PERIOPERATIVE OUTCOMES IN PATIENTS WITH RARE BLEEDING DISORDERS

METHODOLOGICAL CONSIDERATIONS FOR THE ASSESSMENT OF PERIOPERATIVE OUTCOMES IN PATIENTS WITH RARE BLEEDING DISORDERS

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ABSTRACT

Rare bleeding disorders are a group of inherited conditions caused by a deficiency of blood coagulation factors. Due to the low prevalence of these conditions in the general population, there is a scarcity of data to make informed, evidence-based clinical decisions. In this population who are highly susceptible to excessive bleeding, surgeries and invasive procedures pose an additional level of risk for bleeding-related and non-bleeding-related complications, especially in the perioperative period. The data scarcity in patients with rare bleeding disorders is further compounded by an infrequent rate of invasive procedures, sometimes attributed to the hemostatic challenges faced by such interventions among other factors.

To address the problem of insufficient data for healthcare decision-making, as well as the assessment of perioperative outcomes in this population, this thesis explores the use of routinely collected data for the creation of a novel surgical database used for the assessment of perioperative hemostasis, complications, and initial surgical plan deviations in patients with rare bleeding disorders.

Across five chapters, this thesis provides the methodology for the creation of the Indiana Hemostasis and Thrombosis Center (IHTC) Surgical Database, a descriptive analysis of the population and procedures, and assessment of perioperative outcomes. Approaches to ensure the validity of study results including confounder adjustment by variable selection methods, data quality improvement, missing data description, and imputation methods, were explored. Evidence from randomized controlled was also reviewed using Cochrane methodology to summarize the efficacy of clotting factor concentrates for the prevention of bleeds and bleeding-related complications in patients with hemophilia.

Based on findings from the different approaches (observational study designs, randomized controlled trials, and systematic review methodology), recommendations were made regarding methodological and analytical considerations required to ensure valid and reliable perioperative outcome assessment in patients with rare bleeding disorders.

The following provides a brief outline of each chapter.

Chapter 1 is an introduction that outlines each of the studies in this thesis.

Chapter 2 is a descriptive overview of the design, structure, and exploratory analysis of data captured in the IHTC-Surgical Database over a 21-year period.

Chapter 3 is a retrospective cohort study that assessed the association between inhibitor status and perioperative hemostasis, complications, and initial surgical plan deviations in patients with hemophilia A and B.

Chapter 4 is a systematic review that examined the efficacy of clotting factor concentrates for the prevention of bleeds and bleeding-related complications in patients with hemophilia.

Chapter 5 outlines key findings, limitations, implications of the research in this thesis, and methodological considerations for the assessment of perioperative outcomes in patients with bleeding disorders.

PUBLICATIONS RELATED TO THIS THESIS

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Olasupo OO, Lowe MS, Krishan A, Collins P, Iorio A, Matino D. Clotting factor concentrates for preventing bleeding and bleeding-related complications in previously treated individuals with haemophilia A or B. *Cochrane Database Syst Rev*. 2021 Aug 18;8(8):CD014201. doi: 10.1002/14651858.CD014201. PMID: 34407214; PMCID: PMC8407508.

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CONTRIBUTIONS BY OTHERS

A full account of the authors' contributions appears at the end of each chapter.

TABLE OF CONTENTS

LIST OF ABBREVIATIONS

AHCDO	Australian Haemophilia Centre Directors' Organization
ATHN	American Thrombosis and Hemostasis Network
BPAs	Bypassing agents
CBDR	Canadian Bleeding Disorders Registry
CDC	Centers for Disease Control and Prevention
CFC	Clotting factor concentrates
CI	Confidence Interval
EACH2	European Acquired Hemophilia Registry
EUHASS	European Hemophilia Adverse Event System
FDA	Food and Drug Administration
FVIII	Factor VIII
FIX	Factor IX
GRADE	Grading of Recommendations, Assessment, Development and Evaluation
HA	Hemophilia A
HB	Hemophilia B
Haem-A-QoL	Haemophilia Quality of Life Questionnaire for Adults
Haem-QoL	Haemophilia Quality of Life Questionnaire
HRI	High-responding inhibitors
HRQoL	Health-related quality of life
IHTC	Indiana Hemophilia and Thrombosis Center
ICTRP	International Clinical Trials Registry Platform
ISTH	International Society on Thrombosis and Hemostasis
LRI	Low-responding inhibitors
MCMC	Markov Chain Monte Carlo

MD	Mean difference
MRI	Magnetic resonance imaging
NHD	UK National Hemophilia database
NHF	National Hemophilia Foundation
MD	Mean difference
MRI	Magnetic resonance imaging
PROBE	Patient Reported Outcomes, Burdens, and Experiences
PTPs	Previously treated patients
PwRBDs	People with rare bleeding disorders
RBDs	Rare bleeding disorders
RCT	Randomized controlled trials
RR	Relative Risk
SSC	Scientific and Standardization Committee
UKHCDO	United Kingdom Haemophilia Centre Doctors Organization
VTE	Venous thromboembolism
vWD	von Willebrand disease
WFH	World Federation of Hemophilia
WHO	World Health Organization

CHAPTER 1: INTRODUCTION

Rare diseases affect a very small percentage of the population compared with other diseases.[1,2] They are also known as orphan diseases as they were historically **neglected due to small patient numbers**.[3] No consensus exists on the universally accepted definition of a rare disease, as definitions vary usually based on prevalence thresholds by geographical location or country, and by patient, provider, payer, or health technology assessment agency perspective.[2]

According to the Orphan Drug Act of the US FDA, a rare disease is one that affects less than 200,000 people in the US, [4] while in Europe and Canada, a rare disease affects 1 in 2,000 people.[5–7] **Prevalence thresholds** also range from 5 cases per 100,000 people in Korea to 76 cases per 100,000 people in China.[2,8] Threshold definitions for ultrarare conditions such as 1 in 1,000,000 people have also been used.[2]

There are approximately 7,000 rare diseases with new ones being reported on an ongoing basis. The majority of rare diseases (80%) are genetic or congenital in origin while other causes include infections, allergies, and environmental factors.[1]

Rare bleeding disorders are a group of conditions characterized by inadequacies in the coagulation pathway such that blood does not clot properly.[9] The switching on of the coagulation cascade or pathway[10] after a bruise or trauma ensures the stoppage of bleeding (hemostasis) by the formation of blood clots. Examples of rare bleeding disorders include deficiencies in coagulation Factor VIII (FVIII; hemophilia A), Factor IX (FIX; hemophilia B), von Willebrand disease (vWD), and platelets disorders. Others include deficiencies in fibrinogen, Factor II (FII), FV, FVII, combined FV/FVIII, FX, FXI, and FXIII. The prevalence of these conditions range from 1 in 500,000 for FVII deficiency to 1 in 2,000,000 for prothrombin and FXIII deficiency.[9,11]

Due to the low prevalence of these conditions, challenges and peculiarities faced in the clinical decision-making and research management include the scarcity of large epidemiological data, lack of sufficient understanding of the natural history, challenges in participant recruitment for randomized controlled trials (RCTs), and relatively fewer RCTs. The overall consequence of these is a limitation in evidence generation.

The scarcity of large longitudinal epidemiological data in this population also makes forecasts and predictions of long-term effectiveness speculative and often based on expert opinion as opposed to data driven.

1.1 Surgeries and invasive procedures in patients with bleeding disorders

Surgeries, either elective or emergent, are sometimes unavoidable and do not exempt people with rare bleeding disorders (PwRBDs) - a population at an increased risk for blood loss and hematological complications during the perioperative period. The intrusion into anatomical spaces which takes place during surgeries results in additional hemostatic challenge and could be a deterrent to surgical interventions in PwRBDs – thereby amplifying the dearth of epidemiological data for perioperative outcomes assessment.

A review of existing literature on the assessment of perioperative outcomes in bleeding disorders highlights practical approaches for the prevention and management of perioperative bleeding including the use of pharmacological agents such as clotting factor concentrates, tranexamic acid, desmopressin, fibrinogen, and prothrombin complex concentrate.[12] Meta-analysis of perioperative outcomes of laparoscopic splenectomy for hematological disorders has also been conducted with the conclusion that laparoscopic splenectomy is preferred to open splenectomy, based on shorter length of hospital stays, lower complication rates, but increased length of procedure times.[13(p)]

Retrospective data collection and analysis of 35 orthopedic procedures in patients with rare bleeding disorders have also been conducted in an Italian hospital. In this study, a description of the hemostatic agents used to achieve perioperative hemostasis, and bleeding complications were reported. This study also highlights the need for the combination of strict hemostatic control approaches, appropriate surgical techniques, and the involvement of specialized hemophilia centers for the successful outcome of orthopedic surgeries in patients with rare bleeding disorders.[14]

The Indiana Hemophilia and Thrombosis Center (IHTC) is a center of excellence for the management of **rare genetic and acquired bleeding disorders** with a multidisciplinary team providing comprehensive care for conditions such as hemophilia, thrombosis, von Willebrand disease (vWD), sickle cell disease, and other bleeding and clotting disorders.[15]

In Chapter 2, we describe the development of the IHTC-Surgical Database which captures data collected both retrospectively and prospectively at the IHTC from 1998 and ongoing. The IHTC surgical database is the only currently existing database dedicated to data collection on surgeries in PwRBDs. In addition to its novelty, the database serves as a central organized system to communicate across surgical care teams and therefore provides clinical decision support in the planning and surgical management in this population. Event sequencing in the perioperative period (pre-, intra-, and post-operative) as well as recommendations such as dosing schemes based on individual patient status and medication pharmacokinetics are also captured and integrated into the database. In this report, we described the database design, scope, structure, data collection methods, and an overview of contextual data captured. Following data verification, exploratory analysis of surgeries conducted over a 21-year period (1998-2019) was done to estimate the prevalence and outcome patterns across different bleeding disorders.

1.2 Perioperative hemostasis, complications, and deviations from pre-surgical plans

Perioperative outcomes pre-, intra-, and post-procedure captured in the IHTC-Surgical database include:

i. Perioperative hemostatic control:

Achieving adequate control of bleeding following surgeries, i.e., perioperative hemostasis is critical for surgical success as inadequate perioperative hemostasis is associated with undesirable outcomes, such as hemorrhage (excess bleeding) and associated blood loss, the need for transfusions, shock, increased length of hospital stay, and higher risk of mortality.[16]

In the IHTC surgical database and in our analyses, hemostatic control was assessed based on World Federation for Hemophilia (WFH) definitions regarding minimal perioperative blood loss and blood component transfusions comparable to the non-hemophilic population.[17] Using this criteria, perioperative hemostasis or hemostatic control was captured as:

- adequate if "excellent" or "good" or
- inadequate if "fair" or "poor"

ii. Complications

Complications have been defined as "any deviation from the ideal post-operative course that is not inherent in the procedure and does not comprise a failure to cure".[18] An assessment of the incidence and prevalence of perioperative complications in PwRBDs is highly beneficial to identify risk factors for these events and to prevent the inherent morbidity and mortality associated with these events.[19]All adverse hematological and non-hematological complications including pain, fever, infections, nausea, and vomiting were collected.

iii. Deviation from initial surgical plans

As a subset and complement of the data captured on complications, changes to the pre-determined surgery plan are also an important piece of information in improving surgical planning and improving surgical outcome in PwRBDs and in surgical population in general.[20] Deviations from preoperative surgical plans have been associated with increased risk of adverse events and therefore require proper monitoring, evaluation.[20]

Changes to the pre-surgical plan including such as event timing, scheduling of procedures, medications, the dose medications to achieve desired hemostatic range, changes in the length of hospitalization, techniques, personnel, and all peri-operative interventions not specified in the initial surgery plan, were captured in the IHTC database for future identification of risk factors.

1.3 Impact of neutralizing antibodies on perioperative outcomes

Based on needs assessment and consultation with the clinical team at the IHTC, the development of neutralizing antibodies (inhibitors) to clotting factor concentrates (CFCs) was identified as a major treatment-related complication in the management of hemophilia which results in the inability to achieve hemostasis through these standard therapies.

In **Chapter 3**, using the data from the IHTC surgical database, we assessed the association between inhibitor status and perioperative outcomes. Analytical methods to ensure the validity of study results were explored including variable selection methods in confounding adjustment, sub-group analysis, and multiple imputation methods to address missing data. Independent risk factors for perioperative hemostasis, complications, and surgical plan deviations in patients with hemophilia were also assessed.

1.4 Efficacy of clotting factor therapies for the prevention of bleeds and bleeding-related complications in previously treated patients (PTPs) with hemophilia

Recurrent bleeding into joints and soft tissues is a distinct feature of severe hemophilia resulting in progressive joint damage and sometimes, a need for joint replacement surgery. Prophylaxis using clotting factor concentrates is therefore a standard recommendation by the WFH.[17] However, controversies abound regarding the efficacy of this approach especially when joint damage has already taken place i.e., secondary prophylaxis.[21]

In Chapter 4, we conducted a systematic review to assess the efficacy of secondary prophylaxis using clotting factor concentrates and the effect of these therapies on bleed frequency (total bleeds and joint bleeds), clinical joint function, health-related quality of life (HRQoL), pain scores, radiologic joint score, or descriptions of joint damage. The risk of bias of included studies was assessed using the Cochrane risk of bias tool 1.0 and the certainty of the evidence was determined using the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) approach.[22,23]

1.5 Conclusions, recommendations, and future directions

In **Chapter 5**, we summarize the key findings, limitations, and future research direction based on the work in this thesis. Methodological recommendations to be considered in the assessment of perioperative outcomes in patients with rare bleeding disorders were also outlined.

Areas of duplication

The first two studies in this thesis use data from the IHTC-Surgical database. Hence, there is some repetition in the description of data across these two papers. Also, the first and third studies have been published in peer-reviewed journals while the second article is under peer-review.

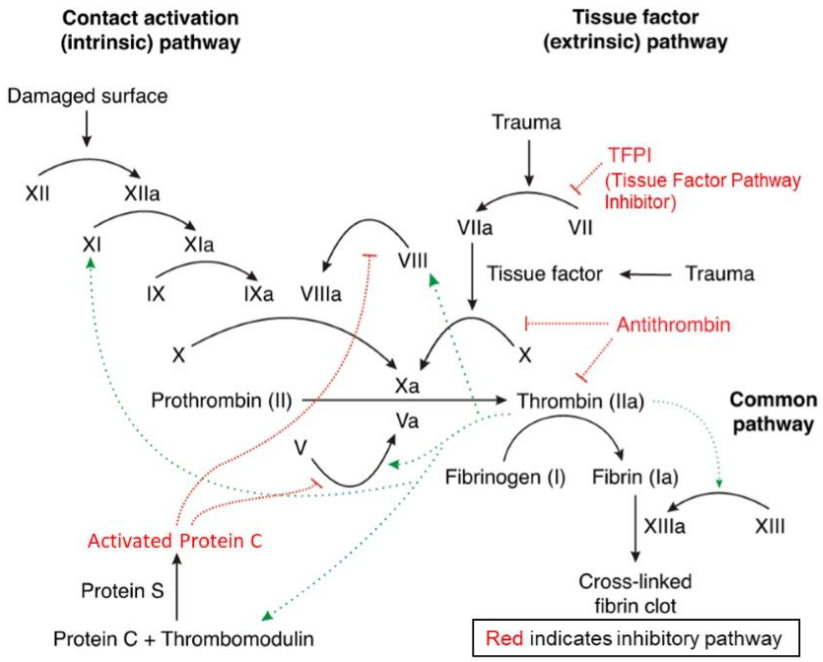

Figure 1: Coagulation Cascade[10]

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CHAPTER 2: UTILIZATION OF A SURGICAL DATABASE TO PROVIDE CARE AND ASSESS PERIOPERATIVE TREATMENT AND OUTCOMES IN PATIENTS WITH BLEEDING DISORDERS

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2.1 Abstract

Introduction: Perioperative care in bleeding disorders depend on clinician judgment and expert recommendations. A standardized system for planning and managing surgeries was developed at the Indiana Hemophilia & Thrombosis Center (IHTC) for clinical decision support and assessment of perioperative outcomes.

Aim: To describe the IHTC surgical database, its key components, and descriptive and exploratory analyses of surgeries from 1998 to 2019.

Methods: Surgical plan data across bleeding disorders entered historically (1998-2006), and prospectively (2006-2019) were stored and extracted. Perioperative outcomes (hemostatic control, complications, and surgical plan deviations) by bleeding disorder type and data collection period were assessed.

Results: Within the 21-year period, 3,246 surgical procedures were conducted in 1,413 patients. At surgery, the median(range) age of patients was 36.8 years (0month-96.1years), and 52.9% were males. The median(range) number of surgeries per patient was 1 (1-22), and the population included 48.6%, 26.5%, 11.6% and 13.2% with a diagnosis of von Willebrand disease, hemophilia A, hemophilia B, and other bleeding disorders, respectively. Major surgeries accounted for 36.7% (1,190/3,246) compared to 63.3% (2,056/3,246) minimally invasive procedures. Hemophilic patients had 1,492 (46.0%) procedures with 4.8% (72/1492) conducted in 20 inhibitor patients. Adequate hemostatic control was achieved in 90.9% and complications occurred in 13.6% of all procedures. Comparing surgeries in hemophilia patients with/without inhibitors, hemostatic control was higher in surgeries involving non-inhibitors (89.2% vs 63.6%, $p<0.001$) and complications occurred more frequently in surgeries involving inhibitors (31.2% vs 13.8%, $p=0.001$). Surgical plans were followed without deviation in 68.9% of procedures.

Conclusion: The surgical database is an important resource in surgical management in bleeding disorders. Further evaluation will facilitate use for development of predictive models and principles of care.

Key Words: Surgery, Data Management, Bleeding Disorders, Hemostasis, Hemophilia, Database, Perioperative Care.

2.2 Background

Surgeries in hemophilia, von Willebrand disease (vWD), and other bleeding disorders are challenging due to knowledge gaps in the implementation of evidence-based hemostatic management guidelines (1). Advancements such as the availability of clotting factor concentrates, bypassing agents, and improved understanding of hemostasis and thrombosis, have, however, significantly reduced surgical hazards (2). Despite these advances, perioperative care standards in bleeding disorders remain insufficient (3).

The need for a clinical decision-making framework in hemophilia treatment has resulted in guideline development by organizations including the National Hemophilia Foundation (NHF), World Federation of Hemophilia (WFH), the Australian Haemophilia Centre Directors' Organization (AHCDO) and the United Kingdom Haemophilia Centre Doctors Organization (UKHCDO) (1,4-7). Current guidelines include over-arching treatment recommendations regarding minor/major surgeries, desired target factor activity levels for specified number of days perioperatively, and pharmacological agents to avoid e.g., antiplatelet agents.

Also, as new products become available, treating providers rely on published data from pre- or post-licensure clinical trials, case reports or series to determine optimal regimens for minor/major surgical interventions. To address this, registries have been used to capture clinical/treatment-related information to assess efficacy of different treatment modalities (8-12).

Existing databases such as the American Thrombosis and Hemostasis Network (ATHN) and the UK National Hemophilia database (NHD), are multicenter, multipurpose databases focused on many aspects of care. Databases with a more restrictive scope e.g., the European Hemophilia Adverse Event System (EUHASS) and the European Acquired Hemophilia Registry [EACH2]) also exist, but none are focused specifically on surgeries.

Also, existing databases do not serve as a central, organized system to generate, uniformly communicate, and store peri-operative surgical plans across centers and surgical care teams (13-16). This lack of a standardized system for surgical interventions in bleeding disorders presents challenges for planning and surgical management of these patients.

To standardize perioperative care in bleeding disorders, the Indiana Hemophilia and Thrombosis Center (IHTC) developed a novel surgical database specific to this population to facilitate surgical planning, tracking and evaluation of peri-operative outcomes, and development of principles of care.

With a reach across the state of Indiana, the IHTC provides comprehensive care to 2,200 patients with hemophilia and rare bleeding disorders; of whom 1,413 patients have recorded 3,246 surgeries over a 21-year period.

This report describes key components of the IHTC surgical database, its use as a clinical decision support tool, and a review f operative procedures conducted at the IHTC from database inception until the end of December 2019. Description of patients and surgical procedures by type of bleeding disorder and setting (in- or out-patient), as well as an overview of surgical outcomes by bleeding disorder and data collection period, were assessed.

2.3 Methods

In this report, we describe the database design, scope, structure, and overview/summary of contextual data captured.

Database Information and Components

Database Creation and time horizon

The IHTC Surgical Database was created in 2006 with retrospective data extraction from electronic medical records. Data entry was validated through review by two nurses and physicians proficient in bleeding disorder care. From 2006 onward, data collection has been prospective and ongoing.

Basic Data Entry

Data entry is performed by IHTC nursing staff specifically assigned to the planning/management of surgeries, labor, and delivery. The database is integrated with the clinical management flow, and communication within the comprehensive care team initiating and executing the surgical plan. A clinician member of the care team initiates the **surgical plan** followed by a designated hematologist review. The surgical plan on initiation is captured in the database which generates a structured Surgery Letter (**Appendix III**). Procedures are recorded using Current Procedural Terminology (CPT) codes for consistency and to allow query of similar procedures.

Database fields

Information on patient characteristics and procedures – ranging from outpatient, minimally invasive (e.g., dental work, cutaneous biopsies), to more invasive and complex/major surgeries (e.g., central line placement, organ biopsies, orthopedic joint replacement, and cardiovascular

surgery) are reported. Demographic and clinical information captured, and standardized pick lists and free text fields available are provided in **Appendix I and Appendix II.**

Coverage/Catchment Areas

Procedures captured include same- and external-site surgeries. Same-site surgeries are planned and conducted at IHTC while external-site surgeries are IHTC planned but conducted at a different location. Same-site locations include St Vincent Surgery Admitting, St. Vincent Women's Hospital, and the Peyton Manning Children's Hospital with communication to the IHTC Pharmacy, Coagulation Laboratory and Blood Bank/Stat Laboratory to coordinate patient care.

Database Infrastructure and Privacy

The surgical database is hosted on Microsoft Access platform (Microsoft Access 16.0 Object Library, Microsoft Corporation Redmond, Washington, USA). To ensure privacy and information security, the database is deployed on a local intranet on the IHTC network, with remote access available to staff through a virtual private network (VPN). Access to the surgical database requires a user to be logged in and authenticated.

Data collection, storage, and analysis for the IHTC database are conducted in compliance with Health Insurance Portability and Accountability Act (HIPAA) regarding patient privacy and the protection of medical data. Data summaries presented in this report are considered exempt by the institutional review boards of relevant institutions.

Registry Data flow and Clinical decision support

Surgical Procedure Planning

To ensure complete and accurate planning of procedures, this database contains a specific surgical/procedural graphical user interface (GUI) to document and communicate peri-operative instructions and events, procedure location and timing, with an ability to share the plan with associated care providers, e.g., hospital/laboratory staff, primary care physician, surgeon etc.

Procedures were classified into major or minimally invasive based on level of surgical invasiveness (defined by general/spinal anesthetic requirement, need for respiratory assistance and penetration of a major body cavity), and WFH Guideline recommendations for number of consecutive peri-operative days of hemostatic support [2,15].

Event Sequencing

A "Surgery Events" section of the database sequences pre-, intra-, and post- operative events for each procedure including required infusions (primary and secondary products as indicated), laboratory draws, medication administration and other clinically relevant parameters in a time-specified manner.

The Surgical Database is programmed to suggest dosing based on the deficiency, inhibitors status, product utilized and published guidelines, for desired factor levels, and administration duration. Dosing algorithms are suggested based on the volume of distribution and expected half-life of each product including use of bypassing agents in inhibitor patients. Dosing schema may be utilized as suggested or individualized for patients with altered pharmacokinetics or known differential response.

Other recommendations e.g., antifibrinolytics use in dental procedures, colonoscopies, and mucosal-based surgeries are also suggested based on individual patient status and clinical judgement.

Surgical Outcomes or Endpoints

The final feature includes a utility to enter and analyze events and outcomes. Surgical outcomes are measured using three metrics:

1) hemostatic control

2) non-hemostatic complications

3) deviation from the initial surgical plan

Hemostatic control during and post operatively is assessed as adequate if "excellent" or "good" based on WFH definitions regarding minimal perioperative blood loss and blood component transfusions comparable to the non-hemophilic population [2]. Hemostatic control is assessed as inadequate if "fair" or "poor" according to this criterion. Non-hemostatic adverse events (e.g., infection, myocardial infarction, etc.) are also collected.

Post-procedure data entry is based on chart reviews in the historic data collection period. In the prospective data collection period, follow-up for post-operative outcomes is collected after two weeks by telephone call and information from the clinical discharge summary. Follow up longer than two weeks are also captured with patients' self-report.

Efficacy of surgical plans can be assessed according to variables such as patient age, bleeding disorder, clotting factor level, inhibitor status, type of procedure, etc., and data-based models created for patients with bleeding disorders undergoing invasive procedures.

Analysis

Evidence Review of Peri-operative Cases (1998 – 2019)

To assess outcomes of surgical plans and procedures captured in the database from inception to end December 2019, historic and prospectively entered data were extracted for analysis in 2020.

Data Extraction

Demographic and clinical data, surgeries and outcomes were extracted and entries across the database linked using appropriate patient and surgery identifiers. Patients who had surgeries within the specified period were categorized into four groups based on the diagnosis of Haemophilia A (HA), Haemophilia B (HB), and vWD. Other bleeding disorders were grouped into the "Other /Unspecified bleeding disorder" category. Entries with bleeding disorder diagnosis missing were also included in the 'Other' bleeding disorder group.

Statistical Analysis.

To describe the patient population, summary statistics (mean, standard deviation, median, range) were obtained for continuous variables while percentages were accessed for categorical variables. Chi-square and Fisher's exact tests were used to compare characteristics of unique patients based on bleeding disorder diagnosis.

Description of procedures by bleeding disorder diagnosis, surgical invasiveness, and settings, as well as an overall description of surgical outcomes (hemostatic trol, complications, and deviations from pre-surgery plan) by type of bleeding disorder and data collection period were conducted. An *a priori* significance level of $\alpha = 0.05$ was used in statistical tests.

Missing Data. Complete case analysis was done, and a description of missing data assessed. Data were analysed using SAS Software 9.4 version (c) 2016, SAS Institute Inc., Cary, NC, USA.

2.4 Results

Evidence Review of Peri-operative Cases

From 1998 to the end December 2019, 3,246 surgical plans in 1,413 patients were prepared and included in the surgical database.

Description of Patient Population

Patients' age ranged from neonates to 96 years with a median(range) age of 36.8 (0.0-96.1) years at the time of surgery. The median weight(range) at time of surgery was 78.4 (3.2-160.7) kg. Most patients were males (52.9%) with increased prevalence of HA and HB in males, while vWD and other bleeding disorders were more prevalent in the female population. 26.5% of the population had HA, 11.6% had HB, 48.6% had vWD and 13.2% had other bleeding disorders. Patient characteristics by bleeding disorder diagnosis are provided in **Table 1**.

Of the 1,413 unique patients, 52.7% had one procedure while 47.3% (668/1,413) had more than one procedure. The highest number of surgeries in a patient was 22 and the median number per patient was 1 (mean=2.3; SD=2.2; range 1-22). Five patients who underwent more than 15 surgeries (16-22) predominately had severe disease and comorbidities including heart disease, cancer and progressive arthropathy. Frequencies and distribution of surgeries across the patient population are provided in **Appendix IV.**

Inhibitors were present at the time of surgery in 20 unique patients (15 with HA; 5 with HB). Patient characteristics based on inhibitor presence/absence at the time of surgery are provided in **Appendix V**.

