussion

Prior to emicizumab, the treatment of hemophilia A involves lifelong use of FVIII. The results of this study suggest that emicizumab may be a cost-saving option compared to SHL and EHL FVIII as prophylactic treatment of severe hemophilia A. Emicizumab was found to have higher effectiveness for a lower cost.

In the sensitivity analysis, the results were highly sensitive to the utility scores and costs of treatment. The utility scores obtained from CBDR were similar to other cost-effectiveness studies. The CADTH report used a baseline utility score of 0.908 across all treatments [142], similar to scores obtained from CBDR. The results were similar to another cost-utility analysis comparing EHL and SHL FVIII [161], where it was concluded that EHL FVIII generates greater quality of life and reduced costs. The utility score of emicizumab may be an underestimation, due to the significant decrease in bleeding rates and injection frequency. The PSA displayed large uncertainties in ICER values, in which a small change in utility scores for SHL FVIII, EHL FVIII, and emicizumab resulted in very large positive and negative ICER values. This further suggests that obtaining accurate utility estimates may provide a better estimate on the most cost-saving treatment. In addition, a small change in the monthly usage of SHL, EHL FVIII, and emicizumab resulted in high variance in cost despite fixing the unit costs of SHL, EHL FVIII, emicizumab, and rFVIIa.

Similarly to this cost-utility analysis, where the average wholesale price was used in the base-case analysis, the unit cost of EHL FVIII in the base-case scenario is higher or equal compared to SHL FVIII in various cost-effectiveness analysis. [161, 163] Sensitivity analysis show that the costs of prophylactic treatment options were highly sensitive parameters. [161, 164] Obtaining the actual cost of FVIII and emicizumab is paramount in determining more

reliable ICER comparisons between treatment options. Costs and QALY results from the base-case estimate were similar to CADTH [142], with a cost of $32,574,676 and QALY of 31.476.

The median ABR obtained from CBDR for SHL FVIII was 1.02, but higher in other economic evaluations [161, 163]. This may be attributed to patients with ≥70% infusions recorded per year were included in the CBDR dataset, therefore the patient population is likely to have greater adherence towards FVIII use. Subjects recorded in CBDR are more likely to be monitored closely by healthcare professionals and thus potentially lowering their chances of bleeding.

The cost-utility analysis provides several advantages compared to previously published economic evaluations. First, this analysis uses real-world data to obtain quality-of-life scores. Obtaining a registry with a large number of patients is very difficult in hemophilia due to the rare nature of the disease. This analysis looks at the cost of hemophilia over a lifetime horizon unlike other evaluations.

The model has several limitations. First, the inhibitor development rate between SHL and EHL FVIII seem to vary, however that has not been completely confirmed nor included. Inhibitor development rate would decrease quality of life, and its costs and utilities should be included for a more accurate representation of hemophilia treatment.

Second, the probability for a minor bleed given a bleeding event occurred was assumed to be equivalent for FVIII treatments. If the variables were modeled using two different variables (one for SHL and one for EHL), the one-way sensitivity analysis would reveal that SHL FVIII dominates EHL FVIII when the probability for a minor bleed for SHL FVIII is greater than 0.975. However, due to the absence of data in literature that states that the probability for a minor

bleed is different between the two treatments, they are treated as equivalent. Once data becomes available, the variables should be separated.

Third, bleeding rates were assumed to be consistent throughout the time horizon. However, individuals who suffer from a joint bleed are at a much higher risk for having another bleeding event, and thus would have a higher bleeding rate compared to an individual without a previous bleed.

The analysis demonstrates conservative estimates for emicizumab, as model parameters were biased against emicizumab due to the lack of data and literature required to quantify several model parameters, for example the assumption that the probability of emicizumab was assumed to be equivalent to FVIII. Emicizumab is also administered subcutaneously as opposed to frequent intravenous infusions, thus posing a potential benefit in compliance to medication regimen. The benefit of greater compliance to emicizumab compared to FVIII was not factored into the model.

Due to the low bleeding rates seen in clinical trials [165], emicizumab may be a favourable treatment option for decreasing bleeds and minimizing healthcare costs. Ultimately, the cost of emicizumab must be considered when determining whether treating hemophilia patients with prophylactic emicizumab is the most cost-effective option.

7.5 Conclusion

The cost-utility analysis showed that emicizumab is more effective and may be less costly than FVIII for patients with hemophilia A in Canada, conditional on drug cost assumptions. However, the actual costs of FVIII and emicizumab may be inaccurate due to the discounted costs during the tender bidding process. Despite these uncertainties, our model indicates that emicizumab may be a potential favourable treatment option for minimizing healthcare costs and providing higher effectiveness.

Chapter 8: Discussion, Conclusions, and Future Directions

8.1 Discussion

The overarching objective of this thesis was to explore the pharmacokinetic and economic implications when switching between hemophilia A treatments.

Prophylactic treatment of factor concentrates has been used for hemophilia A and have been the preferred treatment over on-demand treatment due to the reduction in bleeding episodes. Due to the high inter-individual variability and low between-subject variability for the PK of factor concentrates, individualized dosing using PopPK models and patient covariates such as age and weight have been shown to be useful in providing predictable concentration-time profiles to achieve trough concentrations above 1% to prevent spontaneous bleeding episodes. However, due to various reasons, including national plan coverage, side effects, and drug shortages, patients may switch between hemophilia A treatment options, in which individual PK parameters are not known, may result in a prophylactic dose that may not be appropriate due to under-dosing, leading to increased risk of bleeds, or resource wastage, due to unnecessary use of factor concentrates.

Chapter 2 is a scoping review that discusses the lack of research and guidance when using PK for tailoring prophylactic treatments for people switching between treatments in hemophilia A. This review notes that while at the population level some factor VIII concentrates may have a higher half-life at the population level, individual PK parameters are highly variable. The study by Young et al. displays a half-life ratio of 0.79 to 2.98 for subjects on a SHL FVIII and Eloctate. [69] While at the population level Eloctate has a longer half-life compared to SHL FVIII, there are subjects in which switching to Eloctate yields a shorter half-life. The potential risk of assuming an increase in half-life when switching from a standard-acting to a long-acting

factor concentrate may lead to increased risk of bleeds due to under dosing. Without assessing individual PK parameters, the current approach of using population level information to switch between factor concentrates may not yield expected results. Combining the knowledge of the individual's PK of a factor concentrate prior to switching with the knowledge of the population PK characteristics of the factor concentrate after the switch may result in better individual PK estimates of the new factor concentrate, however the accuracy and precision of such an approach was not yet studied. Using the WAPPS-Hemo database, this research project can be performed due to the amalgamation of data from hemophilia subjects across the globe who have switched between various FVIII concentrates.

Chapter 3 aims to address the research question that arose in Chapter 2. It was hypothesized that the use of individual PK parameters from a prior factor concentrate may be useful in determining a dosing regimen when switching prophylactic treatment to a new factor concentrate. Three different switching regimens were compared, including 2 SHL FVIII and 1 EHL FVIII (Advate to Novoeight, Novoeight to Advate, and Advate to Eloctate). Three different experimental methods to predict individual PK were explored: Method 1 used the typical population value of CL, V_1, Q, and V_2 of the second product from its PopPK model, assuming that all individuals have the same PK parameters; Method 2 used the calculated values of CL, V_1, Q, and V_2 for the second product based on the individual with a given set of covariates and the PopPK model of the second product, assuming that all individuals with identical fat-free mass and age will have the same PK parameters; and Method 3 used the values of CL, V_1, Q, and V_2 for the second product based on an individual with a given set of covariates and the PopPK model of the second product, along with the predicted η-values of CL and V_1 from the first product and its PopPK model, taking into account what had happened on the first product in

addition to Method 2. It was shown that ignoring the variability (Method 1) is the least efficient approach for choosing a safe and effective dosing regimens for many individuals at the moment of switching, with differences in predicted to observed half-life ranging up to 17 hours. When taking covariates that influence PK into consideration (Method 2), some individuals were still not well represented from using this method, suggesting that the potential differences seen may be due to some unexplained variability or other contributing factors not included in the PopPK model. Using prior PK knowledge along with the PopPK model of the second product and individual covariates (Method 3) resulted in the best method in predicting half-life, and while the predicted individual half-life still differed up to 10 hours, it is still significantly less compared to Method 1 and Method 2.