Description of Surgeries

Surgeries by Diagnosis

Patients with HA accounted for 31.2% of the surgeries, 14.8% were in patients with HB, 46.3% were in patients with vWD and 7.7% were in patients with other bleeding disorders. In the overall population, more surgeries were done in adults compared to children (69.8% vs 30.2%, p<0.001). However, in patients with other bleeding disorders, more surgeries were done in children compared to adults (52.6% vs 47.4%, p<0.001). In patients with available data, most surgeries were planned compared to emergent (90.0% vs 10.0%, p<0.001). Antifibrinolytics were not recommended in most surgeries (61.2%) involving patients with HA, HB or vWD. However, surgeries involving other types of bleeding disorders had antifibrinolytics recommended in 70.9% of procedures.

The majority of surgeries in HA were in patients with severe disease (50.8%), the majority of procedures in HB were in those with moderate disease (39.7%), while disease severity was mild in most procedures involving patients with vWD (84.9%) and other bleeding disorders (79.3%). vWD severity was recorded as Type 1, 2 (A, B, M, N) and 3, and these subtypes were regrouped as mild, moderate, and severe respectively for analysis.[16] Major surgeries accounted for 36.7% (1,190/3,246) while minimally invasive procedures e.g., colonoscopies, cardiac catheterization, port placement and removal accounted for 63.3% (2,056/3,246). Details of procedures based on bleeding disorder are provided in **Table 2**.

A list of major and minimally invasive procedures is provided in **Table 3**.

In HA and HB, 1,492 surgeries were conducted in 539 patients with 72 (4.8%) procedures performed in 20 inhibitor patients. HA had more surgeries with inhibitors compared to hemophilia

B (54.2% vs 45.8%, p=0.011). Description of surgical procedures based on inhibitor status is provided in **Appendix V**.

Surgeries by Setting (inpatient vs outpatient)

More surgeries were conducted in the in-patient setting compared to the out-patient setting (51.6% vs 46.8%). Based on planning type, 83.5% of outpatient surgeries were planned compared to 81.3% in in-patients (p<0.001). Description of the surgeries based on setting is provided in **Appendix VI.**

Surgical outcomes

Surgical outcomes by type of bleeding disorder

Deviations from initial surgery plan occurred in 68.7% of surgeries with reasons for plan changes including rescheduling of procedure, clotting factor dose adjustments to achieve desired hemostatic range, and changes in length of hospitalization post-procedure. Hemostatic control was achieved in 90.9% of surgeries, ranging from 88.3% in HA, to 93.2% in other bleeding disorders (p=0.017). Complications occurred in 13.6% of procedures, ranging from 12.1% in vWD, to 15.4% in other bleeding disorders (p=0.164). Non-hemostatic complications reported include fever, pain, nausea and vomiting, and infections. Summary of surgical outcomes based on bleeding disorder is provided in **Table 4**. Details of complications recorded are provided in **Appendix VII.**

Surgical outcomes by presence/absence of inhibitors at time of surgery.

In hemophilia patients, adequate hemostatic control was achieved in 87.9% of surgeries – with hemostatic control achieved in a higher proportion in non-inhibitor patients compared to those with inhibitors (89.2% vs 63.6%, p<.001). Complications occurred more frequently in inhibitor patients compared to those without inhibitors (31.2% vs 13.8%, p=0.001). Details of outcomes of surgical procedures based on inhibitor status is provided in **Appendix V**.

Surgical Outcomes by data collection period

Deviations to the initial surgery plan occurred in 25.1%% of procedures in the retrospective period (1998-2006) compared to 34.2% in the prospective data collection period (2006-2019). Hemostatic control was higher in the prospective compared to the retrospective data collection period (92.4 vs 88.3%, p<0.001). Occurrence of complications was higher in the prospective compared to the retrospective data collection period (14.3% vs 12.3%, p<0.001). Summary of the surgical outcomes based on data collection period is provided in **Table 5**.

2.5 Discussion

Treatment guidelines are optimally developed through analysis of large-scale controlled trials. In the absence of such studies in diverse bleeding disorder patients undergoing surgical interventions, the creation of “best practice” requires a comprehensive system for facilitating communication among health providers, followed by extensive assessment of care provided and associated outcomes.

The IHTC Surgical Database represents a uniform tool for surgical planning, communication, management, and evaluation in patients with bleeding disorders undergoing invasive procedures and addresses a significant information gap for this population.

Numerous bleeding disorder-related studies and registries have measured hemostatic efficacy and outcomes of surgical procedures through limited endpoints. Balkan *et al*., define efficacy regarding the requirement of transfusions, while Zulfikar *et al.* measure efficacy based on hemostatic control and a return to baseline activity post-operatively as expected in surgical, non-bleeding disorder patients (17, 19).

In the current analysis, we describe 3,246 surgical plans within the database. Most procedures were in vWD patients, compromising 48.6% of the population and accounting for 46.3% of procedures. Initial surgical plans were followed without changes in 68.7% of procedures, with more surgeries completed without deviations in the historic data-collection period compared to the prospective period (73.9% vs 65.8%, $p<0.001$). This could be attributed to surgeries being already completed at the time of data collection and comparison with pre-surgical plans could not be optimally compared.

Adequate hemostatic control was achieved in 90.9% of procedures, ranging from 88.3% in HB to 93.2% in other bleeding disorders. This is consistent with 78% - 100% reported in published case series (20-22).

Occurrence of complications occurred in 13.6% of procedures, ranging from 12.1% in surgeries involving patients with vWD to 15.4% in procedures involving other bleeding disorders ($p=0.164$). The higher occurrence of complications in the prospective versus historic data collection period (14.3% vs 12.3%, $p<0.001$) could be due to more complicated procedures performed in recent times.

Retrospective data entry into the database could result in challenges with missing data. The extent and nature of missingness in the database was explored. Identified missing data patterns will be addressed in future studies using appropriate statistical approaches, in combination with other data quality improvement initiatives. Inclusion of variables in prospective data entry into this database has been progressive over time, with variables e.g., planning type included when identified as clinically important. Also, the development and use of this database have also been subjected to electronic medical records availability timelines, with the associated learning curves over time (23).

Future studies will include more granular assessment in relation to individual surgery types, specified bleeding disorders, outcomes (e.g., complications, breakthrough bleeds), population sub-groups, use of novel therapies (e.g., emicizumab), presence of inhibitors and other variables.

Possible confounders (e.g., demographic, and clinical characteristics) were not controlled for in the current analysis. In future studies, independent risk factors for specified perioperative outcomes will be explored. Work is also underway to explore the use of this database in the development of predictive models for individualized hemostatic control for patients with these rare disorders.

As observational data, there are limitations to the use of this database including inadequacy for use in determining causal associations, which are best studied in randomized controlled trials. However, it offers the advantage of a large sample size to study outcomes in association with observable variables. Also, this database records details in peri-operative period, and may not capture other elements of the comprehensive care provided; these details could however be sourced from other medical records.

The IHTC Surgical database can be adopted by other hemophilia treatment centers (HTCs) and is available through the IHTC website with permission at: http://www.ihtc.org/medical-professionals/interventions-and-operative-procedures/.

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OO, AS, AI designed the study. OO, HC, NC, AS, AI performed the research. OO analyzed the data. The IHTC care team developed the database. All authors contributed to the writing of the paper.

CONFLICT OF INTEREST DISCLOSURES

The authors have no competing interests.

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TABLES AND FIGURES CAPTION LIST

TABLES

Table 1: Characteristics of patients in the IHTC surgical database

Characteristics	Total Patients N (%)	Hemophilia A	Hemophilia B	Von Willebrand Disease	Other Bleeding Disorders
	1,413 (100%)	**375 (26.5%)**	**164 (11.6%)**	**687 (48.6%)**	**187 (13.2%)**
Sex †					
Male	748 (52.9)	326 (86.9)	146 (89.0)	199 (29.0)	77 (41.2)
Female	665 (47.1)	49 (13.1)	18 (11.0)	488 (71.0)	110 (58.8)
Inhibitors present at any time of surgery ‡					
Yes	20 (3.7)	15 (4.0)	5 (3.0)	-	-
No	519 (96.3)	360 (96.0)	159 (97.0)	-	-
Severity §					
Mild	210 (39.0)	158 (42.1)	52 (31.7)	vWD Subtypes	-
Moderate	109 (20.2)	39 (10.4)	70 (42.7)	Type 1: 542 (78.9)	-
Severe	213 (39.5)	172 (45.9)	41 (25.0)	Type 2A : 23 (3.3)	-
Not reported	7 (1.3)	6 (1.6)	1 (0.0)	Type 2B : 36 (5.2)	-
				Type 2M : 24 (3.5)	
				Type 2N : 3 (0.4)	
				Type 3: 20 (2.9)	
				Others: 39 (5.7)	

† Hemophilia in females includes carrier females with factors levels < 50% and acquired hemophilia.

‡ Inhibitors accessed for persons with hemophilia A/B (N=539). Inhibitor status specific to any time of surgery. Some patients with multiple surgeries had inhibitors present in some surgery times and inhibitors absent at other surgery times. A patient was classified as having inhibitors present if inhibitors were present in at least one surgery

§ Severity for von Willebrand disease (vWD) reported as sub-types 1,2 and 3. Severity not defined or applicable in most of the other bleeding disorder category (N=539).

Other bleeding disorder category include: Dysfibrinogenemia, Easy Bruising, Ehlers-Danlos Syndrome, Factor VII deficiency, Factor X Deficiency, Factor XI Deficiency, Factor XII Deficiency, Factor XIII Deficiency, Family history of VWD, Glanzmann Thrombasthenia, History of bleeding, Hypofibrinogenemia, Inherited Platelet Disorder, Low level VIII carrier, Menorrhagia, Plasminogen activator inhibitor-1 (PAI-1), Plasminogen Deficiency, Platelet Disorder, Platelet Function Defect, Storage Pool Disease, Thrombocytopenia with Absent Radius (TAR) Syndrome, Thalassemia, Undefined Bleeding Disorder.

Table 2: Surgical procedures by type of bleeding disorder

	Procedures N (%)	Hemophilia A	Hemophilia B	von Willebrand Disease	Other Bleeding Disorders	
	3,246 (100)	**1,012 (31.2)**	**480 (14.8)**	**1,503 (46.3)**	**251 (7.7)**	**p-value**
Age at time of surgery;						
median, yrs	36.8	36.7	41.3	36.7	17.2	
Range	0.0 – 96.1	0.0 – 96.1	0.0 – 91.5	0.2 – 91.2	0.1 – 86.9	
Adult/Pediatric						
Adult	2,266 (69.8)	680 (67.2)	380 (79.2)	1,087 (72.3)	119 (47.4)	<.001
Pediatric	980 (30.2)	332 (32.8)	100 (20.8)	416 (27.7)	132 (52.6)	
Weight at time of surgery, kg; mean (SD)	74.8 (31.0)	69.2 (32.2)	86.7 (31.4)	74.7 (26.9)	47.4 (27.9)	<.001
Median	78.4	74.5	91.9	75.7	44.4	
Range	3.2 – 160.7	3.2 – 160.7	7.9 -141.4	5.6 – 147.0	9.4 – 90.9	
Planning Type †						
Emergent	111 (10.0)	53 (16.5)	32 (18.7)	19 (4.1)	7 (4.7)	<.001
Planned	994 (90.0)	269 (83.5)	139 (81.3)	445 (95.9)	141 (95.3)	
Inhibitors present at time of surgery ‡						
Yes	72 (4.8)	39 (3.9)	33 (6.9)	-	-	0.011
No	1,420 (95.2)	973 (96.1)	447 (93.1)	-	-	
Antifibrinolytic Recommended						
Yes	1,259 (38.8)	272 (26.9)	169 (35.2)	640 (42.6)	178 (70.9)	<.001
No	1,987 (61.2)	740 (73.1)	311 (64.8)	863 (57.4)	73 (29.1)	
Severity §						
Mild	1,682 (57.5)	391 (39.1)	141 (29.4)	1150 (79.5)	-	<.001
Moderate	522 (17.8)	102 (10.2)	190 (39.7)	230 (15.9)	-	
Severe	722 (24.7)	508 (50.7)	148 (30.9)	66 (4.6)	-	
Surgery Type *						
Major	1,190 (36.7)	364 (36.0)	177 (36.9)	566 (37.7)	83 (33.1)	0.4855
Minor	2,056 (63.3)	609 (60.2)	277 (57.7)	937 (62.3)	168 (66.9)	

†Complete cases only (N=1,105).

‡Inhibitors assessed only in procedures involving persons with hemophilia A/ B (N=1,492)

§ Complete cases only (N=2, 926). Severity in vWD regrouped: Type 1=Mild, Type 2= Moderate, Type 3= Severe.

* Procedures were classified as major and minor based on degree of surgical invasiveness, involvement of significant risk of large volume blood loss or blood loss into a confined anatomical space and clinical judgement.

Table 3: Types of Procedures based on Surgical Invasiveness

	Total Procedures N = 3,246 (%)	Hemophilia A 1,012 (31.2%)	Hemophilia B 480 (14.8%)	vWD 1,503 (46.3%)	Others 251 (7.7%)
Major Surgeries					
Orthopedic surgeries	**358 (11.0)**	**153 (15.1)**	**55 (11.4)**	**126 (8.4)**	**27 (10.8)**
Total joint replacement (Arthroplasty)	132 (4.1)	66 (6.5)	21 (4.4)	33 (2.2)	12 (4.8)
Joint fusion (Arthrodesis)	33 (1.0)	20 (2.0)	8 (1.7)	5 (0.3)	0 (0.0)
Osteotomy	22 (0.7)	5 (0.5)	1 (0.2)	13 (0.9)	3 (1.2)
Synovectomy	17 (0.5)	9 (0.9)	7 (1.4)	1 (0.1)	0 (0.0)
Other major orthopedic	155 (4.8)	53 (5.2)	18 (3.7)	72 (4.8)	12 (4.8)
Abdominal surgeries	**185 (5.7)**	**48 (4.7)**	**32 (6.7)**	**100 (6.7)**	**5 (2.0)**
Appendectomy	14 (0.4)	5 (0.5)	4 (0.8)	5 (0.3)	0 (0.0)
Cholecystectomy	62 (1.9)	12 (1.2)	12 (2.5)	36 (2.4)	2 (0.8)
Hernia repair	82 (2.5)	25 (2.4)	16 (3.3)	38 (2.5)	3 (1.2)
Other major abdominal surgery	27 (0.8)	6 (0.6)	0 (0.0)	21 (1.4)	0 (0.0)
Cardiovascular surgeries	**30 (0.9)**	**8 (0.8)**	**6 (1.2)**	**13 (0.9)**	**3 (1.2)**
Aortic valve replacement	6 (0.2)	1 (0.1)	1 (0.2)	4 (2.1)	0 (0.0)
Coronary artery bypass	14 (0.4)	6 (0.6)	1 (0.2)	6 (0.4)	1 (0.4)
Other major cardiovascular	10 (0.3)	1 (0.1)	4 (0.8)	3 (0.2)	2 (0.8)
Neurological surgeries	**67 (2.1)**	**12 (1.2)**	**5 (1.0)**	**45 (3.0)**	**5 (2.0)**
Spinal fusion	44 (1.4)	5 (0.5)	4 (0.8)	31 (2.1)	4 (1.6)
Other major neurological	23 (0.7)	7 (0.7)	1 (0.2)	14 (0.9)	1 (0.4)
Tissue removal surgeries	**373 (11.5)**	**111 (11.0)**	**62 (12.9)**	**171 (11.4)**	**29 (11.6)**
Major tissue removal	199 (6.1)	40 (4.0)	19 (4.0)	118 (7.9)	22 (8.8)
Tissue/Organ biopsy	59 (1.8)	14 (1.4)	14 (2.9)	28 (1.9)	3 (1.2)
Tumor removal	39 (1.2)	21 (2.1)	4 (0.8)	11 (0.7)	3 (1.2)
Transjugular Liver Biopsy	63 (1.9)	35 (3.5)	22 (4.6)	6 (0.4)	0 (0.0)
Other major tissue removal	13 (0.4)	1 (0.1)	3 (0.6)	8 (0.5)	1 (0.4)
Urologic/Gynecologic surgeries	**72 (2.2)**	**3 (0.3)**	**2 (0.4)**	**61 (4.1)**	**6 (2.4)**
Hysterectomy	71 (2.2)	2 (0.2)	2 (0.4)	61 (4.1)	6 (2.4)
Other major urologic/gynecologic	1 (0.0)	1 (0.1)	0 (0.0)	0 (0)	0 (0.0)

Other major Surgeries	**102 (3.1)**	**28 (3.2)**	**15(3.1)**	**51 (3.4)**	**8 (3.2)**
ENT	8 (0.2)	3 (0.3)	1(0.2)	3 (0.2)	1 (0.4)
Eyelid surgery	11 (0.3)	3 (0.3)	(0)	7 (0.5)	1 (0.4)
Organ Transplant	12 (0.4)	8 (0.8)	1 (0.2)	3 (0.2)	0 (0.0)
Wisdom & multiple tooth extraction	16 (0.5)	4 (0.4)	2 (0.4)	9 (0.6)	1 (0.4)
Other major surgeries	55 (1.7)	10 (1.0)	11 (2.3)	29 (1.9)	5 (2.0)
Minimally Invasive					
Orthopedic surgeries	**139 (4.3)**	**39 (3.9)**	**26 (5.4)**	**64 (4.3**	**10 (4.0)**
Arthroscopy	122 (3.8)	31 (3.1)	21(4.375)	62 (4.1)	8 (3.2)
Other minor orthopedic surgeries	18 (0.6)	9 (0.9)	5 (1.0)	3 (0.2)	2 (0.8)
Others	**1917 (59.1)**	**609 (60.2)**	**277 (57.7)**	**873 (58.1)**	**158 (62.9)**
Cardiac Catheterization	51 (1.6)	17 (1.7)	11 (2.3)	23 (1.5)	0 (0.0)
Cataract removal	33 (1.2)	4 (0.4)	17 (3.5)	12 (0.8)	0 (0.0)
Catheters	16 (0.5)	9 (0.9)	(0)	6 (0.4)	1 (0.4)
Central line placement	4 (0.2)	4 (0.4)	0 (0.0)	0 (0)	0 (0.0)
Circumcision	63 (2.0)	34 (3.4)	14 (2.9)	9 (0.6)	6 (2.4)
Dental Extraction	29 (0.9)	15 (1.5)	5 (1.0)	8 (0.5)	1 (0.4)
Endoscopies	771 (23.8)	229 (22.6)	124 (25.8)	358 (23.8)	60 (23.9)
Excisions	56 (1.8)	14 (1.4)	7 (1.5)	29 (1.9)	6 (2.4)
Fine needle biopsies	22 (0.7)	1 (0.1)	3 (0.6)	18 (1.2)	(0)
Port Removal & Placement	219 (6.7)	169 (16.7)	27 (5.6)	23 (1.5)	(0)
Rotator cuff repair	8 (0.2)	2 (0.2)	1 (0.2)	5 (0.3)	(0)
Septoplasty, nasal, & sinus surgeries	63 (1.9)	11 (1.1)	3 (0.6)	41 (2.7)	8 (3.2)
Tonsillectomy and Adenoidectomy	217 (6.7)	19 (1.9)	12 (2.5)	130 (8.6)	56 (22.3)
Other minor surgeries	365 (11.2)	81 (8.0)	53 (11.0)	211 (14.0)	20 (8.0)

* Procedures were classified as major and minimally invasive based on degree of surgical invasiveness or involvement of significant risk of large volume blood loss or blood loss into a confined anatomical space.

Other major orthopaedic surgeries = Fractures (36), Hardware removal (18), Osteoplasty (2), Revision Orthopaedic surgery (13), Open Reduction and Internal Fixation (ORIF, N=16), Bone graft (4), Radial head resection/excision (8), Reconstruction (Knee, Ligament, bone, N=31), Toe repair and reconstruction (19), Toe amputation (1), Radialization(2), Synostosis(2).

Other major abdominal surgeries= Bladder surgery (5), Abdominoplasty (2), Abdominal liposuction (3), Abdominal myomectomy, resection, removal of abdominal mass (11), Transjugular intrahepatic portosystemic shunt (TIPS) procedure(1), Gastric bypass (3), Gastric banding (1), Clip sphincter muscle of pancreas (1).

Other major urologic/gynecological surgeries = vaginal reconstruction (1)

Other major neurological surgeries = Resective epilepsy surgery(1), Coiling of Cerebral Aneurysm(1), Tendon transfer(1), Tendon graft (3), Tendon lengthening(3), Decompression(13), Nerve transposition(2)

Other major tissue/organ removal = Parotidectomy(4), Cyst removal (6), Loop electrosurgical excision procedure (LEEP, N=1), Malone antegrade continence enema (MACE) procedure (1), Resection of right flank soft tissue mass(1).

Other major cardiovascular surgeries = Cardiac ablation(3), Carotid artery surgery(2), Vein stripping (2), Attenuated total reflection (ATR, N=1), Implantable cardioverter-defibrillator (ICD) lead revision (1), Aortic valve replacement (6).

Other major surgeries = Bariatric Surgery(1), Breast construction and augmentation(25), Insertion of drug eluting beads(3), Orchiopexy (3), Transarterial chemoembolization (TACE,N=8), Delivery (2), Caldwell-Luc procedure (1), Labral tear repair (3), Skin grafts (5), Ventriculoperitoneal (VP) shunt placement and revision (5).

Other minor orthopedic surgeries = Orthotripsy(1), NUSS procedure(2), bursa sac(1), closed reduction and pinning of finger (3), Radiosynovectomies (7), Prosthesis removal(3), Vertebroplasty(2).

Other minor surgeries = Endometrial Ablation(11), Uterine ablation(6), Other types of ablation (7), Urethral implant, sling, dilatation(3), Glaucoma (1), Nail removal(6), Node dissection (3), Y90 mapping procedure (2), Embolization (3), Tunnel release surgeries (Carpal, Tarsal, N=20), Other release surgeries (15), Coagulation of hemorrhoids (4), coil occlusion right radial artery (1), Cyst removal (10), Egg retrieval (1), Eye muscle surgery (7), Labioplasty (1), Laser surgery (6), Lasik surgery (2), Lumbar puncture (4), Ligation (5), Lysis of adhesions (2), Meniscus tear repair (9), Tendon repair & stabilization (7), Other repairs (25), Botox injections (3), Tube placements (12), Implants and removal (9), Spinraza injection (10), Epidural injections (5), Other injections (11), Incisions (15), Recorder insertion (1), Stent placement and removal (7), D&C (20), Transcatheter aortic valve replacement (TAVR, 3), Lithotripsy & Extracorporeal Shock Wave Lithotripsy (ESWL) for kidney stones (14), Undefined = 14, SPARC procedure for urinary incontinence (3), Spinal Cord Stimulator Trial (1), Tisseel placement (2), VNS Placement (2), Other placements (5), Baclofen pump (3), Pacemaker (re)placements(6), Other removals (26), Wound debridement (8), Imaging & Tests (12).

Table 4: Outcomes of surgical procedures by bleeding disorder.

Outcomes	Procedures N (%)	Hemophilia A	Hemophilia B	Von Willebrand Disease	Other Bleeding Disorders	
	3,246 (100)	**1,012 (31.2)**	**480 (14.8)**	**1,503 (46.3)**	**251 (7.7)**	**p-value**
Hemostatic Control †						
Adequate	2,591 (90.9)	815 (89.5)	363 (88.3)	1,234 (92.4)	179 (93.2)	0.017
Inadequate	259 (9.1)	96 (10.5)	48 (11.7)	102 (7.6)	13 (6.8)	
Complications ‡						
None	2,397 (86.4)	752 (85.2)	342 (85.3)	1,143 (87.9)	160 (84.7)	0.164
Yes	376 (13.6)	131 (14.8)	59 (14.7)	157 (12.1)	29 (15.4)	
Original Plan §						
Plan Followed	2,041 (68.7)	565 (59.6)	253 (57.8)	1,077 (77.8)	146 (73.0)	<.001
Plan Altered	929 (31.3)	383 (40.4)	185 (42.2)	307 (22.2)	54 (27.0)	

†Hemostatic control based on WFH definitions regarding minimal perioperative blood loss and blood component transfusions comparable to non-hemophilic population. Adequate hemostatic control includes excellent and good hemostatic control. Complete cases only; N=2,850. ‡Complications include both hemostatic complications such as venous thromboembolism (VTE) and non-hemostatic complications such as infections and myocardial infarction (N=2,773).
§ Complete cases only (N=2,970).

Table 5: Outcomes of surgical procedures by data collection period

Outcomes	Procedures N (%)	Retrospective Data Collection (1998 – 2006)	Prospective Data Collection (2006 – 2019)	
	3,246 (100)	**1,103 (34.0)**	**2,143 (66.0)**	**p-value**
Hemostatic Control†				
Adequate	2,591 (90.9)	914 (88.3)	1,674 (92.4)	<.001
Inadequate	259 (9.1)	121 (11.7)	138 (7.6)	
Complications ‡				
None	2,397 (86.4)	890 (87.7)	1,507 (85.7)	<.001
Yes	376 (13.6)	125 (12.3)	251 (14.3)	
Original Plan §				
Plan Followed	2,041 (68.7)	784 (73.9)	1,257 (65.8)	<.001
Plan Altered	929 (31.3)	277 (25.1)	652 (34.2)	

†Hemostatic control based on WFH definitions regarding minimal perioperative blood loss and blood component transfusions comparable to non-hemophilic population. Adequate hemostatic control includes excellent and good hemostatic control. Complete cases only (N=2,850).
‡ Complications include both hemostatic and non-hemostatic complications. Complete cases only (N=2,751).
§ Complete cases only (N= 2,970).

FIGURES

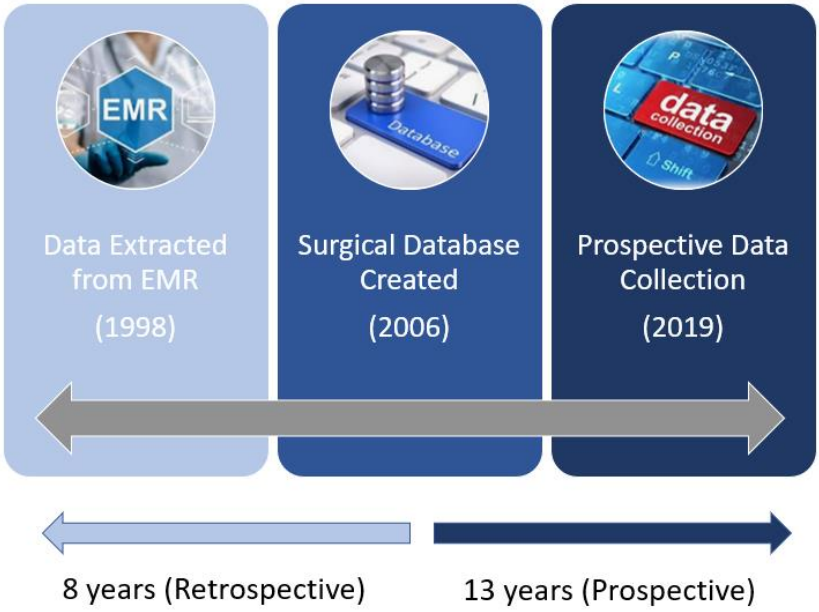


Figure 1: Schematic Diagram of the IHTC-Surgical Database

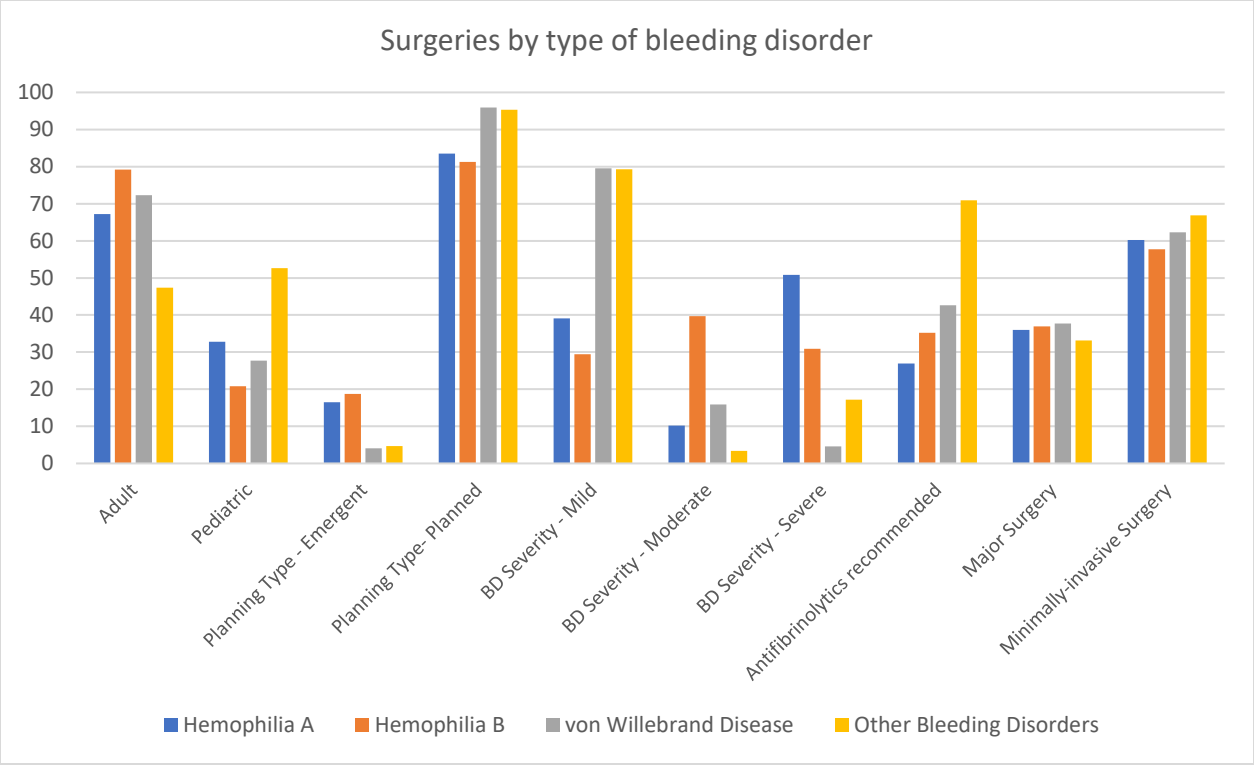


Figure 2: Surgeries by type of bleeding disorder

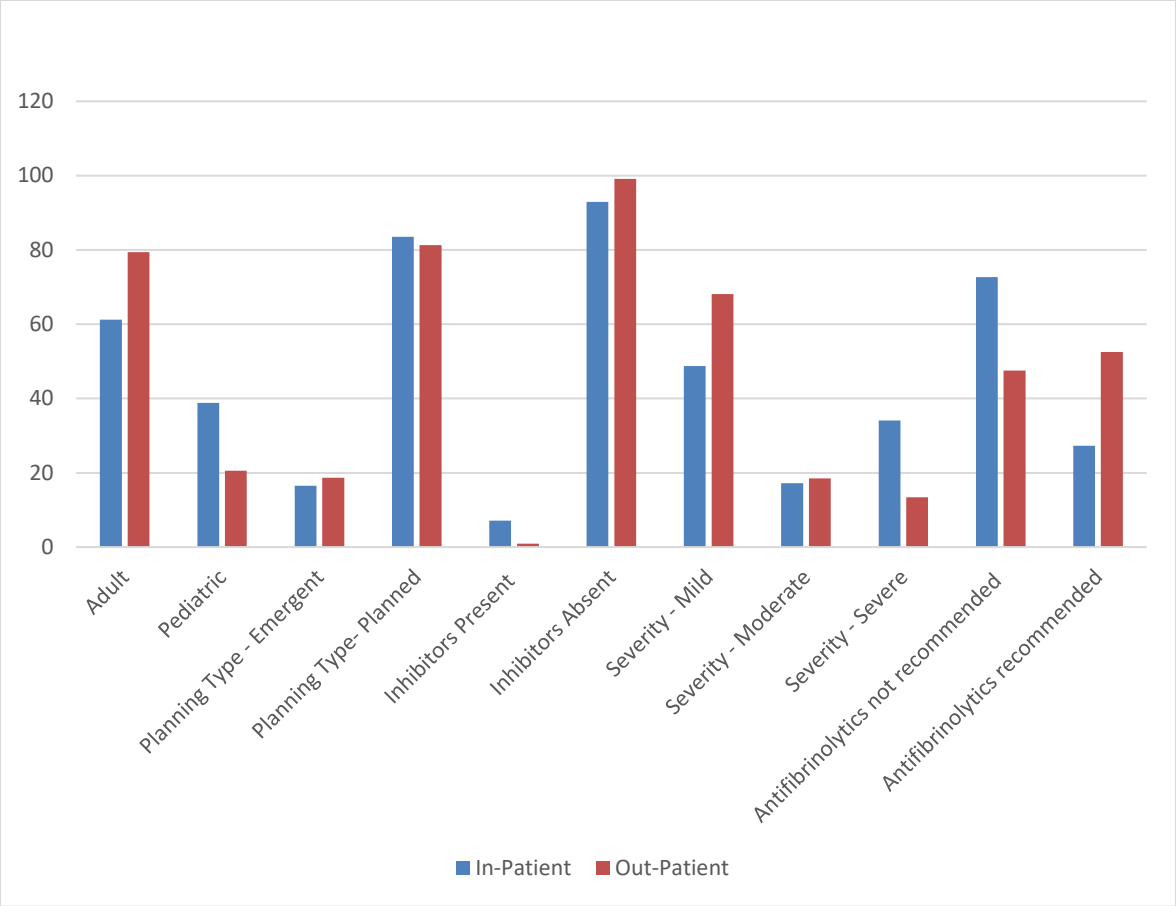


Figure 3: Surgeries by setting (Inpatient versus Outpatient)

APPENDICES

APPENDIX I – DATA FIELDS AVAILABLE IN THE IHTC SURGICAL DATABASE

Patient information (N=1,413)
Description: Data entries of all patients in the IHTC Surgical Database. Each patient has one unique record in this table.

1. Patient ID
2. Status - Active, Inactive, Expired
3. IHTC Homecare – Yes, No
4. Type – Amish, Non-PHS, PHS
5. Diagnosis
6. Severity
7. Level of Severity
8. Inhibitor Level
9. Inhibitor Date
10. Inhibitor History
11. vWD subtype
12. Venous Access

(tblPatients)

Surgery (N=3,246)
Description: Table of all surgeries in the IHTC Surgical Database. Each unique surgery has one unique record in this table. A patient may have 1-to-many surgeries listed in this table.

1. Surgery ID
2. Patient ID
3. Surgery Date
4. Surgery Time
5. Surgeon
6. Surgeon Location
7. Pre-Surgery Factor Level
8. Infusion Lab Location
9. Surgeries ID
10. Inpatient or Outpatient
11. Inpatient admission Info
12. Outpatient admission Info
13. Drip Bolus
14. Add Notes
15. Daily Lab Time
16. Post Infusion Time
17. Inpatient Infusion (Units/kg per hour)
18. Discharge Correction
19. Discharge Factor
20. Discharge Infuse – Unites per Kg after discharge
21. Discharge Days
22. Discharge BOOST level

23. Pt Weight
24. Device Lot Number
25. Factor
26. AmicarRec – Was Amicar recommended?
27. Adult/Pediatric? Adult =1, Pediatric =2
28. Complications – Yes or No
29. AmicarText: Text to appear IF AmicarRec = Yes
30. STATCHECK_Admit: Yes=-1, No=0. Send Labs STAT?
31. STATCHECK_PreInf: Yes=-1, No=0. Send Labs STAT?
32. STATCHECK_PostInf: Yes=-1, No=0. Send Labs STAT?
33. STATCHECK_Daily: Yes=-1, No=0. Send Labs STAT?
34. STATCHECK_PACU: Yes=-1, No=0. Send Labs STAT?
35. LabSend_Admit: Send Labs to…OPTIONAL
36. LabSend_ PreInf: Send Labs to…OPTIONAL
37. LabSend_ PostInf: Send Labs to…OPTIONAL
38. LabSend_Daily: Send Labs to…OPTIONAL
39. LabSend_PACU: Send Labs to…OPTIONAL
40. PreOp Infusion Type – Bolus / Infusion
41. Inpatient Infusion Type – Bolus / Infusion
42. Discharge Infusion Type – Bolus / Infusion
43. Follow TXT
44. Inp Time – Date/Time – Get Factor Level at certain time of day
45. Inp Time [MIN-HOURS]– Get Factor Level X minutes/hours after the surgery
46. Inp TimeFrame – Choose Minutes/Hours
47. Inp SendTo
48. FILEPATH
49. Stimate – Yes/No
50. StimatePuffs – Yes/No
51. StimateTime – Date/Time
52. StimatePuffTime
53. StimateUnits
54. StimateLocation
55. StimateComments
56. Primary Product
57. Secondary Product
58. Events (One to 16) – Description, Time, InfType, InfCorr, InfUnitsKg, InfDays, Free, Drug, DrugDose, DrugRoute, DrugInst, DrugComm
59. Planning Type Emergent
60. Surgery Discovery
61. Created By
62. Time Created

(tblPtSurgery)

Surgeries (N=1,671)
Description: Table of all unique surgery names in the IHTC Surgical Database. These are viewed in a drop-down list when the surgery letter is being created. Use of this table promotes consistency in naming and classification.

1. SurgeriesID
2. Surgery: Other, Appendectomy, Adenoidectomy, Amputation, Angiogram, Ankle Fusion, Appendix remove, Arteriogram, Arthrodesis, Arthroplasty, Arthroscopic, Arthroscopic sy, Back Surgery, Bariatric, Biopsy, Bladder Surgery, Bone graft, Bowel Resectjon, Brain Surgery, Breast Surgery, Bronchoscopy, Bunionectomy, CABG, Cardiac Cathete, Cardioversion, Carpal Tunnel, Casting, Cataract, Cauterization, Cervical Fusion, Cholesystectomy, Circumcision, Cleft Repair, Colon Surgery, Colonoscopy, Cosmetic Relate, Cryosurgery, C-Section, Cuff Repair ….. Removal of Port

(tlkpSurgeries)

Outcomes (N=3,092)
Description: Table of all surgery outcomes in the IHTC Surgical Database. There is a one-to-one relationship between this table and the Surgery table; however, not all Surgeries will have a Surgery Outcome.

1. (tbl) Outcomes ID
2. (tbl) Pt Surgery ID SurgeryID
3. Surgery Type – Planned, Emergent
4. (ov) Outcome [Hemostasis] – Adequate, Inadequate, Unknown
5. (ov) Outcome [Non-Hemostasis-COMP] – Yes, No, Unknown
6. Intra [Hemo] – Yes, No
7. Post-Op [Hemo] – No
8. Plan Compliance – Plan altered, Plan followed as written, Unknown
9. Plan Compliance DTL –
10. Collection – Historic, Prospective
11. IHTC Provided Care – Yes, No
12. Created By
13. Time Created – Date, Time

(tblOutcomes)

Surgery Services (N=1,881)
Description: Reference table used to populate drop-down/choice lists within the application, used in both creation of surgery letter or documentation of surgery outcome. Provides consistent choices/selections for any of the following: Complication, Clotting Factor Name, Laboratory (Name), Facility/Location Name.

1. Item ID
2. Other ID – ID from previous table
3. Item
4. Item Type – Factor, Supply, Lab for Lab, Loc for Location
5. Unit of Measure
6. LabLink – Used to ID which labs are Diagnostic specific

(tlkpSurgSvc)

Surgery Items (N=16, 591)
Description: Reference table used to document different events in the surgery plan.

1. **Surgery ID**
2. Item ID
3. PrePostDaily
4. Time
5. Hours
6. Notes
7. Correction
8. Quantity
9. AdminRoute

(tblPtSurgItems)

Correction (N=40) - (tlkpCorrection)
Description: Reference table used to populate field "factor level prior to surgery must be at least…"
Increments of 5's from 5 – 200

Outcome_Events (N=1,107)
Description: The Outcomes table (above) describes surgery outcomes from a broad and high-level (ex: Was Hemostasis maintained?). This table allows for specific events to be recorded (ex: Bleeding on post-op day 2). There is a 0-to-many relationship between the table Outcomes and this table.

1. (tbl) Outcomes Event ID
2. (tbl) Outcomes ID
3. Event Number
4. Event Type
5. Post-Op Day
6. Plan Compliance
7. Plan Compliance DTL
8. Regimen Compliance
9. Description
10. Intervention
11. Resolution
12. DEL_FLAG
13. DEL_REASON
14. DEL_USER
15. DEL_DT
16. Created By
17. Time Created – Date, Time

(tblOutcomesEvents)

Product List (N=106)
Description: Reference table used to populate drop-down/choice lists within the application, specific to clotting factor and other medical supplies.

1. Product ID
2. Product Name

3. Unit of Measure
4. Product Type – Factor, Med Supplies
5. RXItem – Yes/No

(ProductList)

Factor (N=43)

Description: Reference table used to populate drop-down/choice lists within the application, specific to clotting factor.

1. Pharm ID
2. Product Name
3. Unit of Measure
4. Product Type
5. RX Item – Yes/No

(tlkpPtFactor)

Infusion Type (N=7)

Description: Reference table used to populate drop-down/choice lists within the application, specific to types of infusions.

1. Bolus
2. Continuous Drip
3. Discharge
4. Infusion
5. Peri
6. Post-Op
7. Pre-Op

(tlkpInfusionType)

LabPrePostDaily Type (N=7)

Description: Reference table used to populate drop-down/choice lists within the application, specific to when lab need to be drawn.

1. PrePostDaily : Daily, Discharge, Infusion, Peri, Post-Op, Pre-Op
2. Number

(tlkpLabPrePostDaily)

Physicians (N=1,606)

Description: Reference table used to populate drop-down/choice lists within the application, specific to both primary hematologist (patient-level) and name of surgeon (surgery-level).

1. Physician ID
2. First Name
3. Last Name
4. IHTC Physician: Yes/No
5. Beeper Number

(tlkpPhysician)

APPENDIX II – STANDARDIZED AND FREE TEXT FIELD OPTIONS

Supplementary Table 1. Standardized and free text field options

Demographics/Medical History	**Variable Type**	**Variable Description**
Patient ID	Text field	
Gender	Drop-down menu	Male/female
Date of Birth	Text field	m/d/yyyy
Address	Text field	Place of residence
Physician	Drop-down menu	Capability to add physician(s)
Homecare	Check box	Check = yes; blank=no
Clinical History		
Allergy status	Text field	Details of allergies, treatment
Hematological Diagnosis	Drop-down menu	
Status	Drop-down menu	Active/Inactive
Severity	Drop-down menu	Mild, moderate, severe
Level of Severity	Text field	Percent of normal
Inhibitor Level	Text field	Bethesda Units
Venous Access	Text field	
VWD Subtype	Drop-down menu	
Prophylaxis	Drop-down menu	
Type	Drop-down menu	
Prior Surgical Procedures	Text fields	Date(s), type(s) and detail(s)
Surgery/Procedure		
Procedure Type		
CPT Code		
Date and Time		
Surgeon		
Surgery Location		
Laboratory Location		
Admitting Team		
Time of Admission		
Type of Admission		Inpatient or outpatient
		Adult or pediatric
Antifibrinolytic Recommendation	Text field	
Address for Surgical Letters and Plans	Text field	
	Variable Type	**Variable Description**

Surgery Events		
Primary Hematologic Product	Drop-down menu	
Secondary Product	Drop-down menu	
Event Type	Drop-down menu	Infusion, lab draw-admit, daily, pre-op, PACU, 15 min post infusion, infusion, drug administration
Timing of Event	Drop-down menu	Inpatient or outpatient
Type of infusion or drug administration	Drop-down menu	Bolus, constant, route, dosage, frequency
Dose Calculator	Text fields	Weight, total IU or mg
Further Instructions	Text field	
Output Link to View Surgery Letter	Button	
Output Link to View Surgical Outcomes	Button	

APPENDIX III – Surgery Letter

June 23, 2011

To: [PHYSICIAN NAME], M.D. From: [PHYSICIAN NAME], M.D.
St. Vincent Admitting
St. Vincent Pharmacy
Stat Lab
Special Coagulation Lab
Orthopedic Preop Pavilion

[PATIENT NAME] is a 20 year-old male with severe (<1%) factor VIII deficient hemophilia. He is followed by the Indiana Hemophilia and Thrombosis Center. [PATIENT NAME] is scheduled for right total knee replacement on July 11th, 2011 at 12:00 p.m. at St. Vincent Hospital. Surgery will be performed by [PHYSICIAN NAME]. [PATIENT NAME] will be admitted postoperatively to the 6th floor hematology/oncology unit to be followed by Dr. [PHYSICIAN NAME] and Dr. [PHYSICIAN NAME].

The factor concentrate to be used during the hospitalization is Advate. Factor concentrate is very expensive. Always infuse the entire contents of each vial. Factor concentrate should be kept in the medication refrigerator, not frozen or at room temperature. Factor concentrate is only compatible with normal saline. No dextrose or other IV fluids should be used or piggybacked into the Factor drip. All lot numbers and expiration dates of factor given should be recorded in the patient's medical record.

Two to three hours prior to surgery, [PATIENT NAME] will come to the IHTC clinic where he will have the following labs drawn and sent STAT:

CBC with Diff and Platelets
CMET
Factor VIII Inhibitor

Immediately after the lab draw, he will be infused with Advate 4680 total IU (65 units/ kg for his current weight of 72 kg). Fifteen (15) minutes after the infusion, he will have a factor VIII activity drawn and sent STAT. The result should be called to the IHTC clinic nurse at 871-0000. She will notify the Orthopedic Pavilion Nurse of the level.

Do not proceed with surgery until the result of the factor VIII level has been obtained and determined to be within therapeutic range, 100%. All preoperative labs and infusion will be done at the IHTC clinic.

Upon arrival to the Orthopedic Preop Pavilion, [PATIENT NAME] will be started on a continuous infusion of Advate 4 units/kg/hr (288 units/hr). The infusion will continue throughout his hospitalization. The IHTC clinic nurse will accompany [PATIENT NAME] to start the infusion.

Prepared by

Upon arrival to PACU, [PATIENT NAME] should have a factor VIII level drawn and sent STAT. The result should be called to Dr. [PHYSICIAN NAME] on pager #6718.

At 9 p.m. the evening of surgery, he should have a STAT factor VIII activity drawn, and the result called to the IHTC adult physician on call at 871-0000.

[PATIENT NAME] should have the following labs drawn daily at 6:00 AM and sent STAT:

Basic Metabolic Profile
CBC with Diff and Platelets
Factor VIII Activity

All daily labs should be called to Dr. [PHYSICIAN NAME] on pager #6718.

[PATIENT NAME]'s discharge infusion plan is as follows:

Advate, 2160 IU (30 units/ kg) every 12 hours through the 7th postoperative day (July 18th).

Advate, 3600 IU (50 units/kg) daily on postoperative days 8-14 (July19th-July 25th).

Advate, 3600 IU, three times weekly, for two weeks (July 26th-August 9th).

At this time his infusion plan will be re-evaluated.

Arrangements will be made by the IHTC pharmacy for delivery of factor and supplies for [PATIENT NAME]'s postoperative home infusions prior to discharge.

The IHTC physical therapists will also follow [PATIENT NAME] postoperatively.

Please avoid the use of Toradol and epidural anesthesia in this patient.

Please discharge the patient with a well functioning saline lock.

If hemostasis is not maintained, please call Indiana Hemophilia and Thrombosis Center at 317-871-0000.

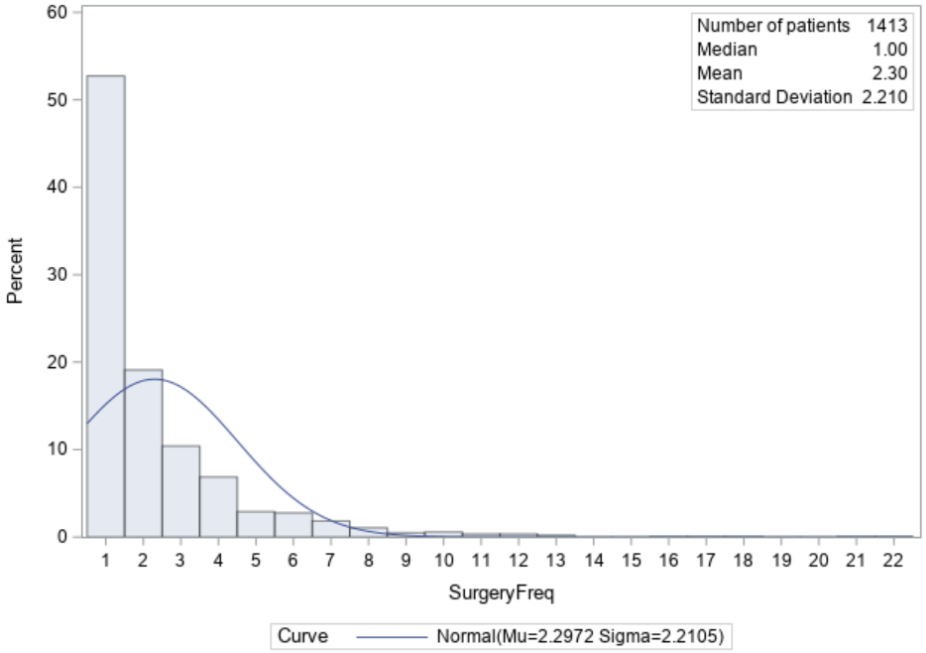
It is imperative that IHTC be notified if there are any changes to the surgery procedure or the date of the procedure. This will assure the patient receives all appropriate medications in regards to the surgery procedure to prevent potential complications.

APPENDIX IV – FREQUENCIES AND DISTRIBUTION OF PROCEDURES ACROSS PATIENTS

Suppl. Table 4.1 Frequency of Procedures per patient

Frequency of Surgeries per patient	Number of patients	Cumulative number of patients	Percentage of patients	Cumulative Percentage of Patients	Number of procedures	Cumulative number of procedures
1	745	745	52.7	52.7	745	745
2	270	1015	19.1	71.8	540	1285
3	147	1162	10.4	82.2	441	1726
4	97	1259	6.9	89.1	388	2114
5	41	1300	2.9	92.0	205	2319
6	39	1339	2.8	94.8	234	2553
7	26	1365	1.8	96.6	182	2735
8	15	1380	1.1	97.7	120	2855
9	7	1387	0.5	98.2	63	2918
10	8	1395	0.6	98.7	80	2998
11	5	1400	0.4	99.1	55	3053
12	5	1405	0.4	99.4	60	3113
13	3	1408	0.2	99.7	39	3152
16	1	1409	0.1	99.7	16	3168
17	1	1410	0.1	99.8	17	3185
18	1	1411	0.1	99.9	18	3185
21	1	1412	0.1	99.9	21	3224
22	1	**1413**	0.1	100.0	22	**3246**

Suppl. Figure 4.1: Frequency of procedures per patient



APPENDIX V – INHIBITORS

Suppl. Table 5.1: Characteristics of hemophilia patients in the IHTC surgical database based on presence/absence of inhibitors at time of surgery

Characteristics	Total Patients N (%)	Inhibitors Present‡	Inhibitors Absent	
	539 (100)	**20 (3.7)**	**519 (96.3)**	**p-value**
Sex†				
Male	472 (87.6)	20 (100.0)	452 (87.1)	0.156
Female	67 (12.4)	0 (0.0)	67 (12.9)	
Hemophilia A/B				
A	375 (69.6)	15 (75.0)	360 (69.4)	0.805
B	164 (30.4)	5 (25.0)	159 (30.6)	
Severity				
Mild	210 (39.5)	1 (5.0)	209 (40.8)	<0.001
Moderate	109 (20.5)	0 (0.0)	109 (21.3)	
Severe	213 (40.0)	19 (95.0)	194 (37.9)	

†Hemophilia in females includes carrier females with factors levels < 50% and acquired hemophilia.

‡Inhibitor status specific to any time of surgery. Some patients with multiple surgeries had inhibitors present in some surgery times and inhibitors absent at other surgery times. A patient was classified as having inhibitors present if inhibitors were present in at least one surgery.

Suppl. Table 5.2 Surgical procedures in hemophilia patients showing inhibitor status at the time of surgery.

	Procedures N (%)	Inhibitors Present	Inhibitors Absent	
	1,492 (100)	**72 (4.8)**	**1,420 (95.2)**	**p-value**
Diagnosis				
Hemophilia A	1,012 (67.8)	39 (54.2)	973 (68.5)	0.011
Hemophilia B	480 (32.2)	33 (45.8)	447 (31.5)	
Adult/Pediatric				
Adult	1,032 (69.2)	40 (55.6)	992 (69.9)	0.012
Pediatric	423 (28.4)	28 (38.9)	395 (27.8)	
Planning Type[†]				
Emergent	85 (17.2)	11 (31.4)	74 (16.2)	0.021
Planned	408 (82.8)	24 (68.6)	384 (83.8)	
Severity				
Mild	532 (36.0)	1 (1.4)	531 (37.7)	<.001
Moderate	292 (19.7)	0 (0.0)	292 (20.7)	
Severe	656 (44.3)	71 (98.6)	585 (41.6)	
Antifibrinolytics Recommended				
No	1,051 (70.4)	45 (62.5)	1,006 (70.9)	0.130
Yes	441 (29.6)	27 (37.5)	414 (29.2)	

[†]Complete cases only (N= 493); Analysis does not include surgeries with missing entries.

Suppl. Table 5.3 Outcomes of surgical procedures based on presence/absence of inhibitors

	Procedures N (%)	Inhibitors Present	Inhibitors Absent	
	1,492 (100)	**72 (4.8)**	**1,420 (95.2)**	**p-value**
Hemostatic Control†				
Adequate	1,178 (87.9)	42 (63.6)	1,136 (89.2)	<.001
Inadequate	144 (10.8)	23 (34.9)	121 (9.5)	
Complications ‡				
None	1,094 (84.0)	41 (67.2)	1,053 (84.8)	0.001
Yes	190 (14.6)	19 (31.2)	171 (13.8)	
Original Plan				
Plan Followed	818 (58.2)	20 (29.9)	798 (59.6)	<.001
Plan Altered	568 (40.4)	46 (68.7)	522 (39.0)	

†Complete cases only (N= 1,322); ‡Complete cases only (N= 1,284).