Chapter 4 aims to address limitations that arose in Chapter 3, including switching between EHL FVIII products and looking further into trends to see which individuals may benefit more from utilizing their PK parameters from a prior factor concentrate when switching between factor concentrates. Three different switching regimens were compared, including SHL FVIII and 2 EHL FVIII (Adynovate to Eloctate, Eloctate to Adynovate, and SHL FVIII to Eloctate). Similar conclusions were formulated, where the population mean half-life reported does not describe the changes in half-life in the individual level. Utilizing PK parameters from a prior factor concentrate when switching between factor concentrates was particularly beneficial for subjects with extremely low or high half-life values. On average, higher number of observations (at least 5 or more) used during Bayesian estimation to acquire η-values led to better precision of PK parameter estimates obtained when using the η-method. For subjects with hemophilia without extreme half-life predictions on the prior factor concentrate, utilizing the η-method (Method 3) performed similarly to the PopPK method (Method 2). In particular,

individuals at lower η_{CL} percentiles were sometimes statistically better predicted on the η-method compared to the PopPK method. However, for those that are not in the extremes with respect to PK, individuals would benefit from acquiring PK estimates using either method.

With the approval of emicizumab in Canada as prophylactic treatment, this provides subjects with hemophilia with several advantages, including subcutaneous route of administration, reduction of bleeding episodes, and reduction in dosing frequency. Emicizumab is dosed based on body weight at 1.5 mg/kg weekly, 3 mg/kg every 2 weeks, or 6 mg/kg every 4 weeks and has predictable PK, similar to other monoclonal antibodies. If prophylactic FVIII concentrates are not needed to treat hemophilia, weight-based dosing of emicizumab may eliminate the need for individualized dosing. Chapter 5 discusses the use of PopPK to illustrate the changes in time-to-trough levels and the cost-savings when modifying emicizumab dose to the nearest vial size. Individuals with a higher body weight may benefit from maintaining their dosing frequency and rounding dose down with a decrease in emicizumab trough concentrations by no more than 13%. Since the target for emicizumab is to maintain a trough concentration ≥45 μg/mL to achieve zero ABR in ≥50% of patients [123], a decrease of up to 13% is most likely insignificant in maintaining the target. Individuals with a lower body weight may benefit from reducing dose frequency and administering the entire vial, resulting an annual reduction in emicizumab usage by up to 46%. The reduction in emicizumab usage is greater on the QW regimen as compared to the Q2W and Q4W regimens. a decrease in annual consumption of emicizumab can result in significant cost savings for the payer and may potentially improve quality of life because of decreased number of subcutaneous injections administered per year. The results of this study have been implemented into an online resource called Calibra, (http://calibra.app) which was made available to help find the most effective combination of

emicizumab vials and suggests an optimum combination of dose and frequency to achieve the same plasma concentrations seen in clinical trials.

Chapter 6 presents results from CBDR and WAPPS-Hemo regarding the relationship between FVIII trough levels, ABRs, as well as compare the difference in ABR between SHL and EHL FVIII. A sensitivity analysis comparing the results by including patients with a minimum of 90 vs. 365 days of treatment was also explored to determine if including only longer FVIII treatment periods make a difference in ABR results. The proportional of individuals with zero bleeds was similar to a clinical 3 study by Klamroth et al. [135] in which the proportion of patients of patients with hemophilia A in the FVIII trough level of 1-3% was reported to be 42% for rurioctocog alfa pegol compared to 43.8% in the CBDR and WAPPS-Hemo dataset. The proportion of subjects with zero bleeds was higher for EHL FVIII compared to SHL FVIII for each FVIII trough level group. Higher FVIII trough levels resulted in lower ABR when comparing to FVIII trough level of <1%. However, higher ABR was noted for estimated FVIII trough levels >5%. There may be multiple reasons for targeting higher FVIII trough levels or administering higher doses. Patients with hemophilia A may be undergoing immune tolerance induction therapy, which would result in high doses but low actual FVIII trough levels. Lower FVIII trough levels for severe hemophilia patients may result in their FVIII levels to be <1%, resulting in spontaneous bleeding and consequently increasing their ABR. In order to determine the FVIII trough level that is most cost-effective for the hemophilia population, using the value of ABR alone is insufficient without additional information regarding the numerous factors affecting bleeding risk. The usage of SHL FVIII was generally higher than in EHL FVIII, which may be due to less frequent dosing and a longer reported half-life of EHL FVIII at the population level. [69]