APPENDIX VI – Surgical procedures by setting (In-patient versus Out-patient)

Suppl. Table 4

	Procedures N (%)	In-Patient	Out-Patient	
	3,246 (100)	**1,674 (51.6)**	**1,518 (46.8)**	**p-value**
Adult/Pediatric				
Adult	2,266 (69.8)	1,024 (61.2)	1,205 (79.4)	<.001
Pediatric	980 (30.2)	650 (38.8)	313 (20.6)	
Weight at time of surgery, kg; mean (SD)	74.8 (31.0)	73.2 (33.2)	76.4 (28.2)	0.071
Median	78.4	77.0	80.4	
Range	3.2 – 160.7	3.2 -160.7	4.6 – 150.0	
Planning Type †				
Emergent	111 (10.0)	53 (16.5)	32 (18.7)	<.001
Planned	994 (90.0)	269 (83.5)	139 (81.3)	
Inhibitors present at time of surgery ‡				
Yes	72 (4.8)	63 (7.1)	5 (0.9)	0.011
No	1,420 (95.2)	828 (92.9)	563 (99.1)	
Antifibrinolytic Recommended				
Yes	1,259 (38.8)	457 (27.3)	797 (52.5)	<.001
No	1,987 (61.2)	1,217 (72.7)	721 (47.5)	
Severity §				
Mild	1,724 (57.8)	743 (48.7)	957 (68.1)	<.001
Moderate	531 (17.8)	263 (17.2)	260 (18.5)	
Severe	727 (24.4)	520 (34.1)	189 (13.4)	

†Complete cases only (N=1,105).

‡Inhibitors assessed only in surgeries involving hemophilia A and B (N=1,492; Inpatients = 891, Outpatients = 568)

§ Complete cases only (N=2,982). Severity in vWD regrouped: Type 1=Mild, Type 2= Moderate, Type 3= Severe.

APPENDIX VII– Complications

Supplementary Table 5. Perioperative Complications Complications	Total Events (n=490) *
Bleeding Related Complications	(n=132)
Hemorrhage	**48**
Hematemesis	3
Hematochezia	1
Hematoma	11
Hematuria	4
Hemorrhage (Incision)	7
Hemorrhage (paralysis)	1
Hemostatic complications	6
Anemia	**15**
Thrombosis	**9**
Menorrhagia with clots	1
Inhibitor development	**6**
Complications with devices & lines	20
Non-Bleeding Related Complications	(n=358)
Infections	28
Fever	26
Pain (Inadequate pain management)	65
Swelling, bruising	29
Nausea and Vomiting	20
Hypertension	8
Wound dehiscence	13
Wound drainage/oozing	19
Allergic reactions, hives, itching	10
Fluid and electrolyte disorders	9
Pleural effusion	7
Urinary retention	6
Respiratory complications	7
Hypertension	1
Hypotension	4
Headache	6
Hyperglycemia	1
Additional steps/procedure required	3
Multiple complications	23
**Others	64

Of the 3,246 surgeries, 376 procedures had complications reported, with multiple complications associated with some surgeries.

*Intra-operative complications including complications with devices and lines (4), hypertension(1), additional steps/procedures required (4), arrythmia (1), ECG Changes(1), seizure(1) and inadequate intra-operative hemostatic control (n=259) not included. Pre-operative events including hematemesis(2), anxiety(1), arrythmia(1) and injury prior to surgery are also not included.

**Other post-operative events include arrythmia, arterial occlusion, atrial fibrillation, bowel obstruction/Ileus, carcinoma after transplant, cellulitis, crackles, decreased range of motion, delirium, dermatitis, dyspnea, ECG Changes, incontinence, lethargy/weakness, lightheadedness, memory loss, Acute Myocardial Infarction (AMI), mortality unrelated to surgery, numbness, falls/error with device by patient, pneumothorax, procedure failure, rash, seizure, stroke, syncope / fainting, thrombocytopenia, visual disturbances, wheezing and unfavorable biopsy/colonoscopy result.

CHAPTER 3: PERIOPERATIVE OUTCOMES ASSOCIATED WITH INHIBITOR STATUS IN PATIENTS WITH HEMOPHILIA – A RETROSPECTIVE COHORT STUDY

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Running Title: Inhibitors and perioperative outcomes in hemophilia A and B.

3.1 Abstract

Introduction: The development of antibodies (inhibitors) to clotting factors compromises the management of Hemophilia A (HA) and B (HB), resulting in resistance to standard clotting-factor replacement, and in many cases, the need for bypassing agents (BPAs) to achieve hemostasis.

Aim: To evaluate the association between the presence of inhibitors and achievement of perioperative hemostasis, development of complications, and pre-surgical plan deviations.

Methods: We conducted a retrospective study using data from the Indiana Hemophilia and Thrombosis Center surgical database (1998–2019). Association between perioperative outcomes and inhibitor status were assessed while controlling for patient and procedural characteristics.

Results: A total of 1,492 surgeries were conducted in 539 patients with hemophilia, with 72(4.8%) procedures conducted in 20 patients with inhibitors (15 HA; 5HB). Inhibitor surgeries included 27 procedures with high-responding inhibitors (HRI;>5BU/mL), 13 procedures involving low-responding inhibitors (LRI; ≤5BU/ml), and 32 procedures in patients with historically persistent inhibitors. Adjusting for surgery setting (inpatient/outpatient), hemostatic agent, data collection period, and surgery type (major/minor), inhibitors were associated with a 31% lower risk of achieving perioperative hemostasis (65.6% vs 91.4%; adjRR=0.69[0.51-0.94], p<.001). Reported complications include hemorrhage, fever, pain, thrombosis, and infections. Complications occurred more frequently in inhibitor surgeries (31.7% vs 14.6%; adjRR=1.68 [1.07–2.64]; p=0.024). Deviations from pre-surgical plans e.g., hemostatic medication dose adjustments, procedure rescheduling, and changes in the length of postoperative hospitalization, occurred more frequently in inhibitor surgeries compared to non-inhibitor surgeries (70.8 vs 39.5%; adjRR= 1.49[1.24–1.79]; p<.001).

Conclusion: Inhibitor surgeries were associated with higher risks of adverse perioperative outcomes compared to those without inhibitors.

Key Words: Inhibitors, Hemophilia, Surgery, Perioperative outcomes, Database.

3.2 Background

The development of neutralizing antibodies to clotting factor therapy with Factor VIII (FVIII) in hemophilia A (HA) or Factor IX (FIX) in hemophilia B (HB) is a major treatment-related complication, which results in the inability to achieve hemostasis with standard clotting factor replacement therapy.[16,17] The incidence of these antibodies, also known as inhibitors, is higher in severe disease compared to moderate or mild disease. The lifetime risk of inhibitor development ranges from 25-40% in severe HA, while in moderate to mild disease, the cumulative lifetime risk is 5-15%.[3,4] Inhibitor development occurs less frequently in HB and is almost exclusively seen in severe disease with a lifetime risk ranging from 1-10%.[1,4-6]

In addition to disease severity, other risk factors associated with inhibitor development include multiple genetic and non-genetic factors such as age and regimen intensity at first exposure, type of treatment regimen (prophylaxis or on-demand), and the presence of immune danger signals such as surgery, trauma, or infection. [7,8] Polymorphisms in genes involved in the immune response and factor concentrate type have also been implicated as contributors to inhibitor development.[9-11]

Based on antibody response to exogenous clotting factor replacement therapy, inhibitors are classified into low-responding inhibitors (LRIs) or high-responding inhibitors (HRIs). On exposure to infused clotting factors, LRIs have titers remaining ≤5 Bethesda Units (BU)/mL while HRIs achieve inhibitor titers of >5 BU/mL.[12,13]

Inhibitors to FVIII concentrates in HA can be eradicated by the process of Immune Tolerance Induction (ITI) involving frequent and regular exposure to factor concentrates over a long period of time (several months to years).[12,14] An overall success rate of 70%-85% has been reported with this process in HA, with patients being able to achieve hemostasis by regular clotting factor concentrate afterwards.[14,15.]

In HB, although inhibitor development is less common, inhibitors may also be associated with anaphylactoid reactions to FIX replacement therapy and nephrosis with ITI.[16] This has limited the use and overall success of ITI in HB patients. Other treatment options such as plasmapheresis to lower inhibitors and desensitization to suppress the development of reactions to allow for ITI have been reported.[16-18]

Cases with persistent high titer inhibitors require the use of bypassing therapies such as Factor Eight Inhibitor Bypass Activity, Anti-Inhibitor Coagulant Complex (FEIBA®; Baxter, Deerfield, IL, USA), or recombinant human factor VIIa (NovoSeven®; NovoNordisk A/S, Bagsværd, Denmark).[19,20] Also more recently, non-clotting factor therapies such as emicizumab, fitusiran, concizumab, and marstacimab are being introduced as options in hemophilia management.[21-24]

The presence of inhibitors impacts the achievement of hemostatic control thereby complicating surgical interventions.[25] Before 1990, surgeries in inhibitor patients were uncommon and often emergent. However, since then, substantial surgical experience has accumulated in this population.[26, 27] With improvements in hemophilia management, including the use of bypassing agents and non-clotting factor therapies, used in combination with careful planning, major and minor surgical procedures are now often performed safely in hemophilia patients with inhibitors.

The safety and effectiveness of bypassing agents and non-factor therapies in achieving perioperative hemostasis have been reported in hemophilia patients with inhibitors. These reports include a single-center study of 6 HA and 1 HB patient with inhibitors who underwent a total of 26 surgical procedures over a 4-year period. FEIBA was shown to achieve excellent hemostasis in all cases.[28]

In a case series of surgeries conducted at four hemophilia comprehensive care centers in the UK over a 10-year-period (1998-2008), 26 procedures were performed in 18 patients with

inhibitors using FEIBA as the hemostatic agent. Perioperative hemostasis was reported to be excellent or good in 78% of 18 major surgeries, and excellent in all 8 minor surgical procedures. There were no intraoperative hemostatic complications in 17 of the 18 surgeries, while one surgery required transfusion of packed red cells to treat a significant fall in hemoglobin level despite no observed excessive blood loss. Postoperative complications occurred in 10 procedures (38.5%) including transient wound hematomas, wound oozing, and appearance of numerous cerebral infarcts in a patient with pre-existing cerebrovascular disease.[29]

Another review of 36 single-center surgeries between 2008 and 2014, involving 18 hemophilia patients with inhibitors reported hemostatic efficacy of 94.4% (34/36) and a mortality of 5.6% in emergency procedures. However, there was no comparison with patients without inhibitors to estimate the inhibitor influence on reported perioperative outcomes. [30]

While perioperative hemostasis has been assessed in previous studies,[29,30] there were no comparisons of perioperative hemostasis, complications, and other safety outcomes across similar procedures and similar patient populations based on inhibitor status.

Therefore, we aimed to assess the impact of the presence of inhibitors on the achievement of perioperative hemostasis, development of complications, and the need to alter pre-surgical plans, which could be related to the development of hemostatic and non-hemostatic complications.

3.3 Methods

Using data captured in the Indiana Hemophilia & Thrombosis Center (IHTC) surgical database, we conducted a retrospective cohort study according to guidance provided in the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) checklist.[31]

Data Source

The IHTC surgical database was designed to facilitate surgical care plan development and assessment of surgical outcomes in patients with hemophilia and rare bleeding disorders. This database was created in 2006 and contains data collected retrospectively from electronic medical records from 1998 to 2006 after which data has been collected prospectively. Data on demographics, diagnoses, procedures, and surgical outcomes are captured with special features tracking if surgical plans were followed as originally written before surgery. Description of this database, its creation, contents, and scope are provided elsewhere.[26]

Data collection, storage, access, analysis, and reporting are conducted in compliance with Health Insurance Portability and Accountability Act (HIPAA) guidelines with individual patient and surgery data deidentified.[32] Data used for this study was considered exempt by the Institutional Research Ethics Board of relevant institutions.

Data Sharing Agreements

Access to de-identified data is available by contacting the IHTC at ashapiro@ihtc.org

Participants

All patients with a primary diagnosis of HA or HB verified to have undergone a surgical procedure, were eligible for study inclusion. Surgeries in patients with von Willebrand disease (vWD) and other bleeding disorders were excluded. Surgery entries with missing surgery dates or no unique surgery identifiers were also excluded.

Study Variables

Inhibitors were assessed as present or absent, with inhibitor surgeries categorized into 3 sub-groups: low-responding if pre-operative inhibitor titers are ≤5BU/mL, high-responding if >5 BU/mL, and a third category with inhibitor titers not tested pre-surgery due to the presence of historical persistent inhibitors, with bypassing agents being used as the hemostatic agent.

Achievement of adequate perioperative hemostatic control was assessed as the primary outcome.[1] Hemostatic control was defined as "adequate" if excellent or good, and "inadequate" if fair, poor, or none, based on World Federation of Hemophilia (WFH) guidelines for minimal perioperative blood loss and blood component transfusions comparable to the non-hemophilic population.[13] Secondary outcomes assessed include both hemostatic and non-hemostatic complications (e.g., infections, fever, allergic reactions, thrombo-embolism), and pre-surgical plan deviations. Postoperative complications are collected within a two-week follow-up period after surgery, with data collected by chart reviews, telephone contact, and information from the clinical discharge summary. Follow-up longer than two weeks are also captured from patients' self-report.

Patients' characteristics at the time of surgery (e.g., age, weight, sex, hemophilia type, hemophilia severity as well as procedural characteristics (e.g., planning type [planned or emergent], surgery type [major or minor], setting [inpatient or outpatient], data collection period [retrospective or prospective], and antifibrinolytics recommendation), were identified as potential confounders and were controlled for in the analysis.

Surgical procedures were classified into major or minor based on a combination of the level of surgical invasiveness (defined by general or spinal anesthetic requirement, need for respiratory assistance, penetration of a major body cavity), clinical judgment, and WFH Guideline recommendations for planned number of consecutive perioperative days of hemostatic support.[33,34]

Statistical Analysis

Descriptive Analysis

The characteristics of the population and procedures were described using summary statistics (mean, standard deviation, median, and range), frequencies, and percentages. Continuous variables across inhibitor and non-inhibitor surgeries were compared by t-test for normally distributed variables or Mann-Whitney test for non-normally distributed variables. Categorical variables were compared using chi-square and Fisher's exact tests.

Perioperative hemostatic control, complications, and deviations from pre-surgical plans.

Association between inhibitor status and perioperative hemostatic control, complications, and plan deviations were examined by generalized linear models using a negative binomial distribution with a log link function to estimate relative risks (RR) and 95% confidence intervals (CIs). While our study outcomes are binary, estimation of odds ratio by logistic regression models could lead to overestimation of effect estimates as the prevalence of the outcomes are not expected to be rare i.e., <10%.

Patient and procedural characteristics were adjusted for in the model using a stepwise forward method for variable selection.

Criteria for choosing the model with the best fit included the Akaike Information Criterion (AIC), with the model with the smaller value having a better fit, as well as clinical judgement.

In sub-group analysis, perioperative outcomes were assessed for low-responding and high-responding inhibitors in comparison to non-inhibitor surgeries. All analyses were conducted using SAS Software 9.4 version (c) 2002–2012, SAS Institute Inc., Cary, NC, USA.

Missing Data

Complete case analysis was done in the primary analysis. The nature and degree of missingness was explored to identify if missing data was at random, not at random, or completely at random. Missing data was addressed in a sensitivity analysis using multiple imputation by Markov Chain Monte Carlo (MCMC) method. Five (5) complete datasets were created, and the results represent the mean of the imputed datasets.

3.4 Results

Description of surgeries in Patients with Hemophilia A and B.

Within the 21-year study period (1998-2019), 1,492 surgical procedures were conducted in 539 patients with hemophilia at the IHTC. Prevalence of inhibitors at any time of surgery was 3.7% (20/539) in the surgical population; 4.0% (15/375) in HA, and 3.1% (5/164) in HB. A total of 72 procedures were conducted in 20 patients with inhibitors: accounting for 4.8% of the surgeries. In surgeries involving inhibitors, high-responding inhibitors accounted for 37.5% (27/72), low-responding inhibitors accounted for 18.1% (13/72) and inhibitor titer at surgery time was unreported/unmeasured in 44.4% (32/72).

The population with inhibitors comprised only males while those without inhibitors included 12.9% (67/519) females, which comprised carrier females with factor levels <50%. More surgeries were conducted in adults ≥ 18 years overall compared to children or adolescents (69.2% vs 28.4%). In HA, more surgeries involving low- and high-responding inhibitors were conducted in children (66.7% and 73.1%) while the 4 inhibitor surgeries with persistent inhibitors were conducted in adult patients. All 72 inhibitor surgeries were elective procedures and were done in males.

Standard clotting factor replacement therapy was used as a hemostatic agent in 66.8% (948/1420) of non-inhibitor procedures compared to 6.9% (5/72) of inhibitor surgeries. Bypassing agents (FEIBA, rFVIIa) were used as hemostatic agents in 61.1% (44/72) of procedures involving inhibitors.

For 30.2% (450/1492) of surgeries with available data for surgery planning type (planned versus emergency), all inhibitor surgeries were planned, in contrast to 3.0% of emergency non-inhibitor surgeries (3.0% vs 0.0%; p=0.027). The 69.8% of procedures with missing data were

categorized to a third level for the planning type variable in sensitivity analysis addressing missing data. Description of procedures based on inhibitor status is provided in **Table 1**. Description of patient and procedural characteristics based on hemophilia type and inhibitor status is provided in **Appendix I**.

Hemostatic control, Complications and Deviations from pre-surgery plans

Due to the distribution of hemophilia severity and gender in the study population, outcomes were assessed only in procedures involving severe factor deficiency and in male patients. Inhibitor surgeries were absent in females and in patients with moderate factor deficiency. The one inhibitor surgery in a patient with mild hemophilia A with an inhibitor was categorized as an outlier.

Adequate hemostasis was achieved in 88.7% of procedures, with adequate hemostasis achieved in a higher proportion of non- inhibitor surgeries compared to inhibitor surgeries (91.4% vs 65.6%). The relative risk (RR) of achieving adequate perioperative hemostasis was 28% lower in procedures involving inhibitors compared to non-inhibitor procedures (RR=0.72, 95% CI= 0.60-0.86, $p<0.001$). Controlling for inpatient vs outpatient setting, data collection period, hemostatic agent used, surgery type (major vs minor), and surgical planning type (emergency vs planned), adjusted relative risk (adjRR) of achieving perioperative hemostasis was 31% lower in procedures involving inhibitors (adjRR=0.69, 95% CI= 0.51-0.94, p=0.017). Hemostatic agent used, data collection period, and surgery type based on invasiveness (major or minor surgery) were judged to be clinically relevant and were included in the model based on clinical judgement. Details on variable selection in the regression model are provided in **Appendix II**. Surgery setting was identified as an independent risk factor for perioperative hemostasis, with inpatient surgeries associated with 7% lower risk of achieving adequate hemostasis compared to outpatient surgeries

(adjRR=0.93 [0.89-0.98]). Independent risk factors for perioperative outcomes are provided in **Appendix III.**

Complications, hemostatic and non-hemostatic, occurred more frequently in procedures involving inhibitors compared to non-inhibitor surgeries (31.7% vs 14.6%, RR: 2.18; 95%CI=1.42-3.33; p=0.025). Overall, 96 (16.3%) procedures reported complications which included bleeding (n=28), fever (n=22), thrombosis (n=5), anemia (n=6), development of inhibitors (n=6), infections (14), and pain (n=22). Description of reported complications are provided in **Appendix IV**.

In adjusted analysis, the risk of complications was 68% higher in inhibitor surgeries compared to non-inhibitor surgeries (adjRR= 1.68, 95% CI= 1.07 – 2.64; p=0.024). Pre-surgical plan deviations also occurred more frequently in inhibitor surgeries (70.8% vs 39.5%; adjRR= 1.49, 95% CI= 1.24 – 1.79; p<0.001). Adjusted and unadjusted relative risks of perioperative hemostatic control, complications, and preoperative plan deviations are provided in **Table 2**.

Subgroup Analysis

In sub-group analysis, achievement of adequate hemostasis was significantly lower in surgeries involving high-responding inhibitors compared with surgeries not involving inhibitors (RR: 0.73 [0.54 – 0.98]). Low-titer inhibitor surgeries and inhibitor surgeries with unreported inhibitor titers were not significantly different compared to non-inhibitor surgeries. Occurrence of complications was not significantly different across low or high inhibitor titers compared to non-inhibitors. Surgical plans were altered more frequently in inhibitor surgeries regardless of whether the inhibitors were high or low titer. Results of sub-group analysis is provided in **Table 3**.

Sensitivity analysis around missing data

The degree of missingness was 10.8%, 12.6% and 7.4% in the models assessing hemostatic control, complications, and plan deviations respectively, with outcome variables missing at a frequency of 8.4%, 10.2% and 4.4% in each model. Residual missing data (2.4%) were accounted for by the variable surgery setting (2.4%) and age (0.6%). Using 5 imputed datasets created by Markov Chain Monte Carlo (MCMC) simulations, our findings were consistent with the complete case analysis. Sensitivity analysis results are presented in **Table 4**.

3.5 Discussion

The development of inhibitors pose(s) a threat to the effectiveness of clotting factor replacement therapy as well as the successful perioperative management of patients with hemophilia undergoing surgery. In our assessment of 1,492 surgeries in patients with hemophilia, presence of inhibitors at the time of surgery was associated with the development of adverse clinical outcomes including a 31% reduction in the risk of perioperative hemostasis, a 68% increase in complication risk, and a 49% increase in the risk of pre-surgical plan deviation.

In our study population, there were twice as many HA patients as there were HB patients (69.6% vs 30.4%), which is different from the estimated 6:1 prevalence ratio of HA to HB in previous studies in the overall hemophilia population.[35, 36] This relatively higher prevalence of HB compared to HA in our study population (2:1 in contrast to 6:1) is likely reflective of the hemophilia population at the IHTC who required a surgery. However, our findings are consistent with population-based surveillance data published by the Indiana Hemophilia Surveillance Project across Indiana and the US, which shows a 64.8% vs 35.2% prevalence of HA compared to HB.[37] Overall prevalence of inhibitors in the population (3.7%) is also lower compared to estimates in published studies, with 5-7% of inhibitors unresolved following ITI.[1,38] This could be attributed to an aggressive early approach to ITI treatment for inhibitors at the IHTC.

Based on a ten-year study of postoperative complications following dental extractions in patients with inherited bleeding disorders, 18.9% (10/53) of the procedures reported postoperative bleeding. This was further complicated by the development of inhibitors, especially in mild hemophilia.[39] This is similar to the 16.3% (96/656) prevalence of complications in assessed procedures in our study which included 26 (1.7%) dental procedures.[26] Achievement of perioperative hemostasis reported in our study (65.6% to 91.4%) is also similar to rates found in previous studies (78% and 94.4%).[29,30]

Deviation from pre-surgical plan have been shown to be associated with increased risk of adverse intraoperative events in major abdominal surgery.[40] However, our study is the first to report pre-surgical plan deviations specifically in patients with hemophilia A or B in relation to inhibitor status.

Limitations of our study include missing data for variables such as surgery planning type, which was included later after database inception. However, this data was not identified to be an independent risk factor in our complete case analysis. Also, missing data were addressed in sensitivity analysis. In our study, we identified the absence of standard definitions for classifying surgeries into major or minor surgeries.[33,34] Further research should be considered in establishing criteria for classification of surgeries in patients with hemophilia and other genetic bleeding disorders.

With advancements in the management of hemostasis over the study period, e.g., introduction of non-clotting factor therapies, [41] evaluation of perioperative hemostasis in relation to specific hemostatic agents, as well as time trends in relation to pre and post-availability of newer treatment alternatives, would be crucial and would be considered in future analyses.

In conclusion, with higher risks of adverse perioperative outcomes in procedures involving inhibitors, more treatment approaches that prioritize prevention and aggressive eradication of inhibitors in patients with hemophilia will be beneficial. Also, as part of ongoing quality improvement in patient care, tracking outcomes in each hemophilia treatment center and nationally is important to achieve best practice and outcomes.

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CONFLICT OF INTEREST DISCLOSURES

Iorio: McMaster University: Current Employment; Research grants paid directly to the Institution from Bayer, BioMarin, NovoNordisk, Octapharma, Pfizer, Roche, Sanofi, Sobi, Takeda. **Malec**: CSL Behring: Consultancy; Genentech: Consultancy; HEMA Biologics: Consultancy; Pfizer: Consultancy; Sanofi: Consultancy, Research Funding; Takeda: Consultancy.

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TABLES AND FIGURES CAPTION LIST

TABLES

Table 1: Description of surgeries in patients with Factor VIII and IX deficiency with and without Inhibitors

	Procedures N (%)	Inhibitors Present	Inhibitors Absent	p-value
	1,492 (100%)	**72 (4.8%)**	**1,420 (95.2%)**	
Adult/Pediatric				
Adult	1,032 (69.2)	40 (55.6)	992 (69.9)	0.020
Pediatric	423 (28.4)	28 (38.9)	395 (27.8)	
Weight at surgery, kg; mean (SD)	75.3 (33.0)	98.2 (32.6)	74.2 (32.6)	<0.001
Median (range)	80.2 (3.2 – 160.7)	99.0(16.9 – 131.9)	79.2(3.2 -160.7)	
Sex				
Male	1,361 (91.2)	72 (100.0)	1,289 (90.8)	0.002
Female	131 (8.8)	0 (0.0)	131 (9.2)	
Diagnosis				
Hemophilia A	1,012 (67.8)	39 (54.2)	973 (68.5)	0.011
Hemophilia B	480 (32.2)	33 (45.8)	447 (31.5)	
Planning Type*				
Emergent	42 (2.8)	0 (0.0)	42 (3.0)	0.027
Planned	408 (27.4)	12 (16.7)	396 (27.9)	
Unreported	1042 (69.8)	60 (83.3)	982 (69.1)	
Severity of Factor Deficiency				
Mild	532 (36.0)	1 (1.4)	531 (37.7)	<0.001
Moderate	292 (19.7)	0 (0.0)	292 (20.7)	
Severe	656 (44.3)	71 (98.6)	585 (41.6)	
Antifibrinolytics Recommended				
No	1,051 (70.4)	45 (62.5)	1,006 (70.8)	0.130
Yes	441 (29.6)	27 (37.5)	414 (29.2)	
Setting				
In-patient	891 (59.7)	63 (87.5)	828 (58.3)	<0.001
Out-patient	568 (38.1)	5 (6.9)	563 (39.7)	
Data Collection Period				
(1998 – 2006) Historic	597 (40.0)	32 (44.4)	565 (39.8)	0.432
(2006 – 2019) Prospective	895 (60.0)	40 (55.6)	855 (60.2)	
Hemostatic Agent used				
Clotting Factor replacement	953 (63.9)	5 (6.9)	948 (66.8)	<0.001
Bypassing Agent	45 (3.0)	44 (61.1)	1 (0.1)	
Other**	494 (33.1)	23 (31.9)	471 (33.2)	

Procedure Type				
Major	540 (36.2)	27 (37.5)	513 (36.1)	0.813
Minimally Invasive	952 (63.8)	45 (62.5)	907 (63.9)	

*Complete cases only (N= 450). Variable added to the database at a later date.
**Other hemostatic agents include desmopressin, antifibrinolytic agent, and aminocaproic acid.