Chapter 7 addresses CADTH's recent reimbursement recommendation, suggesting that emicizumab should be reimbursed for the treatment of patients with severe hemophilia without FVIII inhibitors if the public payer cost of emicizumab should not exceed the public payer cost of treatment with the least costly FVIII replacement that is being reimbursed. [141] Given the lifelong burden of the disease and the high cost of treatment, an economic evaluation comparing the cost and effectiveness of prophylactic FVIII and emicizumab was conducted to estimate the health and economic effects of using prophylactic EHL FVIII, SHL FVIII, and emicizumab in severe hemophilia A. The results of this study suggest that emicizumab may be a cost-saving option compared to SHL and EHL FVIII as prophylactic treatment of severe hemophilia A. Emicizumab was found to have higher effectiveness for a lower cost. The cost-utility analysis provides several advantages compared to previously published economic evaluations, including the use of real-world data to obtain quality-of-life scores. Obtaining a registry with a large number of patients is very difficult in hemophilia due to the rare nature of the disease. Limitations however existed, such that model parameters were biased against emicizumab due to the lack of data and literature required to quantify several model parameters, for example the assumption that the probability of emicizumab was assumed to be equivalent to FVIII. Emicizumab is also administered subcutaneously as opposed to frequent intravenous infusions, thus posing a potential benefit in compliance to medication regimen, however the benefit of greater compliance to emicizumab compared to FVIII was not factored into the model. Due to the low bleeding rates seen in clinical trials [165], emicizumab may be a favourable treatment option for decreasing bleeds and minimizing healthcare costs. Ultimately, the cost of emicizumab must be considered when determining whether treating hemophilia patients with prophylactic emicizumab is the most cost-effective option.

8.2 Conclusions

The collective objectives of this thesis are to provide insight on the pharmacokinetic and economic implications when switching between hemophilia A treatments, and how the findings of these results may be implemented for real-world use.

The dissertation describes a unique algorithm, the η-method, for providing initial dosing regimen predictions on a new factor concentrate, and has been shown to be beneficial for individuals with η_{CL} values. This algorithm incorporated into PopPK models may aid in predicting individual PK when switching between hemophilia treatments and can be implemented on the WAPPS-Hemo platform to guide clinicians in estimating the individual impact of switching between FVIII concentrates and tailoring the initial regimen on the new concentrate, minimizing the time needed for dose optimization. At the time of this thesis, the WAPPS-Hemo network has expanded to over 700 centres and 11000 patients, empowering hemophilia treatment by facilitating individualized dosing on a global scale.

For patients with hemophilia on emicizumab, the simulations conducted exploring the use of emicizumab dosed based on vial size may have significant economic implications in cost-savings and provide a more practical dosing regimen. This study is highly relevant to real-world practice, and is utilized through Calibra, a software connected to the WAPPS-Hemo portal and research network, to provide the most effective combination of emicizumab vials to reduce unnecessary wastage of the drug.

When looking at FVIII trough levels, higher FVIII trough levels did not correlate with lower annualized bleeding rates. ABR was highest in the <1% targeted FVIII trough group, however ABR decreased as the FVIII trough increased, however at FVIII trough levels >5%,

ABR was not lower than FVIII trough levels 1-5%, potentially due to immune tolerance induction therapy and social factors that may increase bleeding risk.

Finally, the cost-utility analysis showed that emicizumab is more cost effective compared to SHL and EHL FVIII concentrates for patients with hemophilia A in the Canadian healthcare landscape, however the analysis is highly sensitive to drug cost assumptions.

8.3 Future Directions

Hemophilia guidelines are recommending the use of individualized PK monitoring using limited samples and PopPK models. The WAPPS-Hemo platform and PopPK models to individualize patient dosing regimens on factor concentrates is used worldwide by clinicians. The η-method may be implemented into WAPPS-Hemo to provide clinicians with a better understanding of individualized PK of patients with hemophilia when switching between factor concentrates, even prior to their first dose.

Emicizumab may be more effective and may be less costly than FVIII for patients with hemophilia A in Canada. Despite this finding, costs and utility scores are highly sensitive to the model and can ultimately influence the decision on what treatment should be covered by the Canadian healthcare system. Updating the Markov model with more reliable cost estimates, such as having a better understanding of the costs paid by the Canadian healthcare system via the tender bidding process, may lead to more definitive and conclusive results.

The wealth of knowledge in the field of hemophilia continues to grow as newer research and treatment options become available for patients with hemophilia A. Early clinical data on gene therapy options such as valoctocogene roxaparvovec (Roctavian^{TM}, BioMarin, San Rafael, CA) are of particular interest as a potential long-term treatment option in hemophilia A. [166] Clinical trials have shown favourable safety profiles with the use of gene therapy and may be a potential cure of hemophilia A in the near future. [167] When additional clinical trial data is published, cost-effectiveness analysis can be conducted to quantify key areas of uncertainty with the use of gene therapy compared to emicizumab and prophylactic FVIII.

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Appendices

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1) A comparison of methods for prediction of pharmacokinetics across factor concentrate switching in hemophilia patients (https://doi.org/10.1016/j.thromres.2019.10.023)

2) A comparison of methods for prediction of pharmacokinetics when switching to extended half-life products in hemophilia A patients (https://doi.org/10.1016/j.thromres.2020.10.024)

Thank you!

Chapter 5

Chapter 7

Supplemental Information

Table S1. Summary characteristics of subjects in each study and the covariate space used to develop the Advate, Novoeight, and Eloctate PopPK models as implemented in WAPPS-Hemo.

Demographics	Advate to Novoeight dataset median [range]	Advate to Eloctate dataset median [range]	Advate WAPPS model median [range]	Novoeight WAPPS model median [range]	Eloctate WAPPS model median [range]
Subjects (n)	15	29	79	55	164
Age (years)	23 [13-28]	31 [15-62]	20 [1-62]	11 [1-54]	30 [12-65]
Body weight (kg)	77 [57-100]	74 [56-129]	67 [11-133]	43 [12-107]	71 [42-129]

Table S2. NCA and Bayesian half-life results.

Estimation Method	Advate to Novoeight		Advate to Eloctate	
	Advate	Novoeight	Advate	Eloctate
NCA half-life (h)	9.1	9.2	11.4	17.3
Bayesian half-life (h)	9.6	9.9	11.8	17.5
Difference	0.42	0.70	0.37	0.23

Table S3. Individual observed vs. predicted half-life switching from Advate to Novoeight, Novoeight to Advate, and Advate to Eloctate.

Subject	Observed t½ of second product (h)	Method 1 predicted t½ (h)	Method 1 t½ absolute relative error (%)	Method 2 predicted t½ (h)	Method 2 t½ absolute relative error (%)	Method 3 predicted t½ (h)	Method 3 t½ absolute relative error (%)	Closest t½ prediction
Study #1: Advate to Novoeight								
1	8.1	10.8	32.8	12.6	55.5	9.8	20.6	Method 3
2	10.3	10.8	4.8	10.6	2.9	6.9	32.6	Method 2
3	9.4	10.8	15.1	11.8	26.2	9.4	0.1	Method 3
4	12.4	10.8	13.3	10.8	12.8	11.4	8.2	Method 3
5	12.1	10.8	10.7	10.6	12.4	11.2	6.9	Method 3
6	12.8	10.8	15.7	11.7	8.1	13.0	1.8	Method 3
7	7.0	10.8	54.2	11.0	56.7	7.2	2.4	Method 3
8	8.7	10.8	24.4	11.8	36.8	8.8	1.4	Method 3
9	11.1	10.8	3.0	11.1	0.2	10.6	4.9	Method 2
10	6.8	10.8	57.7	11.1	62.7	5.7	16.6	Method 3
11	10.3	10.8	4.2	11.6	11.8	12.9	24.5	Method 1
12	10.2	10.8	5.2	11.0	7.4	8.5	16.6	Method 1
13	7.1	10.8	51.7	11.6	63.3	6.9	2.6	Method 3
14	7.9	10.8	36.3	12.3	55.3	8.7	9.8	Method 3
15	10.4	10.8	4.1	10.5	1.2	7.8	24.9	Method 2
Study #2: Novoeight to Advate								
1	9.8	10.8	10.3	12.6	29.0	8.1	17.1	Method 1
2	7.0	10.8	53.7	10.7	52.5	10.4	48.2	Method 3
3	9.4	10.8	15.0	11.8	26.1	9.4	0.1	Method 3
4	11.4	10.8	5.4	10.8	5.0	12.4	8.9	Method 2
5	11.2	10.8	4.0	10.6	5.9	12.1	7.4	Method 1
6	13.0	10.8	17.2	11.7	9.7	12.8	1.8	Method 3
7	7.2	10.8	50.5	11.0	53.0	7.0	2.4	Method 3
8	8.8	10.8	22.8	11.8	34.9	8.7	1.4	Method 3
9	10.6	10.8	2.0	11.1	5.4	11.1	5.2	Method 1
10	5.6	10.8	93.3	10.9	96.0	6.7	20.2	Method 3