Table 2: Perioperative hemostasis, complications and surgical plan deviations based on inhibitor status.

	Procedures N (%)	Inhibitors Absent	Inhibitors Present	RR (95% CI)	p-value	adjRR (95% CI)	p-value
	656 (100%)	585 (89.2%)	71 (10.8%)				
Hemostatic Control[1]							
Adequate	533 (88.7)	491 (91.4)	42 (65.6)	0.72 (0.60-0.86)	<0.001	0.69 (0.51 – 0.94)	<0.001
Inadequate	68 (11.3)	46 (8.6)	22 (34.4)				
Complications [2]							
None	493 (83.7)	452 (85.4)	41 (68.3)				
Yes	96 (16.3)	77 (14.6)	19 (31.7)	2.18 (1.42-3.33)	<0.001	1.68 (1.07 – 2.64)	0.024
Original Plan[3]							
Followed	359 (57.3)	340 (60.5)	19 (29.2)				
Altered	268 (42.7)	222 (39.5)	46 (70.8)	1.79 (1.49-2.16)	<0.001	1.49 (1.24 – 1.79)	<0.001

[1]Complete cases only (N= 585 in model with best fit)
[2]Complications include both hemostatic complications such as venous thromboembolism (VTE) and non-hemostatic complications such as infections and myocardial infarction. Complete cases only (N= 569 in model with best fit)
[3]Complete cases only (N= 607 in model with best fit)
RR = Relative Risk; adjRR Adjusted relative risk.

Table 3: Sub-Group Analysis

	Procedures N (%) 656 (100%)	adjRR (95% CI)	p-value
Adequate Perioperative Hemostasis			
Inhibitors Present	71 (10.8)	0.69 (0.51 – 0.94)	<0.001
High-Responding inhibitors	26 (4.0)	0.73 (0.54 – 0.98)	0.038
Low- Responding inhibitors	13 (2.0)	0.47 (0.20 – 1.08)	0.076
Unreported inhibitor titers	32 (4.9)	0.67 (0.32 – 1.35)	0.252
Inhibitors Absent (Ref)	585 (89.2)		
Complications			
Inhibitors Present	71 (10.8)	1.68 (1.07 – 2.64)	0.024
High-Titer inhibitors	26 (4.0)	4.54 (0.53 – 39.03)	0.168
Low- Titer inhibitors	13 (2.0)	2.35e-10 (0.00 – 0.00)	0.999
Unreported inhibitor titers	32 (4.9)	1.78e-10 (0.00 – 0.00)	0.999
Inhibitors Absent (Ref)	585 (89.2)		
Surgical Plan Altered			
Inhibitors Present	71 (10.8)	1.49 (1.24 – 1.79)	<0.001
High-Titer inhibitors	26 (4.0)	1.46 (1.10 – 1.94)	0.010
Low- Titer inhibitors	13 (2.0)	1.62 (1.22 – 2.14)	0.001
Unreported inhibitor titers	32 (4.9)	1.42 (1.10 – 1.91)	0.008
Inhibitors Absent (Ref)	585 (89.2)		

Table 4: Sensitivity Analysis

	Procedures N (%)	Inhibitors Present	Inhibitors Absent	adjRR (95% CI)	p-value
	656 (100)	**71 (10.8)**	**585 (89.2)**		
Hemostatic Control					
Adequate	533 (81.2)	42 (59.1)	491 (83.9)	0.77 (0.68 – 0.87)	<0.001
Inadequate	68 (10.4)	22 (31.0)	46 (7.9)		
Missing	55 (8.4)	7 (9.9)	48 (8.2)		
Complications					
None	493 (75.1)	41 (57.7)	452 (77.3)		
Yes	96 (14.6)	19 (26.8)	77 (13.2)	1.11 (1.01 -1.21)	0.023
Missing	67 (10.2)	11 (15.5)	56 (9.6)		
Original Plan					
Followed	359 (54.7)	19 (26.8)	340 (58.1)	1.27 (1.12 – 1.42)	<0.001
Altered	268 (40.9)	46 (64.8)	222 (37.9)		
Missing	29 (4.4)	6 (8.4)	23 (3.9)		

FIGURES

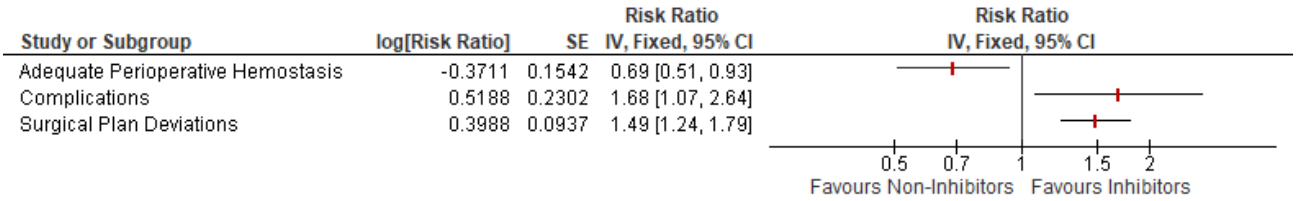

Figure 1: Perioperative outcomes in hemophilia patients based on Inhibitor Status

APPENDICES

APPENDIX I – Patient and procedural characteristics at time of surgery by Factor deficiency type and inhibitor status

	Overall Total	Factor VIII Deficiency (Hemophilia A)					Factor IX Deficiency (Hemophilia B)				
No. of patients, n (%)	539 (100)	375/539 (69.6%)					164/539 (30.4%)				
No. of procedures, n (%)	1,492 (100)	1,012/1,492 (67.8%)					480/1,492 (32.2%)				
Inhibitor titer at time of surgery		>5BU/mL (HRI)	≤5BU/mL (LRI)	Not reported/ measured	Negative	Total	>5BU/mL (HRI)	≤5BU/mL (LRI)	Not reported/ measured	Negative	Total
No. of procedures, n (%)	**1,492 (100)**	**26 (25.7)**	**9 (0.9)**	**4 (0.4)**	**973 (96.1)**	**1,012 (100.0)**	**1 (0.2)**	**4 (0.8)**	**28 (5.8)**	**447 (93.1)**	**480 (100)**
Age											
Adult (≥ 18y)	1,032 (69.2)	5 (19.2)	3 (33.3)	4 (100.0)	652 (65.9)	664 (65.6)	1 (100.0)	3 (75.0)	24 (85.7)	340 (70.8)	368 (76.7)
Pediatric (<18y)	423 (28.4)	**19 (73.1)**	**6 (66.7)**	0 (0.0)	300 (30.3)	325 (32.1)	0 (0.0)	1 (25.0)	2 (7.1)	95 (19.8)	98 (20.4)
Weight, kg; mean(SD)	75.3 (33.0)	47.9 (16.4)	77.0 (0.0)	77.0 (0.0)	69.4 (32.4)	69.2 (32.2)	131.6	83.6(0.0)	120.0 (15.9)	83.7 (30.8)	86.7 (31.4)
Sex											
Male	1,361 (91.2)	26 (100.0)	9 (100.0)	4 (100.0)	877 (90.1)	916 (90.5)	1 (100.0)	4 (100.0)	28 (100.0)	412 (92.2)	445 (92.7)
Female*	131 (8.8)	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	96 (9.9)	96 (9.5)	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	35 (7.8)	35 (7.3)
Planning type											
Emergent	42 (2.8)	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	27 (2.8)	27 (2.7)	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	15 (3.4)	15 (3.1)
Elective	408 (27.4)	5 (19.2)	4 (44.4)	1 (25.0)	268 (27.5)	278 (27.5)	**0 (0.0)**	**0 (0.0)**	2 (7.1)	128 (28.6)	130 (27.1)
Unreported	1042 (69.8)	21 (80.8)	5 (55.6)	3 (75.0)	678 (69.7)	707 (69.9)	1 (100.0)	4 (100.0)	26 (92.9)	304 (68.0)	335 (69.8)
Severity											
Mild	532 (35.7)	**1 (3.8)****	**0 (0.0)**	**0 (0.0)**	390 (40.1)	391 (38.6)	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	141 (31.5)	141 (29.4)
Moderate	292 (19.6)	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	102 (10.5)	102 (10.1)	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	190 (42.5)	190 (39.6)
Severe	656 (44.0)	25 (96.2)	9 (100.0)	4 (100.0)	470 (48.3)	508 (50.2)	1 (100.0)	4 (100.0)	28 (100.0)	115 (25.7)	148 (30.8)
Setting											
Inpatient	891 (59.7)	21 (80.8)	8 (88.9)	4 (100.0)	594 (61.0)	627 (62.0)	1 (100.0)	4 (100.0)	25 (89.3)	234 (52.3)	264 (55.0)
Outpatient	568 (38.1)	3 (11.5)	1 (11.1)	0 (0.0)	359 (36.9)	363 (35.9)	0 (0.0)	0 (0.0)	1 (3.6)	204 (45.6)	205 (42.7)
Antifibrinolytics recommendation											

No	1,051 (70.4)	22 (84.6)	6 (66.7)	2 (50.0)	710 (73.0)	740 (73.1)	1 (100.0)	1 (25.0)	13 (46.4)	296 (66.2)	311 (64.8)
Yes	441 (29.6)	4 (15.4)	3 (33.3)	2 (50.0)	263 (27.0)	272 (26.9)	0 (0.0)	3 (75.0)	15 (53.6)	151 (33.8)	169 (35.2)
Data collection period											
Retrospective	597 (40.0)	16 (61.5)	3 (33.3)	1 (25.0)	399 (41.0)	419 (41.4)	**0 (0.0)**	**0 (0.0)**	12 (42.9)	166 (37.1)	178 (37.1)
Prospective	895 (60.0)	10 (38.5)	6 (66.7)	3 (75.0)	574 (59.0)	593 (58.6)	1 (100.0)	4 (100.0)	16 (57.1)	281 (62.9)	302 (62.9)
Hemostatic Agent											
Clotting factor	953 (63.9)	5 (19.2)	**0 (0.0)**	**0 (0.0)**	602 (61.9)	607 (60.0)	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	346 (77.4)	346 (72.1)
Bypassing agents	45 (3.0)	5 (19.2)	3 (33.3)	4 (100.0)	1 (0.1)	13 (1.3)	1 (100.0)	3 (75.0)	28 (100.0)	**0 (0.0)**	32 (6.7)
Other	494 (33.1)	16 (61.5)	6 (66.7)	**0 (0.0)**	370 (38.0)	392 (38.7)	**0 (0.0)**	1 (25.0)	**0 (0.0)**	101 (22.6)	102 (21.2)
Procedure Type											
Major	542 (36.3)	5 (19.2)	2 (22.2)	2 (50.0)	357 (36.7)	366 (36.2)	**0 (0.0)**	3 (75.0)	15 (53.6)	158 (35.4)	176 (36.7)
Minor	950 (63.7)	21 (80.8)	7 (77.8)	2 (50.0)	616 (63.3)	646 (63.8)	1 (100.0)	1 (25.0)	13 (46.4)	289 (64.6)	304 (63.3)

Unless indicated otherwise, data are presented as frequencies and percentages

Abbreviations: LRI, Low-responding inhibitor; HRI, high-responding inhibitor; BU/mL, Bethesda Units (BU)/mL.

*Hemophilia in females includes carrier females with factors levels < 50%.

**A patient with mild Hemophilia A who had a minor surgery was considered an outlier and was not included in the analysis of inhibitor surgeries.

APPENDIX II – Variable Selection by Stepwise Forward Selection.

Relative Risk (Perioperative Hemostasis)	**Model 1**	**Model 2**	**Model 3**	**Model 4**	**Model 5**	**Model 6***	**Model 7**	**Model 8**	**Model 9**
RR (95% CI)	0.72 (0.60 – 0.86)	0.71 (0.59 – 0.85)	0.70 (0.58 - 0.86)	0.70 (0.58 - 0.85)	0.69 (0.51 – 0.94)	0.69 (0.51 – 0.94)	0.69 (0.51 – 0.93)	0.69 (0.51 – 0.94)	0.69 (0.51 – 0.93)
Standard Error	0.0656	0.0651	0.0995	0.1000	0.1531	0.1533	0.1535	0.1538	0.1538
Pr > ChiSq	0.0003	0.0002	0.0004	0.0004	0.0167	0.0176	0.0155	0.0165	0.0164
Log Likelihood	-198.19229	-197.5854	-190.8787	-192.2041	-191.9963	-191.5329	-191.0928	-191.0287	-190.4617
AIC	**400.3857**	**401.1708**	**390.4347**	**392.4772**	**395.9926**	**397.0657**	**400.4987**	**402.4406**	**402.9234**
BIC	409.1829	414.3666	403.5495	409.8947	422.2223	427.6670	439.5301	445.7735	450.9356
Convergence	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Maximum Likelihood Parameter Estimates (SE)									
Intercept (SE)	-0.0896 (0.0132)	-0.0613 (0.0248)	-0.0389(0.0174)	-0.0415 (0.0239)	-0.0393 (0.0233)	-0.0698 (0.0414)	-0.0446 (0.0517)	-0.0407 (0.0524)	-0.0436 (0.0547)
Inhibitor Present vs Absent	-0.3317 (0.0914)	-0.3416 (0.0916)	-0.3609 (0.0993)	-0.3524 (0.1000)	-0.3665 (0.1531)	-0.3640 (0.1533)	-0.3715 (0.1535)	-0.3685 (0.1538)	-0.3692 (0.1538)
Hemophilia Diagnosis	-	-0.0349 (0.0289	-	-	-	-	-	-	-
Setting (In vs outpatient)	-	-	-0.0745 (0.0283)	-0.0698 (0.0255)	-0.0769 (0.0280)	-0.0649 (0.0305)	-0.0707 (0.0319)	-0.0749 (0.0334)	-0.0763 (0.0336)
Data Collection Period	-	-	-	0.0041 (0.0254)	0.0005 (0.0256)	0.0061 (0.0261)	-0.0061 (0.0301)	0.0021 (0.0378)	0.0045 (0.0394)
Hemostatic Agent (BPA vs CFC)	-	-	-	-	0.0180 (0.2024)	0.0196 (0.2026)	0.0370 (0.2032)	0.0421 (0.2036)	0.0449 (0.2037)
Hemostatic Agent (Others vs CFC)	-	-	-	-	0.0259 (0.0387)	0.0126 (0.0412)	0.0288 (0.0453)	0.0213 (0.0500)	0.0187 (0.0522)
Minor vs Major Surgery						0.0310 (0.0338)	0.0245 (0.0356)	0.0269 (0.0368)	0.0266 (0.0370)
Surgery Planning Type (Emergent vs Planned)	-	-	-	-	-	-	-0.0938 (0.1289)	-0.0873 (0.1302)	-0.0989 (0.1409)
Surgery Planning Type (Unreported vs Planned)	-	-	-	-	-	-	-0.0176 (0.0273)	-0.0204 (0.0290)	-0.0209 (0.0290)

Antifibrinolytics recommendation	-	-	-	-	-	-	-	-0.0159 (0.0448)	-0.0154 (0.0459)
Age	-	-	-	-	-	-	-	-	0.0060 (0.0289)

*****Model with hemostatic agent, data collection period, and type of surgery (major versus minor surgery) was selected based on clinical judgement.

Relative Risk (Complications)	**Model 1**	**Model 2**	**Model 3**	**Model 4**	**Model 5**	**Model 6**	**Model 7**	**Model 8**	**Model 9**	**Model 10**
RR (95% CI)	2.18 (1.42-3.33)	2.13 (1.39-3.27)	1.65 (1.03 – 2.62)	1.65 (1.04 – 2.59)	1.36 (0.64 – 2.89)	1.36 (0.63 – 2.92)	1.35 (0.62 – 2.92)	1.32 (0.63 – – 2.78)	1.32 (0.61 – 2.84)	1.68 (1.07 – 2.64)
Standard Error	0.2169	0.2188	0.2375	0.2322	0.3845	0.3907	0.3957	0.3786	0.3916	0.2301
Pr > ChiSq	0.0003	0.0005	0.0355	0.0318	0.4212	0.4353	0.4529	0.4574	0.4786	0.0235
Log Likelihood	-256.9554	-256.6730	-238.4296	-233.0209	-232.3383	-232.3383	-231.4508	-229.4171	-228.6434	-230.6921
AIC	**517.9108**	**519.3870**	**484.8591**	**476.0419**	**478.6767**	**479.8082**	**480.9015**	**474.8342**	**477.2868**	**471.3841**
BIC	526.6676	532.4812	502.2627	497.7963	509.1329	514.6153	520.0595	509.5853	520.7256	493.1035
Convergence	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Maximum Likelihood Parameter Estimates										
Intercept (SE)	-1.9272 (0.1053)	-1.8026 (0.1905)	-3.0110 (0.4323)	-3.4224 (0.4526)	-3.5162 (0.4631)	-3.6991 (0.5024)	-3.8575 (0.5328)	-3.6763 (0.4855)	-3.9713 (0.5438)	-3.5226 (0.4287)
Inhibitor Present vs Absent	0.7773 (0.2169)	0.7561 (0.2188)	0.4994 (0.2375)	0.4984 (0.2322)	0.3093 (0.3845)	0.3048 (0.3907)	0.2970 (0.3957)	0.2814 (0.3786)	0.2775 (0.3916)	0.5213 (0.2301)
Hemophilia Diagnosis	-	-0.1596 (0.2085)	-0.1229 (0.2155)	-0.1098 (0.2122)	-0.0001 (0.2323)	-0.0151 (0.2316)	0.0100 (0.2345)	0.0367 (0.2365)	0.0496 (0.2392)	-
Setting (Inpt. vs Outpt.)	-	-	1.3830 (0.4122)	1.4768 (0.4116)	1.4984 (0.4143)	1.5794 (0.4226)	1.7020 (0.4418)	1.4900 (0.4146)	1.6855 (0.4433)	1.4702 (0.4126)
Data Collection Period	-	-	-	0.6210 (0.1909)	0.6459 (0.1988)	0.6765 (0.2017)	0.6790 (0.2017)	0.7245 (0.2139)	0.7417 (0.2158)	0.6362 (0.1936)
Hemostatic Agent (BPA vs CFC)	-	-	-	-	0.3679 (0.4600)	0.3543 (0.4679)	0.2702 (0.4844)	0.4836 (0.4626)	0.3622 (0.4908)	-
Hemostatic Agent (Others vs CFC)	-	-	-	-	-0.1208 (0.2521)	-0.1938 (0.2626)	-0.1995 (0.2625)	-0.2550 (0.2884)	-0.2933 (0.2934)	-
Minor vs Major Surgery	-	-	-	-	-	0.1916 (0.2069)	0.1812 (0.2054)	0.1623 (0.2170)	0.1623 (0.2170)	-
Antifibrinolytics recommendation	-	-	-	-	-	-	0.2535 (0.2587)	-	0.2597 (0.2577)	-
Age (Adult vs Pediatric)	-	-	-	-	-	-	-	0.2332 (0.2328)	0.1708 (0.2513)	0.0099 (0.1879)

Surgery Planning Type (Emergent vs Planned)	-	-	-	-	-	-	-	-	-	-
Surgery Planning Type (Unreported vs Planned)	-	-	-	-	-	-	-	-	-	-
Weight	-	-	-	-	-	-	-	-	-	-

Relative Risk (Pre-surgical Plan Deviation)	**Model 1**	**Model 2**	**Model 3**	**Model 4**	**Model 5**	**Model 6**	**Model 7**	**Model 8**	**Model 9**
RR (95% CI)	1.79 (1.49-2.16)	1.66 (1.34-2.03)	1.49 (1.24-1.79)	1.49 (1.24-1.79)	1.47 (1.20-1.79)	1.47 (1.20-1.78)	1.47 (1.11-1.93)	1.45 (1.10-1.90)	1.55 (1.18-2.03)
Standard Error	0.0953	0.1031	0.0949	0.0949	0.1007	0.0999	0.1402	0.1406	0.1377
Pr > ChiSq	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	0.0063	0.0087	0.0014
Log Likelihood	-416.3415	-402.3794	-387.4285	-385.0819	-384.9864	-384.9335	-383.8051	-383.6265	-381.1616
AIC	**836.6830**	**810.7587**	**782.8570**	**780.1638**	**781.9728**	**783.8671**	**785.6102**	**785.2529**	**786.3233**
BIC	845.5649	824.0040	800.5174	8062. 2065	808.4239	814.7268	825.2870	824.9297	839.2256
Convergence	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Maximum Likelihood Parameter Estimates									
Intercept (SE)	-0.9288 (0.0522)	-1.1880 (0.1251)	-1.5066 (0.1422)	-1.4931 (0.1482)	-1.4649 (0.1614)	-1.4831 (0.1704)	-1.3650 (0.1895)	-1.3772 (0.1805)	-1.4531 (0.2248)
Inhibitor Present vs Absent	0.5831 (0.0953)	0.5078 (0.1031)	0.3989 (0.0949)	0.3976 (0.0949)	0.3836 (0.1007)	0.3825 (0.0999)	0.3830 (0.1402)	0.3687 (0.1406)	0.4392 (0.1377)
Setting (Inpt. vs Outpt.)	-	0.3160 (0.1372)	0.3942 (0.1355)	0.3970 (0.1356)	0.3978 (0.1356)	0.4115 (0.1418)	0.3738 (0.1457)	0.3187 (0.1510)	0.3413 (0.1526)
Data Collection Period	-	-	0.5095 (0.0970)	0.5034 (0.0980)	0.5062 (0.0983)	0.5050 (0.0983)	0.4255 (0.1110)	0.4194 (0.1119)	0.3889 (0.1111)
Age (Paed. vs Adult)				-0.0234 (0.0856)	-0.0093 (0.0923)	-0.0261 (0.1048)	-0.1367 (0.1307)	-0.1544 (0.1324)	-0.2059 (0.1309)
Diagnosis (HA vs HB)	-	-	-	-	-0.0454 (0.1034)	-0.0563 (0.1080)	-0.1052 (0.1188)	-0.1048 (0.1222)	-0.0682 (0.1254)

Minor vs Major Surgery					0.0366 (0.1122)	0.0342 (0.1155)	0.0683 (0.1227)	0.0651 (0.1246)
Hemostatic Agent (BPA vs CFC)	-	-	-	-		-0.0249 (0.2026)	0.0353 (0.2106)	-0.0367 (0.2145)
Hemostatic Agent (Others vs CFC)	-	-	-	-		0.2021 (0.1411)	0. 2055 (0.1407)	0. 2113 (0.1390)
Antifibrinolytics recommendation	-	-	-	-			-0.1359 (0.1349)	-0.1097 (0.1347)
Surgery Planning Type (Emergent vs Planned)	-	-	-	-				0.5443 (0.2667)
Surgery Planning Type (Unreported vs Planned)	-	-	-	-				0.1616 (0.1104)

APPENDIX III – Independent Risk Factors for Perioperative Hemostasis, Complications and Surgical Plan Deviations.

	L'Beta Estimate	SE	adjRR (95% CI)	p-value
Perioperative Hemostasis				
Inhibitor Present vs Absent	-0.3507	0.0995	0.69 (0.51 -0.94)	<0.001
Surgery Setting (Inpatient vs Outpatient)	- 0.0709	0.0244	0.93 (0.89 – 0.98)	0.004
Intercept	-0.0389	0.0174	0.96 (0.93 – 0.99)	0.025
Complications				
Inhibitor Present vs Absent	0.5213	0.2301	1.68 (1.07 – 2.64)	0.024
Surgery Setting (Inpatient vs Outpatient)	1.4702	0.4126	4.35 (1.94 – 9.76)	<0.001
Data collection period (Prospective vs historic)	0.6362	0.1936	1.89 (1.29 – 2.76)	0.001
Intercept	-3.5226	0.4287	0.03 (0.01 – 0.07)	<0.001
Surgical Plan Deviations				
Inhibitor Present vs Absent	0.3976	0.0949	1.49 (1.24 – 1.79)	<0.001
Surgery Setting (Inpatient vs Outpatient)	0.3970	0.1356	1.49 (1.14 – 1.94)	0.003
Data collection period (Prospective vs historic)	0.5034	0.0980	1.65 (1.37 – 2.00)	<0.001
Intercept	-1.4931	0.1482	0.22 (0.17 – 0.30)	<0.001

APPENDIX IV – COMPLICATIONS

Complications /Adverse Events	Intraoperative Events	Postoperative Events	Unspecified Perioperative period	Total Events (n=266)
Allergic reactions, hives, itching		4		4
Anemia		6		6
Arrythmia	1	1		2
Arterial occlusion		1		1
Bowel obstruction/Ileus		1		1
Carcinoma after transplant		1		1
Cellulitis		2		2
Crackles		1		1
Complications with devices& lines	2	17		19
Decreased range of motion		1		1
Delirium		3		3
ECG Changes	1	1		2
Fever		22		22
Headache		4		4
Hematemesis	1	1	1	3
Hematochezia		1		1
Hematoma		10		10
Hematuria		1		1
Hemorrhage	2	22		24
Hemorrhage (Incision)		4		4
Hyperglycemia		1	1	2
Hypertension	1	4		5
Hypotension		2		2
Infections		14		14
Inhibitor development		6		6
Injury prior to surgery			1	1
Lethargy, Weakness		2		2
Memory loss		1		1
Mortality unrelated to surgery		1		1
Multiple	1	4		5
Nausea and Vomiting		4		4
Numbness		1		1
Pain		22		22
Pain and swelling		1		1
Pleural effusion		5		5
Rash		2		2
Respiratory complications		5		5
Stroke		1		1
Swelling, bruising		18		18

Syncope / Fainting		2		2
Thrombosis		5		5
Urinary retention		2		2
Wound dehiscence		8		8
Wound drainage/oozing		15		15
Multiple events	1	8		9
Additional steps/procedure required	3	1		4
Unfavorable biopsy/colonoscopy result		2		3
Undescribed events/Blanks			8	8
Total	**13**	**241**	**11**	**266**

96 (16.3%) of procedures included in analyses had complications, with multiple complications associated with some surgeries.

CHAPTER 4: CLOTTING FACTOR CONCENTRATES FOR PREVENTING BLEEDING AND BLEEDING-RELATED COMPLICATIONS IN PREVIOUSLY TREATED INDIVIDUALS WITH HEMOPHILIA A AND B

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4.1 Abstract

Background: The hallmark of severe hemophilia (A or B) is recurrent bleeding into joints and soft tissues with progressive joint damage, despite on-demand treatment. Prophylaxis has long been used, but not universally adopted, because of medical, psychosocial, and cost controversies.

Objectives: To determine the effectiveness of clotting factor concentrate prophylaxis in managing previously treated individuals with hemophilia A or B.

Search methods: We searched the Cochrane Cystic Fibrosis and Genetic Disorders Group's Coagulopathies Trials Register, compiled from electronic database searches and handsearching of journals and conference abstract books. In addition, we searched MEDLINE and Embase and online trial registries.

Most recent search of Group's Coagulopathies Trials Register: 24 February 2021.

Selection criteria: Randomized controlled trials (RCTs) and quasi-RCTs evaluating people with hemophilia A or hemophilia B, who were previously treated with clotting factor concentrates to manage their hemophilia.

Data collection and analysis: Two authors independently reviewed trials for eligibility, assessed risk of bias and extracted data. The authors used the GRADE criteria to assess the certainty of the evidence.