11	12.9	10.8	16.2	11.5	10.2	10.3	19.7	Method 2
12	8.6	10.8	25.4	11.1	28.8	10.3	19.9	Method 3
13	7.0	10.8	54.8	11.7	67.5	7.1	2.7	Method 3
14	8.7	10.8	24.1	12.3	41.4	7.9	8.9	Method 3
15	7.8	10.8	38.2	10.5	34.7	10.4	33.1	Method 3
Study #3: Advate to Eloctate								
1	14.9	15.4	3.4	18.9	26.7	12.4	17.1	Method 1
2	11.4	15.4	35.4	15.9	39.2	10.9	4.4	Method 3
3	23.6	15.4	34.5	21.4	9.1	23.1	1.8	Method 3
4	28.5	15.4	45.9	18.4	35.4	18.9	33.7	Method 3
5	20.3	15.4	24.0	16.6	18.1	14.1	30.6	Method 2
6	21.4	15.4	28.1	17.5	18.4	16.0	25.4	Method 2
7	12.5	15.4	23.9	14.9	19.8	12.0	3.3	Method 3
8	18.0	15.4	14.1	18.7	4.1	15.5	13.8	Method 2
9	11.4	15.4	34.9	13.6	19.4	11.8	3.3	Method 3
10	12.9	15.4	19.2	15.1	16.4	8.6	33.9	Method 2
11	18.2	15.4	15.1	17.5	3.8	15.5	15.0	Method 2
12	16.8	15.4	8.1	16.2	3.7	14.0	16.9	Method 2
13	16.1	15.4	4.3	17.3	7.3	17.2	6.6	Method 1
14	13.9	15.4	11.3	18.8	35.3	11.2	18.9	Method 1
15	19.1	15.4	19.2	14.0	26.7	16.4	14.0	Method 3
16	14.6	15.4	6.0	16.4	12.6	14.1	2.8	Method 3
17	12.6	15.4	22.7	14.5	15.5	13.6	8.1	Method 3
18	32.3	15.4	52.2	16.8	48.1	25.9	19.9	Method 3
19	19.6	15.4	21.2	16.1	17.7	15.4	21.2	Method 2
20	9.2	15.4	67.9	15.3	65.9	9.2	0.1	Method 3
21	18.9	15.4	18.2	16.9	10.5	15.1	20.0	Method 2
22	15.7	15.4	1.6	14.9	4.8	13.6	13.2	Method 1
23	17.3	15.4	10.6	17.9	3.7	17.3	0.5	Method 3
24	23.0	15.4	33.0	15.6	32.1	19.9	13.6	Method 3
25	16.8	15.4	8.3	13.7	18.3	13.8	18.2	Method 1
26	17.1	15.4	9.9	14.9	13.1	13.0	24.1	Method 1
27	19.3	15.4	20.2	18.0	6.8	17.8	8.2	Method 2
28	14.6	15.4	5.7	14.1	3.3	14.4	1.2	Method 3
29	18.4	15.4	16.2	16.6	9.7	19.4	5.6	Method 3

Table S4. Eligibility criteria and information gathered from CBDR.

Eligibility criteria for information gathered from CBDR
• Patients must be diagnosed with severe hemophilia A (baseline FVIII level <1%) • A minimum of 70% of infusions recorded in CBDR (for SHL FVIII, a minimum of 109 infusions in a year; for EHL FVIII, a minimum of 72 infusions in a year; for emicizumab, a minimum of 8 infusions in a year) • A minimum of 90 days on each recorded treatment plan
Variables obtained from CBDR
• Patient demographics (diagnosis, age, gender, and weight) • Prophylaxis treatment plan (includes specific FVIII concentrate or emicizumab, dose, frequency • Start and end date of treatment plan • Number of bleeding episodes while on prophylaxis • Bleeding treatment plan (includes specific FVIII concentrate or emicizumab and dose) • Quality-of-life score (EQ-5D global score)

Table S5. Utility score according to age group from CBDR dataset.