Main results: Ten trials (including 608 participants) were eligible for inclusion. Eight of the trials (477 participants) had arms comparing two or more prophylactic regimens to one another and four of the trials (n = 258) compared prophylaxis to on-demand treatment (two trials had multiple arms and were included in both comparisons).

Comparison of two or more prophylactic regimens: For trials comparing one prophylaxis regimen to another, given the heterogeneity of the data, none of the data were pooled for this comparison. Considering the individual trials, three trials reported the primary outcome of joint

bleeding, and none showed a difference between dosing regimens (low-certainty evidence). For the secondary outcome of total bleeding events, prophylaxis with a twice-weekly regimen of FIX likely results in reduced total bleeds compared to a once-a-week regimen of the same dose, mean difference (MD) 11.2 (5.81 to 16.59) (one trial, 10 participants, low-certainty evidence). Transient low-titer anti-FVIII inhibitors were reported in one of the trials. Blood-transmitted infections were not identified. Other adverse events reported include hypersensitivity, oedema, and weight gain. These were, however, rare and unrelated to study drugs (very low-certainty evidence).

Comparison of prophylactic and on-demand regimens: Four of the trials (258 participants) had arms that compared prophylaxis to on-demand treatment. Prophylaxis may result in a large decrease in the number of joint bleeds compared to on-demand treatment, MD -30.34 (95% CI -46.95 to -13.73) (two trials, 164 participants, low-certainty evidence). One of these trials (84 participants) also reported the long-term effects of prophylaxis versus on-demand therapy showing improved joint function, quality of life, and pain; but no differences between groups in joint structure when assessed by magnetic resonance imaging (MRI). In one trial (84 participants) validated measures for joint health and pain assessment showed that prophylaxis likely improves joint health compared to an on-demand regimen with an estimated change difference of 0.94 points (95% CI 0.23 to 1.65) and improves total pain scores, MD -17.20 (95% CI -27.48 to -6.92 (moderate-certainty evidence). Two trials (131 participants) reported that prophylaxis likely results in a slight increase in adverse events, risk ratio 1.71 (1.24 to 2.37) (moderate-certainty evidence). No inhibitor development and blood-transmitted infections were identified. Overall, the certainty of the body of evidence was judged to be low because of different types of bias that could have altered the effect.

Authors' conclusions: There is evidence from RCTs that prophylaxis, as compared to on-demand treatment, may reduce bleeding frequency in previously-treated people with hemophilia. Prophylaxis may also improve joint function, pain and quality of life, even though this does not translate into a detectable improvement of articular damage when assessed by MRI.

When comparing two different prophylaxis regimens, no significant differences in terms of protection from bleeding were found. Dose optimization could, however, result in improved efficacy. Given the heterogeneity of the data, pooled estimates were not obtained for most comparisons.

Well-designed RCTs and prospective observational controlled studies with standardized definitions and measurements are needed to establish the optimal and most cost-effective treatment regimens.

4.2 Plain language summary

Review question

Should people, who have previously been treated for joint bleeding, be given regular preventative treatment with clotting factor concentrates to manage their condition?

Background

Hemophilia A and B are X-linked inherited bleeding disorders in which bleeding into joints is a major problem. Repeated joint bleeds can lead to affected joints (commonly referred to as 'target joints') becoming damaged and painful, with limited movement. Currently, bleeding is treated and prevented with plasma-derived or recombinant clotting factor concentrates, and more recently non-clotting factor formulations. This review looked at how useful and effective different clotting factor treatment strategies are for preventing joint bleeding and other outcomes in previously treated people with hemophilia A or B.

Search date

Date of last search: 24 February 2021.

Study characteristics

This review includes 10 randomised controlled trials. Eight had treatment arms that compared the regular use of clotting factor concentrates to prevent joint bleeds with different dosing schemes to identify regimens that may be better; four had treatment arms that compared the regular use of factor concentrates to prevent bleeds to their 'on demand' use to treat bleeds once they occur. Two (two trials had multiple arms and were included in both comparisons).

Key results

In people living with hemophilia A or B previously treated for joint bleeding or with existing joint damage, preventive therapy may reduce the number of joint bleeds compared to 'on-demand therapy'. This reduction in bleeds may lead to an improvement in joint function, pain, and quality of life. However, preventive therapy is linked to an increased use of factor concentrates and therefore higher treatment costs. Further studies are needed to establish the best preventive course of treatment in terms of starting time, frequency and dose level.

Certainty of the evidence

Overall, the certainty of the evidence was judged to be low because of different types of bias that could have affected the results. Future research might have an important role in changing our confidence in these results.

4.3 Background

4.3.1 Description of the condition

Congenital hemophilia is a rare x-linked bleeding disorder caused by a deficiency in clotting factor VIII (FVIII) in hemophilia A and factor IX (FIX) in hemophilia B (Srivastava 2020). Severity of disease is classified according to level of clotting factor naturally present in the blood: severe (with a baseline coagulation factor level of less than 1% of normal); moderate (with clotting factor levels of 1% to 5%); and mild (6% to 49%) (Blanchette 2014).

The physical manifestation of hemophilia varies with the severity of disease. People with mild and moderate hemophilia rarely experience spontaneous bleeding episodes, and often only bleed abnormally following trauma or in association with invasive procedures. People with severe hemophilia are at highest risk for experiencing frequent and severe spontaneous bleeding incidents. This group is also prone to experiencing recurrent or chronic bleeding into joints and muscles, which can develop into haemophilic joint arthropathy and muscle atrophy.

4.3.2 Description of the intervention

While there is no routinely-available cure for hemophilia, symptoms of the disease can be effectively managed by the infusion of exogenous clotting factor concentrates (either FVIII or FIX). The availability of clotting factor concentrates has improved the morbidity, mortality and quality of life (QoL) of people with hemophilia (Lusher 1997; Tobase 2016). Availability of factor concentrate allows for early treatment of acute bleeding incidents, and has resulted in a decrease in joint deformities in untreated or minimally-treated individuals (Ahlberg 1965; Hilgartner 1974; Liddle 2017).

Factor concentrates are generally administered according to two treatment regimens: on-demand (also termed episodic) treatment, where individuals receive clotting factor only in response to a bleeding event; orprophylaxis treatment, where individuals receive regular infusions of clotting factor with the aim to prevent bleeds.

A 1994 study by Aledort, showed that prophylaxis treatment reduced the number of bleeding events and may reduce the incidence of bleeding-related adverse events, such as haemophilic arthropathy (Aledort 1994). This same study showed progressive joint deterioration over the six-year follow-up period in participants using on-demand treatment only (Aledort 1994). Given its preferable outcomes, prophylaxis treatment, in comparison to on-demand treatment, has been recommended for all children with severe hemophilia (Berntorp 2003; MASAC 2010; MASAC 2016; Rayment 2020; Richards 2010; Srivastava 2020).

4.3.3 How the intervention might work

There are two main categories of prophylactic treatment: primary prophylaxis, which is established before joint deterioration (before the second clinically-evident joint bleed and age three years); and secondary prophylaxis, which is established after some joint deterioration. Given the differences in starting times, the aims of primary and secondary prophylaxis differ. Primary prophylaxis aims to use regular infusions of factor concentrate to maintain the individuals' factor level above a desired target, usually in the mild or moderate range (above 1% of clotting factor present in blood), to prevent spontaneous bleeding episodes and joint arthropathy. Secondary prophylaxis aims to slow the progression of existing arthropathy, prevent the development of new arthropathies, and prevent further spontaneous bleeding incidents (Hay 2007).

Secondary prophylaxis is generally started after some degree of joint arthropathy has already occurred (Hay 2007) and can theoretically be started at any time in life. The existing evidence shows that starting secondary prophylaxis in adulthood can reduce bleeding frequency, and delay the progression of joint arthropathy (Tagliaferri 2008). For these reasons, the Medical and Scientific Advisory Council of the US National Hemophilia Foundation (MASAC) has identified that individuals, especially those with severe hemophilia, may benefit from continuing prophylaxis throughout their life (MASAC 2010; MASAC 2016).

4.3.4 Why it is important to do this review

Despite the known benefits of prophylaxis, there are medical, psychosocial and cost barriers that preclude the universal use of prophylaxis (Blanchette 2004; Thornburg 2017). Such concerns may be balanced by strong evidence of the efficacy of prophylaxis treatment. Numerous studies exist citing the efficacy of primary prophylaxis and the previous systematic review (from which this review has been derived) showed that primary prophylaxis was significantly better at preserving joint function in children with hemophilia, in comparison to on-demand treatment (Iorio 2011). Similar evidence, including evidence from randomised controlled trials, for the efficacy of secondary prophylaxis started in adulthood is accumulating, but has not yet been systematically reviewed.

This review aims to clarify the efficacy and safety of secondary prophylaxis in adults by systematically reviewing and summarising the available evidence of prophylactic administration of factor concentrates in previously-treated individuals with hemophilia A or B.

4.3.5 Objectives

To determine the effectiveness of clotting factor concentrate prophylaxis in managing previously treated individuals with hemophilia A or B, for improving short- and long-term outcomes measured by one or more of the following.

Short-term outcomes

1. Number of joint bleeding episodes per year or bleeding frequency
2. Number of total bleeds per year or bleeding frequency
3. Clotting factor concentrate levels in plasma

Long-term outcomes

1. Clinical joint function
2. Orthopedic joint score
3. Radiologic joint score
4. QoL measurements

4.4 Methods

4.4.1 Criteria for considering studies for this review

Types of studies

Randomized or quasi-randomized controlled trials. All identified trials, unpublished or published as an article, an abstract or a letter, without any language limitations, were eligible for inclusion.

Types of participants

Trials including individuals with congenital hemophilia A or B, receiving secondary prophylaxis were eligible. We included all trials which enrolled adults (aged 18 or over) and those trials with participants under 18 years of age if the participants met one of the three following criteria:

1. proven haemophilic arthropathy;
2. presence of one or more target joint;
3. previous on-demand treatment.

We did not exclude based on degree of disease severity, type of previous treatment (if any), or presence of previous joint damage. Trials including participants with factor VIII or IX inhibitors at baseline were excluded.

Types of interventions

We compared intravenous clotting factor concentrates administered as prophylactic treatment in any formulation (e.g. fresh frozen plasma, cryoprecipitate, lyophilised plasma-derived clotting factor concentrate, or recombinant clotting factor concentrate), any concentration,

any frequency and any dose, with no treatment, placebo, on-demand treatment, or with one or more different prophylaxis regimens. We did not include trials of a single treatment and at least one treatment must have been a clotting factor concentrate. Therefore the anticipated comparison groups were as follows:

1. prophylaxis versus prophylaxis with a different regimen;
2. prophylaxis versus on-demand treatment;
3. prophylaxis versus no treatment;
4. prophylaxis versus placebo.

Types of outcome measures

The following primary and secondary outcomes were assessed based on clinical relevance.

Primary outcomes

- Number of joint bleeding episodes or joint bleeding frequency during the trial
- Orthopedic joint score or clinical joint function
- QoL on validated scales (disease-specific where possible)

Secondary outcomes

- Number of total bleeding episodes or total bleeding frequency during the trial period
- Pain scores
- Radiologic joint score or radiologic measurements or descriptions of joint damage
- Clotting factor concentrate plasma levels
- Time loss to school or employment
- Integration into society (i.e. absenteeism)
- Scores on scales recording feeling of well-being and global functioning

- Economic data: cost-effectiveness, cost-benefit, cost-utilisation, cost-minimisation
- Any reported adverse effects or toxicity of clotting factor concentrates (e.g. inhibitors, reactions, transmission of infection)

4.4.2 Search methods for identification of studies

We searched for all relevant published and unpublished trials without restrictions on language, year or publication status.

Electronic searches

We identified relevant trials from the Group's Coagulopathies Trials Register using the term: prophylaxis and (hemophilia* or haemophilia*).

The Coagulopathies Trials Register is compiled from electronic searches of the Cochrane Central Register of Controlled Trials (CENTRAL) (updated each new issue of the Cochrane Library) and weekly searches of MEDLINE and the prospective handsearching of one journal - Haemophilia. Unpublished work is identified by searching the abstract books of major conferences: the European Haematology Association conference; the American Society of Hematology conference; the British Society for Haematology Annual Scientific Meeting; the Congress of the World Federation of Hemophilia; the European Association for Haemophilia and Allied Disorders, the American Society of Gene and Cell Therapy and the International Society on Thrombosis and Haemostasis. For full details of all searching activities for the register, please see the relevant section of the Cochrane Cystic Fibrosis and Genetic Disorders Group's website.

Date of the most recent search of the Group's Coagulopathies Trials Register: 24 February 2021.

We also searched the following databases and trial registries:

1. MEDLINE Ovid (1946 to June 2016 – search carried out by authors of a previous version of this review
2. Embase Ovid (1974 to June 2016 – search carried out by authors of a previous version of this review);
3. ISRCTN registry (www.isrctn.com/; searched 06 August 2020);
4. US National Institutes of Health Ongoing Trials Register Clinicaltrials.gov (www.clinicaltrials.gov; searched 06 August 2020);
5. World Health Organization International Clinical Trials Registry Platform (WHO ICTRP) (https://apps.who.int/trialsearch; we were unable to carry out a search as access was temporarily unavailable due to the current COVID-19 pandemic. We will try and search this resource when the review is updated).

For details of the search strategies, please see (Appendix 1).

Searching other resources

We checked the bibliographies of included trials and any relevant systematic reviews identified for further references to relevant trials.

The following conference proceedings were also hand searched:

1. International Society for Thrombosis and Haemostasis Biannual Meeting (2004 to 2016);
2. European Association for Haemophilia and Allied Disorders (2004 to 2016).

4.4.3 Data collection and analysis

Selection of studies

Two authors independently screened the titles and abstracts of the retrieved citations and retrieved all available complete manuscripts for potentially relevant trials. The same two authors assessed the full-text manuscripts to select the final trials to be included according to the review's inclusion criteria. A third-party arbitrator helped to settle any differences between the two authors.

Data extraction and management

Two authors independently extracted data using a pre-designed data extraction form. The structured data form included the following information.

- Inclusion criteria of the trial
- Characteristics of the trial (i.e. trial design, location and time frame)
- Participant number and demographics
- The intervention and co-interventions (including dosing and frequency of clotting factor concentrate)
- Outcomes (including primary and secondary outcome measures and description)
- Information regarding limitations and biases

We considered any outcome data recorded as either individual events or as events grouped by time periods.

Assessment of risk of bias in included studies

The authors used the tool in RevMan 5.4 to measure the risk of bias and to produce summary figures (RevMan 2020). The authors assessed the risk of bias using the 'Risk of bias' assessment tool as documented in section 8.5 of the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2017). The following domains were assessed as having either a low, high, or unclear risk of bias:

sequence generation;allocation concealment;blinding (of participants, personnel and outcome assessors);incomplete outcome data;selective outcome reporting;other sources of bias.

To estimate selective outcome reporting, we identified original protocols and compared the results and outcomes reported in the final report to those proposed in the protocol.

Measures of treatment effect

We anticipated that the primary outcome (number of joint bleeding episodes or joint bleeding frequency during the trial) would be reported using mean and standard deviation (SD). For the secondary outcomes, we anticipated continuous outcomes to be reported as either a rate of event, mean and SD, or median and interquartile range (IQR). We anticipated dichotomous outcomes to be reported as the frequency of each option. Given these assumptions, we measured the treatment effect of the primary outcome using a mean difference (MD). We measured the treatment effects of secondary outcomes using the risk difference (RD) or MD for continuous outcomes and risk ratio (RR) for dichotomous outcomes. We reported the 95% confidence interval (CI) of each measure of treatment effect.

Unit of analysis issues

We anticipated that the unit of analysis would be the individual, as disease progression and treatment can vary between individuals. Given the chronic nature of the condition, as well as the rapid onset and short duration of the intervention (factor VIII and IX physiological half-lives are 12 and 24 hours respectively), we anticipated that some trials included would be cross-over in design. We used the generic inverse variance (GIV) method to include cross-over trials in any meta-analyses conducted, as reported in chapter 23 of the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2021). Whenever possible we have used individual patient data to analyze the results of cross-over trials (Aronstam 1976; Aronstam 1977; Morfini 1976). In the Leopold II trial (LEOPOLD II 2015) participants were randomised to receive on-demand or prophylactic therapy with FVIII (two different regimens); participants were crossed-over within their treatment groups, but only with respect to the methods for measuring the content of FVIII in the vials, therefore, we treated this trial as if it had a parallel design.

Dealing with missing data

We attempted to contact trial authors to provide any missing data. We reported the level of missing data and reason for missing data where possible.

Assessment of heterogeneity

Given the small number of trials that were included in a meta-analysis in this review, we did not assess for heterogeneity in most of the analyses. However, where sufficient trials were included in a meta-analysis, we identified the presence of statistical heterogeneity using the Chi^2 value. We also reported the I^2 value as a measure of heterogeneity in the meta-analysis.

We applied the following thresholds, as suggested in the Cochrane Handbook for Systematic Reviews of Interventions (Deeks 2021):

- 0% to 40%: might not be important;
- 30% to 60%: may represent moderate heterogeneity;
- 50% to 90%: may represent substantial heterogeneity;
- 75% to 100%: represents considerable heterogeneity.

Assessment of reporting biases

In future versions of this review, if there are more than 10 trials in the same analysis, we will construct a funnel plot and assess it for symmetry.

Data synthesis

In comparisons where only one trial was assessed, we used the fixed-effect model in the analyses. We used a random-effects model in analyses including multiple trials to account for possible heterogeneity.

Subgroup analysis and investigation of heterogeneity

In future versions of this review, depending on data availability, we plan a subgroup analysis based on Pattersson scores and other measures indicating the extent of disease progression.

Sensitivity analysis

We were unable to aggregate data for a majority of outcomes in this review. However, if there are a sufficient number of eligible and included trials, we will undertake a sensitivity

analysis by looking at trials with a low risk of bias versus a high risk of bias, as measured above.

Summary of findings and assessment of the certainty of the evidence

We presented a summary of findings table for each of the following comparisons.

1. Comparison between two prophylaxis regimens
2. Prophylaxis with standard therapeutic factor concentrate compared to pegylated liposome FVIII formulation
3. Prophylaxis versus on-demand comparison.

The following outcomes were chosen based on relevance to clinicians and consumers and reported in the table.

1. Number of joint bleeding episodes per year or bleeding frequency;
2. Number of total bleeds per year or bleeding frequency;
3. Any reported adverse event.

We determined the certainty of the evidence using the GRADE approach; and downgraded evidence in the presence of a high risk of bias in at least one trial, indirectness of the evidence, unexplained heterogeneity or inconsistency, imprecision of results, high probability of publication bias. We downgraded evidence by one level if we considered the limitation to be serious and by two levels if very serious.

4.5 Results

4.5.1 Description of studies

Description of studies and results of the search are described below.

Results of the search

Our search strategies yielded 322 unique references, of which 68 articles reporting seven studies were included in this review (A-LONG 2014; LEOPOLD II 2015; LipLong 2012; PROPEL III 2020; SPINART 2013; Valentino 2012; Valentino 2014). A further three trials (three articles) (Aronstam 1976; Aronstam 1977; Morfini 1976) were accessed from a previous Cochrane Review (which this current review and one more Cochrane Review in progress, supersedes), and were also included in this review (Iorio 2011). No additional articles were found from searching reference lists of included articles or conference proceedings.

We excluded a further 251 references to 89 trials.

Included studies

See Characteristics of included studies for a full description of each trial.

Trial design

10 trials, with a total of 608 participants were included in the review (A-LONG 2014 (n = 47); Aronstam 1976 (n = 9); Aronstam 1977 (n = 4); LEOPOLD II 2015 (n = 80); LipLong 2012 (n = 143); Morfini 1976 (n = 10); PROPEL III 2020 (n = 115); SPINART 2013 (n = 84); Valentino 2012 (n = 66); Valentino 2014 (n = 50). There was no disagreement between authors regarding trial relevance and inclusion.

One trial was conducted in Italy (Morfini 1976), two in England (Aronstam 1976; Aronstam 1977) and seven were multicentre trials (A-LONG 2014; LEOPOLD II 2015; LipLong 2012; PROPEL III 2020; SPINART 2013; Valentino 2012; Valentino 2014).

Four trials were cross-over in design (Aronstam 1976; Aronstam 1977; Morfini 1976; Valentino 2014). In these trials, the order of intervention was randomised, and all participants received both the control and active treatment. All of the cross-over trials included an adequate washout period before the second treatment intervention was administered. The remaining six trials were parallel in design, four trials were randomised open-label trials (A-LONG 2014; PROPEL III 2020; SPINART 2013; Valentino 2012), one was a randomised double-blind trial with an active control (LipLong 2012). The remaining randomised trial, the LEOPOLD II study, was reported as cross-over, with participants randomised to one of six treatment arms (two low-dose prophylaxis groups, two high-dose prophylaxis groups, and two on-demand treatment groups); participants received treatment based on CS/EP (chromogenic substrate assay per European Pharmacopoeia) or adjusted by a predefined factor to mimic results obtained with the one-stage assay (CS/ADJ) for six months each with an intraindividual cross-over after six months (LEOPOLD II 2015). However, since participants were crossed-over within their treatment groups but only with respect to the methods for measuring the content of FVIII activity in the vials (using the CS/EP or the CS/ADJ). This cross-over trial has been analysed as a parallel trial.

Types of participants

All trials included participants receiving secondary prophylaxis. Two trials included individuals with hemophilia B: the Morfini trial included individuals with severe hemophilia B (FIX levels < 1%) (Morfini 1976); and the 2014 Valentino trial included individuals with moderately severe and severe hemophilia B (FIX levels ≤ 2%) (Valentino 2014). Seven trials included individuals with severe haemophilia A only (FVIII levels < 1% of normal) (A-LONG 2014; Aronstam 1976; Aronstam 1977; LEOPOLD II 2015; LipLong 2012; PROPEL III 2020; SPINART 2013). One trial included participants with moderately severe to severe hemophilia A (FVIII levels ≤ 2% of normal) (Valentino 2012). All trials included participants who were previously exposed to FVIII or FIX, whether through on-demand treatment or through a prophylaxis regimen. All included participants were males and between five years and 65 years of age. None of the participants had an inhibitory antibody to FVIII or FIX at baseline.

There were some boys in the Aronstam 1976 trial who were also included in the 1977 trial: "Those boys who had been on the first double-blind controlled trial (Aronstam 1976) and were still available for a further two terms were selected. There were four such boys, patients 1, 3, 8, and 9 of that trial. The boys selected had each had at least one full school term off prophylaxis before entering the second trial" (Aronstam 1976; Aronstam 1977).

Types of interventions

Two of the trials had multiple arms where a prophylaxis regimen was compared to another prophylaxis regimen, as well as a comparison of a prophylaxis and on-demand regimen (LEOPOLD II 2015; Valentino 2014). Therefore, we included these two trials in two comparisons.

Comparison between two prophylaxis regimens

Eight trials compared two different prophylactic regimens (Aronstam 1976: Aronstam 1977; LEOPOLD II 2015; LipLong 2012; Morfini 1976; PROPEL III 2020; Valentino 2012; Valentino 2014). Of these, four trials had a fixed prophylaxis dose in both arms (LEOPOLD II 2015; LipLong 2012; Morfini 1976; Valentino 2014). We describe the intervention and comparison in the included trials below.

Aronstam 1977: prophylaxis arm A: sufficient dose to increase the FVIII level to 10% of normal versus prophylaxis arm B: sufficient dose to raise the FVIII level to 30% of normal.

Aronstam 1976: prophylaxis arm A: sufficient dose to increase FVIII levels to >/= 0.25 IU/mL versus prophylaxis arm B: sufficient dose to increase FVIII levels to >/= 0.1 IU/mL once weekly.

Morfini 1976: prophylaxis arm A: FIX 7.5 U/kg twice per week versus prophylaxis arm B: FIX 15 U/kg once per week.

Valentino 2012: prophylaxis arm A: standard prophylactic treatment of 20 to 40 IU/kg FVIII every 48 hours versus prophylaxis arm B: PK-tailored prophylactic treatment of 20 to 80 IU/kg FVIII every 72 hours (dose-dependent on PK evaluation).

LEOPOLD II 2015: prophylaxis arm A: high-dose regimen (FVIII 30 to 40 IU/kg thrice-weekly versus prophylaxis arm B: low-dose regimen (FVIII 20 to 30 IU/kg twice-weekly). The factor concentrate used was an experimental full-length rFVIII product referred to as BAY 81-8973. This product was created to improve clinical efficacy by alterations in glycosylation and was also free of any human or animal-derived products. BAY 81-8973 was co-expressed with heat shock protein 70 to improve the in vivo viability of the product.

LipLong 2012: prophylaxis arm A: the investigational drug, BAY 79-4980 consisting of 35 IU/kg of rFVIII and 13 mg/kg of pegylated liposome, administered at a reduced frequency of once per week versus prophylaxis arm B: standard prophylaxis treatment with rFVIII at a dose of 25 IU/kg three times per week.

Valentino 2014: prophylaxis arm A: high-frequency schema (50 IU/kg twice-weekly) versus prophylaxis arm B: low-frequency schema (100 IU/kg once-weekly).

PROPEL III 2020: prophylaxis arm A: PK-guided prophylaxis to achieve FVIII trough levels of 1% to 3% versus treatment arm B: prophylaxis targeting trough levels of 8% to 12%.

Prophylaxis regimen compared to on-demand (episodic) treatment

Four trials compared on-demand treatment to prophylaxis treatment (A-LONG 2014; LEOPOLD II 2015; SPINART 2013; Valentino 2014).

SPINART 2013: on-demand treatment administered on the basis of investigator recommendations versus prophylaxis treatment administered at a dosage of 25 IU/kg

three times per week. This amount could be increased to a maximum of 35 IU/kg over two years in participants with 12 or more bleeding episodes per year on the trial.

A-LONG 2014: on-demand treatment administered at a dose of 10 to 50 IU/kg FVIII as needed versus standard prophylaxis administered at a dose of 65 IU/kg rFVIII once weekly. Additionally, this trial also enrolled individuals who were previously on prophylaxis or on-demand therapy but not willing to be randomised (Arm 1) to be treated with an individualized prophylaxis regimen (N = 118). Since this was a non-randomised arm we did not include it in the analysis.

Valentino 2014: prophylaxis A: high-frequency schema (50 IU/kg twice-weekly) versus prophylaxis B: low-frequency schema (100 IU/kg once-weekly). These two regimens were compared to an on-demand treatment where FIX was given to treat bleeding events as needed. The factor product used for all study arms was nonacog alfa (BeneFIX).

LEOPOLD II 2015: on-demand treatment with BAY 81-8973, a recombinant factor VIII product, was compared with two arms of prophylaxis treatment (prophylaxis A: high-dose regimen (FVIII 30 to 40 IU/kg thrice-weekly and prophylaxis B: low-dose regimen (FVIII 20 to 30 IU/kg twice-weekly).

Types of outcomes

Our primary outcome of interest, joint bleeding events or joint bleeding frequency, was reported in seven out of the 10 studies (A-LONG 2014; LEOPOLD II 2015; LipLong 2012; PROPEL III 2020; SPINART 2013; Valentino 2012; Valentino 2014). Clinical joint function and radiologic measurements were reported in two trials (Morfini 1976; SPINART 2013). Two trials also reported conducting QoL measurements

(SPINART 2013; Valentino 2012) and one trial (SPINART 2013) reported the results of pain assessment.