	Prophylactic SHL FVIII			**Prophylactic EHL FVIII**			**Combined FVIII (Assumed equivalent to emicizumab)**		
Age	**2-20**	**20-40**	**40+**	**2-20**	**20-40**	**40+**	**2-20**	**20-40**	**40+**
N	41	110	81	12	23	13	53	133	94
Median EQ-5D	1.000	0.911	0.802	0.962	0.924	0.843	1.000	0.924	0.817

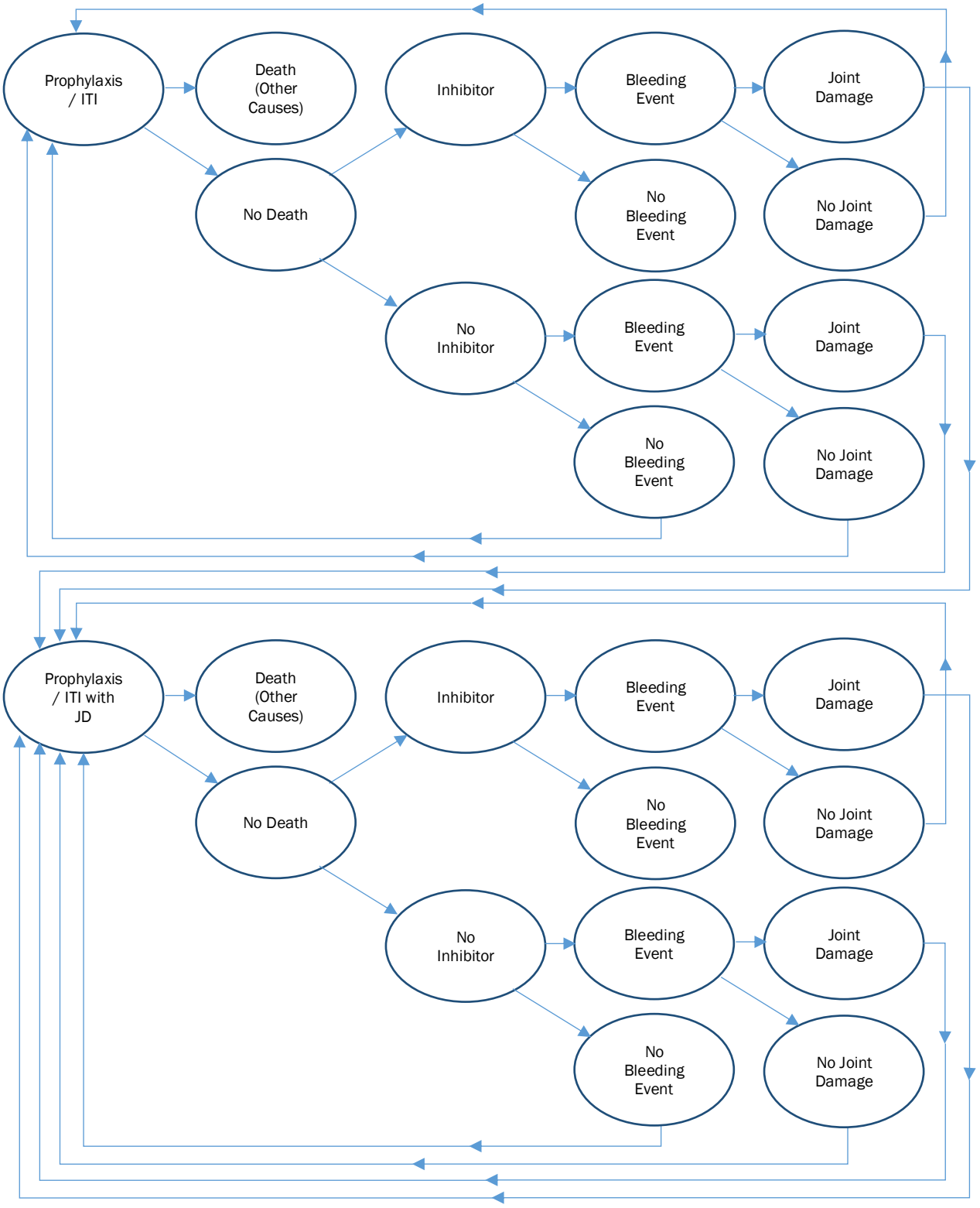

Figure S1. Detailed Markov model decision tree of prophylactic SHL FVIII, EHL FVIII, and emicizumab. ITI = Immune Tolerance Induction; JD = Joint Damage.