Overall bleeding events or overall bleeding frequency were reported in all 10 trials. The quantity of factor concentrate used was reported in four trials (LEOPOLD II 2015; PROPEL III 2020; SPINART 2013; Valentino 2012). Adverse event reporting, including the development of inhibitors, was reported in seven of the trials (A-LONG 2014; LEOPOLD II 2015; LipLong 2012; PROPEL III 2020; SPINART 2013; Valentino 2012; Valentino 2014).

Excluded studies

See Characteristics of excluded studies for more details of the excluded trials.

We excluded 89 trials (251 references) from this review. A total of 40 trials were excluded because they were not randomised studies, including 22 prospective and 18 retrospective observational studies. 15 trials had an intervention arm that included non-clotting factors, e.g. concizumab (n = 9), emicizumab (n = 5), investigational RNA inteference therapeutic (n = 1). Six trials were excluded because they were conducted in participants with inhibitors, 13 additional trials were not eligible because they included individuals on primary prophylaxis. 10 trials assessed pharmacokinetic parameters and four were reported in conference abstracts only and detailed descriptions of trial participants were not available. One trial was a feasibility study with no hypothesis testing, no useable results and concluded that the trial lacked feasibility.

4.5.2 Risk of bias in included studies

We present an overall risk of bias assessment graphically in the figures section (Figure 1; Figure 2).

Allocation (selection bias)

Random sequence generation

While all trial reports indicated that the trial was randomised, only four of the 10 included trials provided some detail of the method used for random sequence generation (LEOPOLD II 2015; PROPEL III 2020; SPINART 2013; Valentino 2012). In two of these trials, the method used was judged to be sound and of low risk of bias (PROPEL III 2020; Valentino 2012). Eight trials were judged to be of unclear risk of bias.

Allocation concealment

Four trials indicated the method for allocation concealment; these were judged to be at low risk of bias for this domain (LEOPOLD II 2015; Morfini 1976; SPINART 2013; Valentino 2012). The remaining six trials had an unclear risk of bias (A-LONG 2014; Aronstam 1976; Aronstam 1977; LipLong 2012; PROPEL III 2020; Valentino 2014).

Blinding (performance bias and detection bias)

Performance and detection bias

Three of the included trials employed an appropriate method to blind participants and personnel to minimise performance bias (Aronstam 1976; Aronstam 1977; LipLong 2012). The remaining seven trials were open-label and we judged these to be at high risk of bias (A-LONG 2014; LEOPOLD II 2015; Morfini 1976; PROPEL III 2020; SPINART 2013; Valentino 2014; Valentino 2012). In the Manco-Johnson trial, bleeding events were patient-reported using an electronic diary, but for other outcomes such as the MRI evaluation of hemophilic arthropathy by radiologists and the joint physical examination performed by the physiotherapists, the assessors were blinded. The open-label trial design may also have influenced the results of the HRQoL (SPINART 2013). Similarly, in the Morfini trial, even though this is an open-label trial, it is reported that the assessors of orthopedic and radiological outcomes were blinded (Morfini 1976).

Incomplete outcome data (attrition bias)

Eight of the 10 included trials either had no missing data or the losses to follow-up were balanced and explained. We judged these trials to be at low risk of bias (A-LONG 2014; Aronstam 1976; Aronstam 1977; LEOPOLD II 2015; Morfini 1976; PROPEL III 2020; SPINART 2013; Valentino 2014). One included trial had dropouts not balanced across groups and with the reason cited as “PK results”. Since this seems to be a treatment-related difference, we judged this to be at a high risk of bias (Valentino 2012). The LipLong trial was prematurely discontinued by the sponsor based on the recommendation of an independent data and safety monitoring board and was analysed per protocol (LipLong 2012). Also, higher consent withdrawal was reported in the investigational drug arm (N = 8 versus N = 2).

Selective reporting (reporting bias)

We judged all included trials to have a low risk of bias for this domain. The protocols were not available in four of the 10 trials, but all expected outcomes were reported in these trials (Aronstam 1976; Aronstam 1977; Morfini 1976; Valentino 2014). We acquired the protocols for five trials and there was agreement between the outcomes outlined in the protocol and those presented in the final reports (A-LONG 2014; LEOPOLD II 2015; LipLong 2012; SPINART 2013; Valentino 2012). For one trial, authors provided a three-month timeframe from the time of request to make the protocol available; all expected and stated outcomes in this trial were, however, reported (PROPEL III 2020).

Other potential sources of bias

In three of the cross-over trials, the washout period was unclear, therefore we judged these to have an unclear risk of bias (Aronstam 1976, Aronstam 1977; Morfini 1976). The Liplong trial is marked high risk for other potential sources of bias due to the possibility of over-estimation or "freezing-effect" that could arise from premature discontinuation of clinical trials (LipLong 2012; Wang 2016). In the remaining six trials, we did not identify any other potential sources of bias and so marked them as low risk for other potential sources of bias A-LONG 2014; LEOPOLD II 2015; PROPEL III 2020; SPINART 2013; Valentino 2012; Valentino 2014).

4.5.3 Effects of interventions

Comparison between two prophylaxis regimens

The certainty of the evidence has been graded for those outcomes included in the summary of findings table (Summary of findings table 1). For the definitions of these gradings, please refer to the summary of findings tables.

We included eight trials (477 participants) in this comparison (Aronstam 1976; Aronstam 1977; Morfini 1976; LEOPOLD II 2015; LipLong 2012; PROPEL III 2020; Valentino 2012; Valentino 2014). One of the included trials compared a standard prophylaxis treatment regimen to a PK-tailored regimen (Valentino 2012). One trial compared prophylaxis with a standard therapeutic factor concentrate to a pegylated liposome FVIII formulation (LipLong 2012), this comparison is reported separately below. Overall, given the heterogeneity in reporting these trials, we did not aggregate data.

Primary outcomes

1. Number of joint bleeding episodes or joint bleeding frequency

Three included trials reported on joint bleeding (LEOPOLD II 2015; PROPEL III 2020; Valentino 2014). The LEOPOLD II trial found no difference in joint bleed prevention when a thrice-weekly, higher-dose prophylaxis regimen was compared to a twice-weekly (at 12 months follow-up) lower-dose prophylaxis, MD -1.70 (95% CI -5.06 to 1.66) (59 participants) (moderate-certainty evidence) (Analysis 1.1) (LEOPOLD II 2015). Comparing a PK-guided prophylaxis regimen targeting trough levels of 8% to 12% or 1% to 3% in the PROPEL III trial, no difference was also found between the two prophylaxis arms (at 12 months follow-up); MD -1.50 (95% CI -3.54 to 0.54) (115

participants) (moderate-certainty evidence) (Analysis 1.2) (PROPEL III 2020). No difference was also seen in spontaneous joint bleeds between the two regimens, MD -1.50 (95% CI -3.22 to 0.22) (Analysis 1.3) (PROPEL III 2020). In the Valentino 2014 trial, no difference was also reported in annualized joint bleeding in the low-frequency prophylaxis arm (100 IU/kg once weekly) compared to the standard frequency regimen (50 IU/kg twice weekly); MD of 1.70 (95% CI -1.09 to 4.49) (50 participants) (Analysis 1.4) (Valentino 2014).

2. Orthopedic joint score or clinical joint function

One included (cross-over) trial (10 participants) assessed joint function (Morfini 1976). While joint evaluations were conducted, data were not presented for individual treatment groups, rather results were presented that encompassed both arms. It was noted that through the 12 months of replacement therapy, range of motion was improved in 23 of 26 target joints. As well, there was also no deterioration in any joint, target or normal, over the course of treatment.

3. QoL on validated scales

One included trial (66 participants) assessed QoL using the SF36v1 scale (Valentino 2012). Data for individual treatment arms were not provided. Rather trial authors stated that there was no difference in overall QoL between prophylactic regimens.

Secondary outcomes

1. Number of total bleeding episodes or total bleeding frequency

Given the differences in treatment regimens and populations, we id not pool data for these trials and instead we report the results individually.

Seven trials reported on total bleeding. When comparing the use of a thrice-weekly, higher-dose prophylaxis with a twice-weekly, lower-dose prophylaxis regimen (at 12 months follow-up), results suggested no difference in overall bleeding rate, MD -1.40 (95% CI -4.91 to 2.11) (moderate-certainty evidence) (Analysis 1.5) (LEOPOLD II 2015). There was also no difference seen in total bleeding between prophylaxis to increase FVIII level to 30% or 15%, MD 10.20 (95% CI -1.29 to 21.69) (Analysis 1.6) (Aronstam 1977).

Comparing a standard prophylaxis regimen to a PK-tailored regimen, no reduction in bleeds across the comparison was indicated, MD -0.30 (95% CI -0.86 to 0.26) (66 participants) (Analysis 1.7) (Valentino 2012). When considering the effect of prophylaxis on 10 participants with haemophilia B, we see that the twice-a-week regimen (7.5 IU/kg) was favoured over the once-a-week regimen (15 IU/kg), MD 11.20 (5.81 to 16.59) (moderate-certainty evidence) (Analysis 1.8) (Morfini 1976). In the 2014 Valentino trial, comparing two different dosing frequencies in people with haemophilia B, only a P value of 0.22 was reported in the comparison of the two treatment regimens (50 IU/kg twice-weekly versus 100 IU/kg once-weekly) (Valentino 2014).

When comparing the overall bleeding frequency in nine participants in the Aronstam cross-over trial, there was a significant reduction in the overall bleeding frequency in the prophylaxis group with dosing producing at least 0.25 IU/mL of factor VIII compared to

the dosing producing at least 0.01 IU/mL once weekly, MD 3.44 (95% CI 2.42 to 4.46) (Analysis 1.9) (Aronstam 1976).

In the comparison between the prophylactic arm targeting trough levels of 1% to 3% or 8% to 12% in the PROPEL III trial, no difference was seen in bleeding frequency between the two groups, MD 2.00 (95% CI -0.13, 4.13) (115 participants) (Analysis 1.10) (PROPEL III 2020).

2. Pain scores

None of the included trials reported this outcome.

3. Radiologic joint score or radiologic measurements or descriptions of joint damage

Only one trial (10 participants) reported this outcome (Morfini 1976). Trial authors stated that the 12 months of prophylaxis treatments improved the radiological picture in six cases with grade II or III arthropathy, but had no effect in those with grade IV arthropathy, but no numeric data were given.

4. Clotting factor concentrate plasma levels

One included trial (115 participants) assessed clotting factor concentrate plasma levels (PROPEL III 2020). In this trial, initial PK assessments showed mean (SD) plasma half-lives (t½) of 15.3 (4.2) and 14.7 (5.1) hour in the 1% to 3% and 8% to 12% arms to be respectively. FVIII activity was a median (Q1 to Q3) 17.30 (15.2-21.7) and 35.0 (29.2 - 40.9) IU/dL during the first six months, and 17.30 (14.5 - 22.4) and 30.9 (24.9 - 41.2) IU/dL during the second six months for the 1% to 3% and 8% to 12% arms, respectively.

Observed FVIII activity trough levels during the second six months were within the intended ranges of 1% to 3% and 8% to 12%; with median FVIII troughs ranging from 2.1 to 3.0 IU/dL and 10.7 to 11.7 IU/dL.

5. Time loss to school or employment

None of the included trials reported this outcome.

6. Integration into society

None of the included trials reported this outcome.

7. Scores on scales recording feeling of well-being and global functioning

None of the included trials reported this outcome.

8. Economic data

None of the included trials reported this outcome.

9. Any reported adverse effects or toxicity of clotting factor concentrates

There was no reported inhibitor development reported in six of the trials in this comparison (Aronstam 1976; Aronstam 1977; LEOPOLD II 2015; Morfini 1976; Valentino 2012; Valentino 2014).

Transient low-titer anti-FVIII inhibitory antibodies, which resolved before the end of the trial, was reported in one out of 58 participants in the PROPEL III trial, in the arm targeting trough levels of 8% to 12% (PROPEL III 2020).

The Valentino trial reported (at 32 weeks follow-up) no differences in total treatment-emergent adverse events, MD 1.00 (95% CI 0.54, 1.84) (Analysis 1.11) (Valentino 2014).

Three trials did not report the rate of adverse events by treatment groups (Aronstam 1977; LEOPOLD II 2015; Morfini 1976). However, in the LEOPOLD II trial, there were three reported treatment-related adverse events, but no details regarding the type of event or group were given (LEOPOLD II 2015).

In the 2012 Valentino trial that compared standard prophylaxis to a PK-tailored regimen, there was no difference in mean rates of adverse events between the two regimens at 12 months follow-up, MD 0.27 (95% CI -0.44 to 0.98) (Analysis 1.12) (Valentino 2012).

Serious and non-serious adverse events were reported in the PROPEL III trial. However, two out of 101 and two out of 103 of these events were estimated to be treatment-related in the arm targeting 1% to 3% and 8% to 12% respectively (PROPEL III 2020). In the arm targeting trough levels of 1% to 3%, no serious adverse event was treatment-related, and in the arm targeting trough levels of 8% to 12%, one serious adverse event was estimated to be treatment-related.

We assessed the certainty of the evidence as very low.

Prophylaxis with standard therapeutic factor concentrate compared to pegylated liposome FVIII formulation

The certainty of the evidence has been graded for those outcomes included in the summary of findings table (Summary of findings table 2). For the definitions of these gradings, please refer to the summary of findings tables.

One trial was included in this comparison (LipLong 2012).

The 2012 LipLong trial (143 participants) compared a standard prophylaxis dose to a new investigational drug, pegylated liposome FVIII formulation (BAY 79-4980), given once-weekly (LipLong 2012); 73 participants were randomised to the prophylaxis group and 70 to the BAY79-4980 group. Four randomised participants did not receive the intervention drugs, leaving 139 participants (n = 67 in BAY 79-4980 and n = 72 in the prophylaxis group) for analysis. The sponsor halted the trial prematurely based on the recommendations of the data safety and monitoring board, indicating that the primary and secondary endpoints of non-inferiority with prophylaxis with rFVIII-FS three times/week would not be met. No safety issues were cited as the reason for early termination. The efficacy outcomes of this trial were reported as a per-protocol analysis set.

Primary outcomes

1. Number of joint bleeding episodes or joint bleeding frequency

This outcome was reported in terms of annualised bleeding rates. This comparison showed fewer joint bleeding with the standard prophylaxis regimen compared to the investigational drug BAY 79-4980, MD -7.20 (95% CI -11.01 to -3.39) (low-certainty evidence) (Analysis 2.1) (LipLong 2012).

2. Orthopedic joint score or clinical joint function

This outcome was not reported.

3. QoL on validated scales

This outcome was not reported.

Secondary outcomes

1. Number of total bleeding episodes or total bleeding frequency

This outcome was reported in terms of annualised bleeding rates. There was a statistically significant difference favouring the prophylaxis regimen compared to the investigational drug BAY 79-4980, MD -9.20 (95% CI -13.07 to -5.33) (low-certainty evidence) (Analysis 2.2) (LipLong 2012).

2. Pain scores

This outcome was not reported.

3. Radiologic joint score or radiologic measurements or descriptions of joint damage

This outcome was not reported.

4. Clotting factor concentrate plasma levels

This outcome was not reported.

5. Time loss to school or employment

This outcome was not reported.

6. Integration into society

This outcome was not reported.

7. Scores on scales recording feeling of well-being and global functioning

This outcome was not reported.

8. Economic data

This outcome was not reported.

9. Any reported adverse effects or toxicity of clotting factor concentrates

One participant in the prophylaxis group reported three serious adverse events, which were deemed to be drug-related (LipLong 2012). No specific information was given about the presence of adverse events in the BAY 70-4980 group. No participant developed inhibitors to FVIII over the course of the trial. We judged the certainty of the evidence to be low.

Prophylaxis regimen compared to on-demand (episodic) treatment

The certainty of the evidence has been graded for those outcomes included in the summary of findings table (Summary of findings table 3). For the definitions of these gradings, please refer to the summary of findings tables.

Four trials were reported on this comparison (A-LONG 2014; LEOPOLD II 2015; SPINART 2013; Valentino 2014). In the Valentino 2012 trial, while comparing prophylaxis and on-demand treatments, the comparison was not across the randomised allocation and hence was not included in the following analyses (Valentino 2012). Of note, this trial found that any type of secondary prophylaxis (standard versus PK-adjusted) was significantly protective for total bleeding and joint bleeding when compared to episodic treatment ($P < 0.0001$). Also, this trial reported a significant improvement in QoL for the bodily pain (4.1, $P = 0.0007$) and physical component score

(PCS) (3.6, P = 0.0002) domains as measured on the SF36v1 scale for prophylaxis (any type) versus on-demand treatment (Valentino 2012).

Primary outcomes

1. Number of joint bleeding episodes or joint bleeding frequency

All trials reported this outcome.

Data from two combined trials suggest that the use of a prophylaxis regimen significantly decreases the number of joint bleeds when compared to on-demand treatments, MD -30.34 (95% CI -46.95 to -13.73) (low-certainty evidence) (Analysis 3.1) (LEOPOLD II 2015; SPINART 2013). Considerable heterogeneity was seen in this analysis (I2 = 87%). The data from the A-LONG trial suggest the same effect; however, these data were reported with medians, hence could not be included in the above analysis (A-LONG 2014).

2. Orthopedic joint score or clinical joint function

The three-year follow-up of the SPINART trial measured the joint function using the Colorado Joint Assessment Scale (CAJAS) (SPINART 2013). The CAJAS provides a score taking into account nine items for knee and ankles and seven for elbows. Data from the original report showed a mild improvement in joint health in the prophylaxis group at year three, least square (LS) mean -0.31 (95% CI -0.79 to 0.18), while the on-demand group experienced a mild deterioration, LS mean 0.63 (95% CI 0.08 to 1.18). Comparing the two regimens, the estimated change difference was 0.94 points (95% CI 0.23 to 1.65) in favour of the prophylaxis regimen (Analysis 3.2) (SPINART 2013).

3. QoL on validated scales

The HAEMO-QoL-A and EQ-5D questionnaires were used in the SPINART trial (SPINART 2013). Questionnaires were completed at baseline, six months, years one, two and three. LS mean changes in HAEMO-QoL-A score from baseline to year three showed an improvement in the prophylaxis group and a deterioration in the on-demand group resulting in a 9.98 point (95% CI 3.42 to 16.54) difference in favour of prophylaxis. Similarly, the EQ-5D showed improved HRQoL in the prophylaxis group with a mean (SD) change of 0.06 (0.15), whereas almost no change was seen for the on-demand group with a mean (SD) change of -0.01 (0.16) in utility index score from baseline to year three.

Secondary outcomes

1. Number of total bleeding episodes or total bleeding frequency

Data from two combined trials suggest that the use of a prophylaxis regimen is significantly more protective than on-demand treatment when preventing bleeding episodes, MD -40.24 (95% CI -64.04 to -16.44) (low-certainty evidence) (Analysis 3.3) (LEOPOLD II 2015; SPINART 2013). Considerable heterogeneity was also seen in this analysis (I2 = 93%). Total bleeding rates in the A-LONG trial also suggest a similar effect and were also not included in this analysis as data were reported as medians (A-LONG 2014).

2. Pain scores

The SPINART trial reports the results for the Short-Form McGill Pain Questionnaire total score, determined at baseline and years one, two and three (SPINART 2013). At three years, the participants enrolled in the prophylaxis group reported a 50% decrease in pain for the previous four weeks, mean 17.2 (SD 22.9), whereas on-demand participants reported no change, mean 0.0 (SD 25.1), resulting in a MD of - 17.20 (95% CI -27.48 to -6.92) in total score in favour of prophylaxis (Analysis 3.4) (SPINART 2013).

3. Radiologic joint score or radiologic measurements or descriptions of joint damage

The SPINART trial used the 45-item eMRI scale, previously validated with baseline data. Six index joints (knees, ankles, and elbows) were evaluated and each MRI was independently scored by three radiologists that were blinded to treatment allocation (SPINART 2013). Overall, the results at year three indicated detectable deteriorations on eMRI from baseline in both the prophylaxis group and the on-demand group (mean (SD) 0.75 (1.59) and 0.92 (SD 1.15) respectively) and a total MD -18.39 (95% CI -21.55 to 15.23) (Analysis 3.5) SPINART 2013). However, LS mean changes of -0.71 between the two regimens were not considered significantly different.

4. Clotting factor concentrate plasma levels

This outcome was not reported in any of the included trials for this comparison.

5. Time loss to school or employment

One trial reported the time spent under medical care (Aronstam 1976). In this trial, more than three hours under medical care were noted as one day. The authors reported that children on prophylaxis spent significantly less time confined to bed.

6. Integration into society

This outcome was not reported in any of the included trials for this comparison.

7. Scores on scales recording feeling of well-being and global functioning

This outcome was not reported in any of the included trials for this comparison.

8. Economic data

This outcome was not reported in any of the included trials for this comparison.

9. Any reported adverse effects or toxicity of clotting factor concentrates

When considering the number of individuals who experienced an adverse event, over two trials, more adverse events were reported in the participants on prophylaxis compared to those on on-demand therapy, RR 1.71 (95% CI 1.24 to 2.37) (Analysis 3.6) (A-LONG 2014; SPINART 2013). The distribution of adverse events across groups was not given in the LEOPOLD II trial, and hence it was not included in the above analysis. Of note, there were three reported treatment-related adverse events, but no participant developed an inhibitor during the course of treatment (LEOPOLD II 2015). In the 1976 Aronstam trial, one participant developed antigen-negative hepatitis and was removed from the remaining duration of the trial (Aronstam 1976).

4.6 Discussion

4.6.1 Summary of main results

This Cochrane Review included 10 trials with a total of 608 people with severe or moderate haemophilia A (n = 548) or B (n = 60), who had been previously treated for their disease. These trials yielded two different comparisons:

- comparison between two prophylaxis regimens; including prophylaxis with a standard, commercial rFVIII and a new investigational drug;
- and standard prophylaxis versus on-demand treatment.

Due to differences in treatment schedules and reporting methods, we were only able to aggregate data for our primary outcomes in one of the comparisons.

The data included in the review from the individual studies and the aggregated data suggest that secondary prophylaxis may be superior to on-demand treatment for preventing both joint bleeding incidents and overall bleeding (low-certainty evidence). Prophylaxis may also improve joint function, pain and QoL (low-certainty evidence). However, it seems that the regimens tested were not effective in halting or reversing the progression of arthropathy once structural joint damage has occurred. In fact, no detectable improvement, as assessed by MRI, of articular damage could be found at the three-year observation time-point in the SPINART trial.

When considering the comparison between two prophylaxis regimens, no individual prophylactic treatment schedule investigated proved to be superior at preventing total bleeding events in people in haemophilia A. Finally, standard prophylaxis may be more effective at preventing joint and total bleeding events than the experimental drug BAY 79-4980 (low-certainty evidence).

Individuals with hemophilia B were included in two trials (Morfini 1976; Valentino 2014). The Morfini trial showed that a twice-weekly regimen of prophylaxis may be superior to a once-

weekly regimen in decreasing total bleeding incidence, but these results should be interpreted cautiously given the small number of participants, the extremely low dose used and the fact that none of the participants were blinded to their treatment allocation (low-certainty evidence). The results of the Valentino 2014 trial did not establish a superior prophylaxis regimen; however, this trial did show that prophylaxis at any dosing schedule was superior to on-demand treatment to prevent spontaneous bleeds and joint bleeding incidence (Valentino 2014). When considering these data, it must be kept in mind that the bleeding data were aggregated for only 16 weeks, and the annualized bleeding rates were extrapolated from this time period.

Regarding the incidence of adverse events, when considering the comparison of prophylaxis versus on-demand treatment, the moderate-certainty evidence showed that on-demand treatment probably reduces the incidence of adverse events (131 participants, two trials) (A-LONG 2014; SPINART 2013). However, all individuals with a past history of an inhibitor were excluded from the trials and so information for this group is not available.

Of note, in the LEOPOLD II 2015 trial, participants were crossed over between groups to receive factor that was labelled in different ways (LEOPOLD II 2015). Each participant received six months of the trial drug labelled with a chromogenic substrate assay per European Pharmacopoeia, followed by six months of the trial drug labelled using a correction factor to simulate the results obtained with the one-stage assay. Because of this, trial authors report that participants likely received approximately 20% to 25% higher factor concentrate product in the time period when received FVIII based on the one-stage adjusted labelling method. Since all participants in the trial were given both the factor concentrate based on the two labelling methods, all participants were subject to the fluctuation in factor concentrate. Hence, we did not

deem it necessary to alter our analyses to accommodate for the use of a substrate assay in this trial (LEOPOLD II 2015).

Since one of the goals of initiating secondary prophylaxis is to prevent further deterioration of target joints, we decided to use joint bleeds, rather than total bleeds, as our primary outcome. However, interestingly this outcome was infrequently reported separately from total bleeding events. In addition, only two trials assessed joint function.

One limitation of this review was our inability to aggregate data for most of our outcomes. There were two main reasons for which we were unable to aggregate data:

diversity in participant characteristics and treatment regimens; anddiversity in reporting methods.

We hoped to be able to combine data from trials comparing different secondary prophylaxis regimens in order to give a more powerful estimate of the use of secondary prophylaxis. However, we found that the differences in participants and treatment arms between trials were too great to generate a reliable aggregate result. Many of the outcomes were reported as medians with ranges, while others were reported as means. Medians are often used when data are skewed, as might be the case with bleeding events, where individuals with a very high or very low number of bleeding events may pull an estimate in one direction. Often, a median can be used to approximate to mean values, but since our sample sizes were comparatively small, we decided against using this approach, as this may not have been an accurate approximation. We hope that as haemophilia treatment becomes increasingly optimised, and based on large randomised trials, the barriers that precluded us from aggregating data in this review will no longer exist.

4.6.2 Overall completeness and applicability of evidence

We conducted this review to investigate the effectiveness of clotting factor concentrate prophylaxis in managing previously-treated individuals with haemophilia A or B. In this Cochrane Review, we included only RCTs, and the primary outcome for this review, joint bleeding events or joint bleeding frequency, was reported in seven out of the 10 trials. Overall bleeding events or overall bleeding frequency were reported in all 10 trials. Other secondary outcomes such as clinical joint function and radiologic measurements were reported in two trials (Morfini 1976; SPINART 2013). Two trials also reported conducting QoL assessments (SPINART 2013; Valentino 2012) and one trial reported the results of pain assessment (SPINART 2013). Participants included people with haemophilia A and B and mostly characterised by FVIII or FIX levels < 1% of normal. Two trials included people with severe or moderately severe (factor levels ≤ 2%) haemophilia A or B. The evidence summarised in this review is applicable to individuals with moderate-severe to severe hemophilia A and B on secondary prophylaxis

4.6.3 Quality of the evidence

Overall, we found the included trials to be at low risk or unclear risk of bias for most domains. In particular, while all trial reports indicated that the trial was randomised, only four of the 10 included trials indicated the method used for random sequence generation (LEOPOLD II 2015; PROPEL III 2020; SPINART 2013; Valentino 2012), with only two were assessed as having a low risk of bias for the domain (LEOPOLD II 2015; PROPEL III 2020). When considering the method for allocation concealment four trials were judged to be at low risk of bias for this domain (LEOPOLD II 2015; Morfini 1976; SPINART 2013; Valentino 2012). The

remaining six trials had an unclear risk of bias (A-LONG 2014; Aronstam 1976; Aronstam 1977; LipLong 2012; (PROPEL III 2020; Valentino 2014). Also, three of the included trials used an appropriate method to blind participants and personnel to minimize performance bias (Aronstam 1976, Aronstam 1977, LipLong 2012). The remaining seven trials were open-label. Regarding the possibility of reporting bias, all included trials were judged to have a low risk of bias for this domain.

Overall, the certainty of the evidence was considered to be low because of different types of bias that could have altered the effect. In the comparison of two prophylaxis regimens, the certainty of the evidence was downgraded twice due to performance and detection bias as included studies were open-label and due to incomplete outcome data. The certainty of the evidence was also downgraded due to high levels of heterogeneity across trials In the comparison of prophylaxis and on-demand regimens. Future research might have an important role in changing our confidence in the estimate of effect.

4.6.4 Potential biases in the review process

We attempted to minimise the possibility of bias in the review process and all the authors had access to all the data and critically reviewed the manuscript. Our search strategy has been as inclusive as possible, and no specific restrictions were placed on the language or date of publication when searching databases. It is unlikely that potentially relevant trials were missed, also considering that in addition to the search of the electronic databases the bibliographic references of all retrieved trials and reviews were assessed for additional reports of potential interest. We also handsearched the proceedings of the International Society for Thrombosis and Haemostasis bi-annual meeting and proceedings of the European Association for Haemophilia and Allied Disorders.

4.6.5 Agreements and disagreements with other studies or reviews

Overall the conclusions of this review are in substantial agreement with the recent literature assessing the importance of secondary prophylaxis in haemophilia (Haemophilia 2018). It is also interesting to consider that consistent results were obtained in a 2015 non-randomised study investigating the effects of long-term late secondary prophylaxis compared with on-demand treatment in haemophilia (POTTER 2015). Results from this study support the efficacy of late secondary and tertiary prophylaxis, which ultimately significantly decreased the frequency of all bleeding episodes, including joint bleeds, and improved joint status.

4.7 Authors' conclusions

4.7.1 Implications for practice

There is evidence from randomised controlled trials that the use of prophylactic clotting factor concentrate may result in reduced frequency of total bleeds, and likely improves joint function and quality of life in people with severe or moderate haemophilia A and B.

4.7.2 Implications for research

Prophylaxis treatment is often considered the ideal treatment in high-resource countries. However, there are still knowledge gaps in the understanding of haemophilia treatment with respect to the ideal regimen and when to start prophylaxis. While the results of this review begin to shed light on the use of secondary prophylaxis in managing bleeding, there are still areas that require elucidation, namely the impact of late prophylaxis in people with varying degrees of arthropathy at baseline, the most cost-efficient dosage and frequency, the minimally effective dose

and the role of individualised regimens to a person's bleeding pattern and activity. Further research should be undertaken to attempt to provide evidence-based data for these areas.

Future randomised controlled trials should address the following aspects:

1. comparative efficacy, safety, and effectiveness of different prophylactic regimens (escalating versus fixed-dose, pharmacokinetic-tailored versus fixed-dose);
2. standardised clinical and radiological outcome measures of efficacy;
3. long-term cost-effectiveness;Individualisation of regimens.

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CONTRIBUTIONS OF AUTHORS

Omotola Olasupo assessed eligibility of studies, conducted data extraction and risk of bias assessment, performed, and interpreted analyses, constructed the summary of findings tables and drafted the review text.

Alfonso Iorio drafted the original protocol, assessed eligibility of studies and risk of bias, interpreted analyses, drafted the review text, and commented on the final draft version.

Ashma Krishan performed and interpreted initial analyses.

Peter Collins reviewed and commented on the final draft version.

Megan Lowe conducted risk of bias assessment and data extraction.

Davide Matino assessed eligibility of studies, conducted data extraction and risk of bias assessment, interpreted analyses, and reviewed the review text.

DECLARATIONS OF INTEREST

Olasupo: has no conflict of interest. **Lowe**: has no conflict of interest. **Collins**: has acted as a paid consultant, received lecture fees and support to attend meetings from Novo Nordisk, Bayer, Baxter, CSL Behring. Grant support has been received from CSL Behring. **Krishan**: none known. **Iorio**: does not perceive any relevant conflict of interest, while his institution receives grants from pharmaceutical companies, he does not benefit from these, nor does he have control over the use of the funds. **Matino** reports research grants paid directly to the Institution from Bayer, Pfizer, Novo Nordisk, Sanofi, Spark, Octapharma; personal fees outside the submitted work from Sanofi, Sobi, Novo Nordisk, Bayer, Pfizer, Octapharma for participation in advisory boards, lectures and preparation of educational material.

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TABLES AND FIGURES CAPTION LIST

TABLES

Characteristics of included studies

A-LONG 2014

Methods	Open-label parallel trial. Partially randomized trial Three-armed trial - two arms were randomised. The study enrolled 165 participants into 1 of 3 treatment arms: • Arm 1, individualized prophylaxis (25 - 65 IU/kg every 3 - 5 days, n = 118) (not randomised); • Arm 2, weekly prophylaxis (65 IU/kg, n = 24); or • Arm 3, episodic (on-demand) treatment as needed for bleeding episodes (10 - 50 IU/kg, depending on bleeding severity, n = 23). All participants on a prophylactic regimen prior to trial entry were enrolled into arm 1; those on an episodic regimen prior to trial entry had the option to enter into arm 1 or be randomized into either arm 2 or arm 3, with randomization stratified based on individual bleeding episodes in the past 12 months. Trial termination occurred after completion of the specified pharmacokinetic assessments and achievement of the prespecified rFVIIIFc exposure required to ensure acceptable inhibitor detection (e.g, a minimum of 104 participants from any arm with ≥ 50 exposure days to rFVIIIFc).
Participants	Previously treated males aged 12 years or more with severe hemophilia A Number of participants randomised: 47
Interventions	1. weekly prophylaxis: 65 IU/kg (n = 24) 2. episodic treatment: 10 - 50 IU/kg (n = 23) Trial visits occurred at screening (≤ 8 weeks), baseline, week 7, week 14, week 28, week 38, and week 52.

Outcomes	Annualized bleeding rate Rate of inhibitor development Adverse events
Notes	Only randomised arms were included in this review. This trial also included an arm that used individualized prophylaxis regimen, which was not randomised. ClinicalTrials.gov identifier: NCT01181128

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "...subjects on an episodic regimen prior to study entry had the option to enter into arm 1 or be randomised into either arm 2 or arm 3, with randomization stratified based on individual bleeding episodes in the past 12 months." Methods of randomisation are not stated. However, since patients were given a choice to enter arm 1, which was an individualized prophylaxis regimen or be randomised, there may have been certain characteristics of individuals that predisposed them to choose to be randomised or not
Allocation concealment (selection bias)	Unclear risk	Methods of allocation concealment are not stated
Blinding (performance bias and detection bias) Clinical Joint Function	Unclear risk	Not assessed
Blinding (performance bias and detection bias) Bleeding	High risk	An open-label trial
Blinding (performance bias and detection bias) Radiologic Joint Score	Unclear risk	Not assessed

Blinding of outcome assessment (detection bias) Bleeding	High risk	The trial was open-label, with the primary endpoint of annualized bleeding rates. It is not stated how bleeding episodes were measured
Blinding of outcome assessment (detection bias) Clinical Joint Function	Unclear risk	Not assessed
Blinding of outcome assessment (detection bias) Radiologic Joint Score	Unclear risk	Not assessed
Incomplete outcome data (attrition bias)	Low risk	Reasons for dropouts were discussed and were likely not due to allocated treatment
Selective reporting (reporting bias)	Low risk	Two outcomes: 1. participants with abnormal vital signs, and 2. participants with abnormal laboratory values, which were listed in the protocol were not reported in the final paper.
Other bias	Unclear risk	Data analysis was conducted by the trial sponsor, Biogen Idec. As well, the initial draft was written by employees of the sponsor

Aronstam 1976

Methods	Single-centre RCT Cross-over trial Boys were studied for a total of 27 boy-school terms. A 'boy-school term' is defined as the whole or any part of any school term during which an individual boy was under observation; the whole study took place during five school terms. Note: there are three school terms per annum in the UK.
Participants	Country: England Participants: males with hemophilia A (factor VIII < 1%)

	Age range: 13 - 17 years Number enrolled: 9
Interventions	Factor VIII concentrate (Blood Products Laboratory - UK) Arm A: sufficient dose to increase FVIII levels to at least 0.25 IU/mL once weekly Arm B: sufficient dose to increase FVIII levels to no more than 0.01 IU/mL once weekly
Outcomes	Bleeding events or frequency
Notes	

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Specifics about random sequence generation methods were not given
Allocation concealment (selection bias)	Unclear risk	Participants were allocated, "... at the beginning of each trial term.. by the Wessex Medical Information Unit." but no specific details were given
Blinding (performance bias and detection bias) Clinical Joint Function	Unclear risk	Not assessed
Blinding (performance bias and detection bias) Bleeding	Low risk	Participants were blinded to the allocation. Further, concentrate products were made to be indistinguishable, and were covered during infusion
Blinding (performance bias and detection bias) Radiologic Joint Score	Unclear risk	Not assessed
Blinding of outcome assessment (detection bias) Bleeding	Low risk	Staff interacting with patients were unaware of allocation. Clinicians assessing bleeding were also unaware of allocation
Blinding of outcome assessment (detection bias) Clinical Joint Function	Unclear risk	Not assessed
Blinding of outcome assessment (detection bias) Radiologic Joint Score	Unclear risk	Not assessed

Incomplete outcome data (attrition bias)	Low risk	There were no missing outcome data
Selective reporting (reporting bias)	Low risk	While the study protocol was not available, all expected outcomes were reported for all participants
Other bias	Unclear risk	Unclear washout period between trial arms

Aronstam 1977

Methods	Single-centre RCT Cross-over trial Trial conducted over two school terms Note: there are three school terms per annum in the UK.
Participants	Country: England Participants: males with hemophilia A (factor VIII < 1%) Age range: 13 - 17 years Number enrolled: 4 All participants completed the trial Those boys who had been on the first double-blind controlled trial (Aronstam 1976) and were still available for a further 2 terms were selected. There were 4 such boys, patients 1, 3, 8, and 9 of that trial. The boys selected had each had at least one full school term off prophylaxis before entering the second trial.
Interventions	Cryoprecipitate (prepared by Wessex Regional Transfusion Centre) or Kryobulin (prepared by Serological Products, UK) Arm A: raise factor VIII to 15% twice weekly Arm B: raise factor VIII to 30% twice weekly
Outcomes	Bleeding events or frequency
Notes	

Risk of bias table

Bias	Authors' judgement	Support for judgement

Random sequence generation (selection bias)	Unclear risk	While authors indicated that random sequence generation was used to allocate participants to groups, no details were given
Allocation concealment (selection bias)	Unclear risk	No details on allocation concealment were given
Blinding (performance bias and detection bias) Clinical Joint Function	Unclear risk	Not assessed
Blinding (performance bias and detection bias) Bleeding	Low risk	Patients and personnel were unaware of allocation
Blinding (performance bias and detection bias) Radiologic Joint Score	Unclear risk	Not assessed
Blinding of outcome assessment (detection bias) Bleeding	Low risk	Outcome assessors were blinded to allocation
Blinding of outcome assessment (detection bias) Clinical Joint Function	Unclear risk	Not assessed
Blinding of outcome assessment (detection bias) Radiologic Joint Score	Unclear risk	Not assessed
Incomplete outcome data (attrition bias)	Low risk	Outcome data is present for all participants
Selective reporting (reporting bias)	Low risk	While the study protocol was not available, all expected outcomes were reported for all participants
Other bias	Unclear risk	Washout period between arms is unclear

LEOPOLD II 2015

Methods	Multicentre RCT
	Open label
	Cross-over trial (see Notes)
	Trial period:12 months

	Conducted at 30 centers in 11 countries in Europe, South Africa, North America, South America, and Asia
Participants	Males aged 12 – 65 years with severe hemophilia A who had not received regular prophylaxis treatment for > 6 consecutive months in the previous 5 years Number randomised: 83; number included in the analysis: 80
Interventions	1. Twice-weekly prophylaxis (20 – 30 IU/kg), 2. Thrice-weekly prophylaxis (30 – 40 IU kg) 3. On-demand treatment with BAY 81-8973: a recombinant factor VIII product Patients were randomized to one of six treatment arms (two low-dose prophylaxis groups, two high-dose prophylaxis groups, and two on-demand treatment groups; participants received treatment based on CS/EP or CS/ADJ for 6 months each with an intraindividual cross-over after 6 months
Outcomes	Annualized number of all bleeding events and adverse events
Notes	ClinicalTrials.gov identifier: NCT01233258 This is not a traditional cross-over study. Participants were randomized to receive on demand or prophylactic therapy with FVIII (two different regimen); patients were crossed-over within their treatment groups but only with respect to the methods for measuring the content of FVIII in the vials (CS/EP or CS/ADJ) therefore this study has been treated as a parallel trial for the analysis, "Study drug was labeled using the chromogenic substrate assay per European Pharmacopoeia (CS/EP) or adjusted by a predefined factor to mimic results obtained with the one-stage assay (CS/ADJ). Because of differences in the detection of FVIII activity between the two potency assays, the difference in the actual amount of FVIII received for prophylaxis injections in the CS/EP and CS/ADJ periods was ~20–25%, with higher amounts received during the CS/ADJ period. Patients received treatment based on CS/EP or CS/ADJ for 6 months each with an intraindividual crossover after 6 months (Fig. 1)."

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"...system generated by the sponsor's randomization management."
Allocation concealment (selection bias)	Low risk	"Patient assignment was performed using a centralized telephone interactive voice response system or interactive web response system"
Blinding (performance bias and detection bias) Clinical Joint Function	Unclear risk	Not assessed
Blinding (performance bias and detection bias) Bleeding	High risk	An open-label trial where participants and outcome assessors were aware of the allocation
Blinding (performance bias and detection bias) Radiologic Joint Score	Unclear risk	Not assessed
Blinding of outcome assessment (detection bias) Bleeding	High risk	An open-label trial. It was unclear how the primary end-point of bleeding events was assessed
Blinding of outcome assessment (detection bias) Clinical Joint Function	Unclear risk	Not assessed
Blinding of outcome assessment (detection bias) Radiologic Joint Score	Unclear risk	Not assessed
Incomplete outcome data (attrition bias)	Low risk	There were 3 participants who were randomised but did not complete the study. Reasons for dropout were given for all of these participants
Selective reporting (reporting bias)	Low risk	All outcomes reported in the protocol were explored in the final study report
Other bias	Unclear risk	Three of the study authors are employees of the funding body, Bayer Healthcare AG

LipLong 2012

Methods	Double-blind, two-arm, parallel, RCT

	Trial duration: 52 weeks
Participants	Males aged 12 - 70 years with severe haemophilia A (<1% FVIII) who were currently using on-demand treatment with any FVIII product Number randomised = 143
Interventions	1. Once-weekly prophylaxis with BAY 79–4980 (35 IU/kg) 2. Thrice-weekly prophylaxis with FVIII-FS (25 IU/kg)
Outcomes	1. total bleeding episodes 2. joint bleeding episodes
Notes	The study Sponsor halted the study prematurely based on the recommendations of the DSMB, indicating that the primary and secondary endpoints of non-inferiority with prophylaxis with rFVIII-FS three times/week would not be met.

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method of randomisation is not stated
Allocation concealment (selection bias)	Unclear risk	No details on allocation concealment were given
Blinding (performance bias and detection bias) Clinical Joint Function	Unclear risk	Not assessed
Blinding (performance bias and detection bias) Bleeding	Low risk	This was a double-blind trial. Investigators employed a similar looking solvent for the different prophylaxis products to blind participation and outcome assessors
Blinding (performance bias and detection bias) Radiologic Joint Score	Unclear risk	Not assessed
Blinding of outcome assessment (detection bias) Bleeding	Low risk	Outcome assessors were unaware of allocation

Blinding of outcome assessment (detection bias) Clinical Joint Function	Unclear risk	Not assessed
Blinding of outcome assessment (detection bias) Radiologic Joint Score	Unclear risk	Not assessed
Incomplete outcome data (attrition bias)	High risk	Efficacy outcome analyzed per protocol. Higher consent withdrawn in the investigational drug arm (N=8 vs N=2).
Selective reporting (reporting bias)	Low risk	All reported outcomes in protocol were reported in paper
Other bias	High risk	The trial was prematurely discontinued by the sponsor based on the recommendation of an independent data and safety monitoring board

Morfini 1976

Methods	RCT Cross-over trial Trial period: 1 year Time unit: 3-month cycles (A-B-A-B versus B-A-B-A)
Participants	Country: Italy Participants: males with hemophilia B (factor IX < 1%) Age range: 5 - 45 years Number enrolled: 10
Interventions	Factor IX concentrate (Bebulin) Arm A: 7.5 U/kg twice weekly Arm B: 15 U/kg weekly
Outcomes	Bleeding events or frequency, joint deterioration
Notes	

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No information given
Allocation concealment (selection bias)	Low risk	Quote: "Allocation to treatment protocols was made on the basis of random envelopes..."

Blinding (performance bias and detection bias) Clinical Joint Function	Low risk	The personnel involved in the orthopedic examinations was blinded
Blinding (performance bias and detection bias) Bleeding	High risk	No blinding
Blinding (performance bias and detection bias) Radiologic Joint Score	Low risk	Radiological examinations were carried out in a blinded fashion
Blinding of outcome assessment (detection bias) Bleeding	High risk	Hematologists were aware of patients' treatment
Blinding of outcome assessment (detection bias) Clinical Joint Function	Low risk	Quote: "Orthopedic and radiological examinations were carried out by staff who were unaware of the trial details."
Blinding of outcome assessment (detection bias) Radiologic Joint Score	Low risk	Quote: "Orthopedic and radiological examinations were carried out by staff who were unaware of the trial details."
Incomplete outcome data (attrition bias)	Low risk	No missing data for primary outcome and minimal missing data for secondary outcomes
Selective reporting (reporting bias)	Low risk	Protocol was not available but all expected outcomes were reported
Other bias	Unclear risk	Washout period between arms was not clear

SPINART 2013

Methods	Open-label, parallel, multicentre RCT. Conducted in 31 centres (USA, 23; Bulgaria, 3; Romania, 3; Argentina, 2) Treatment period: 1 year (of a planned 3-year study)
Participants	Males aged 12 – 50 years (aged 18 – 50 years in Bulgaria and Romania) with severe hemophilia A with no prophylaxis for > 12 consecutive months in the past 5 years and 6 – 24 bleeding episodes in the preceding 6-month period Number randomised: 84

Interventions	1. rFVIII-FS prophylaxis thrice weekly (25 IU/kg) (n = 42) 2. on-demand treatment (n = 42)
Outcomes	Total number of bleeding episodes
Notes	ClinicalTrials.gov identifier: NCT00623480

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Details of the methods for the generation of the randomization not given
Allocation concealment (selection bias)	Low risk	Quote: "Randomization was centralized and managed by use of a customized interactive voice response system"
Blinding (performance bias and detection bias) Clinical Joint Function	Low risk	The physiotherapists performing the joint physical examination were unaware of patients' treatment and bleeding history
Blinding (performance bias and detection bias) Bleeding	High risk	This was an open-label trial
Blinding (performance bias and detection bias) Radiologic Joint Score	Low risk	Radiologists that examined the MRI were blinded
Blinding of outcome assessment (detection bias) Bleeding	High risk	Open-label trial. However, the physiotherapists performing the joint physical examination were unaware of patients' treatment and bleeding history.The open-label study design may also have influenced the results of the HRQoL
Blinding of outcome assessment (detection bias) Clinical Joint Function	Low risk	The physiotherapists performing the joint physical examination were unaware of patients' treatment and bleeding history
Blinding of outcome assessment (detection bias) Radiologic Joint Score	Low risk	Radiologists that examined the MRI were blinded

Incomplete outcome data (attrition bias)	Low risk	Number of patients who dropped out were balanced across groups, and reasons for dropout were well documented.
Selective reporting (reporting bias)	Low risk	All listed outcomes in protocol were reported or addressed
Other bias	Low risk	No other potential sources of bias identified.

Valentino 2012

Methods	Open-label, multicentre, randomised, two-arm, parallel trial Enrolled participants at nine USA and 21 European sites between January 2006 and June 2010 Participants completed the 6-month on-demand period and were randomized to a 12-month prophylaxis period (32 on standard and 34 on PK-tailored prophylaxis)
Participants	Participants aged 7 to 65 with moderately severe or severe hemophilia A, receiving on-demand treatment Number of participants enrolled: 82. Number of participants randomised: 66
Interventions	1. Standard prophylaxis (20 – 40 IU/kg) every other day 2. PK-tailored prophylaxis (20 – 80 IU/kg) every third day
Outcomes	Annualized bleeding rate
Notes	Of note, this trial had a non-randomised longitudinal cross-over portion that compared prophylaxis vs on demand

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "The randomization sequence was created using SAS version 8.2 (Cary, NC, USA), stratified by 0, 1–2 or ‡ 3target joints (defined as a joint in

		which ‡ 4 hemorrhages occurred within a period of 6 months, or > 20 lifetime hemarthroses)..."
Allocation concealment (selection bias)	Low risk	Quote: "...1:1 allocation to treatment regimens using a random block size of 2, and provided to the investigator via an automated assignment system as the subject neared completion of on-demand treatment."
Blinding (performance bias and detection bias) Clinical Joint Function	Unclear risk	Not assessed
Blinding (performance bias and detection bias) Bleeding	High risk	An open-label trial
Blinding (performance bias and detection bias) Radiologic Joint Score	Unclear risk	Not assessed
Blinding of outcome assessment (detection bias) Bleeding	High risk	An open-label trial
Blinding of outcome assessment (detection bias) Clinical Joint Function	Unclear risk	Not assessed
Blinding of outcome assessment (detection bias) Radiologic Joint Score	Unclear risk	Not assessed
Incomplete outcome data (attrition bias)	High risk	Unbalanced dropout rate across groups. Reasons for dropout were included
Selective reporting (reporting bias)	Low risk	Outcomes reported in protocol are present in report
Other bias	Low risk	No other potential sources of bias identified.

Valentino 2014

Methods	Randomised, multicentre, open-label, four-period cross-over trial Study conducted between May 2007 and October 2010 at 18 centres in the USA, Canada and Europe.

	Treatment period: 56 weeks
Participants	Males aged 6 – 65 years with severe or moderately severe haemophilia B with 12 or more bleeding episodes in the prior 12 months
Interventions	1. On demand (2 separate periods) 2. Prophylaxis with FIX once weekly (100 IU/kg) 3. Prophylaxis with FIX twice weekly (50 IU/kg) Participants received nonacog alfa (BeneFIX®; Pfizer, Philadelphia, PA, USA) as on-demand treatment for 16 weeks (Period 1), followed by randomization to a prophylaxis regimen (Period 2) comprising nonacog alfa at 100 IU kg^{-1} once weekly or 50 IU kg^{-1} twice weekly for 16 weeks. During the following 8-week period, participants received on-demand treatment only (Period 3). Participants then crossed over to the alternate prophylaxis treatment regimen for 16 additional weeks (Period 4).
Outcomes	Annualized bleeding rate
Notes	

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Specific methods used to conduct randomisation are unclear: "Randomization to treatment sequence utilized an electronic assignment system."
Allocation concealment (selection bias)	Unclear risk	No details were given regarding allocation concealment
Blinding (performance bias and detection bias) Clinical Joint Function	Unclear risk	Not assessed
Blinding (performance bias and detection bias) Bleeding	High risk	An open-label trial
Blinding (performance bias and detection bias) Radiologic Joint Score	Unclear risk	Not assessed

Blinding of outcome assessment (detection bias) Bleeding	High risk	An open-label trial, outcome assessors were aware of allocation
Blinding of outcome assessment (detection bias) Clinical Joint Function	Unclear risk	Not assessed
Blinding of outcome assessment (detection bias) Radiologic Joint Score	Unclear risk	Not assessed
Incomplete outcome data (attrition bias)	Low risk	Dropouts were balanced between groups and reasons for dropout were noted
Selective reporting (reporting bias)	Low risk	While the original protocol could not be located all expected trial results were reported
Other bias	Low risk	No other potential sources of bias identified.

Footnotes

IU: international units
PK: pharmacokinetic
RCT: randomised controlled trial

Characteristics of excluded studies

Aledort 1994

Reason for exclusion Prospective observational study.

Astermark 1999

Reason for exclusion Retrospective observational study.

Brackmann 1992

Reason for exclusion Retrospective observational study.

Carlsson 1997

Reason for exclusion	Includes paediatric patients previously on prophylaxis.

Chuansumrit 1995

Reason for exclusion	Retrospective observational study.

Collins 2010

Reason for exclusion	Prospective observational cross-over study.

Collins 2014

Reason for exclusion	Includes paediatric patients previously on prophylaxis.

Courter 2001

Reason for exclusion	Prospective observational study.

Dzinaj 1996

Reason for exclusion	Prospective observational study.

Feldman 2006

Reason for exclusion	Prospective observational single-arm dose-escalation study.

Fischer 2005

Reason for exclusion	Retrospective observational study.

Gringeri 2011

Reason for exclusion	Pediatric population on primary prophylaxis.

Kavakli 1997

Reason for exclusion	Prospective observational study.

Kreuz 1998

Reason for exclusion	Prospective observational study.

Liesner 1996

Reason for exclusion	Retrospective observational study.

Lofqvist 1997

Reason for exclusion	Retrospective observational study.

Manco-Johnson 1994

Reason for exclusion	Prospective observational study.

Manco-Johnson 2007

Reason for exclusion	Pediatric population on primary prophylaxis.

Nemes 2007

Reason for exclusion	Prospective observational single arm study.

Nilsson 1970

Reason for exclusion	Retrospective observational study with historical control.

Nilsson 1976

Reason for exclusion	Prospective observational study with historical control.

Nilsson 1992

Reason for exclusion	Retrospective observational study.

Petrini 1991

Reason for exclusion	Retrospective observational study.

Pettersson 1981

Reason for exclusion	Retrospective observational study with historical control.

Ramsay 1973

Reason for exclusion	Prospective observational study.

Royal 2002

Reason for exclusion	Retrospective observational study with parallel groups.

Schimpf 1977

Reason for exclusion	Prospective observational cross-over study.

Schobess 2008

Reason for exclusion	Prospective observational study.

Smith 1996

Reason for exclusion	Retrospective observational switch study.

Szucs 1996

Reason for exclusion	Prospective observational study.

Tagliaferri 2008

Reason for exclusion	Retrospective observational switch study.

Van den Berg 2001

Reason for exclusion	Retrospective observational single-arm study.

Wu 2011

Reason for exclusion	Prospective observation with historical control.

Summary of findings tables

1 Comparison of two prophylaxis regimens

Prophylaxis regimen compared with another prophylaxis regimen for previously treated individuals with haemophilia A or B

Patient or population: children or adults with hemophilia A or B
Settings: outpatient
Intervention: secondary prophylaxis
Comparison: secondary prophylaxis

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Certainty of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Prophylaxis regimen	Prophylaxis regimen				
Number of joint bleeding episodes per year (AJBR) Follow-up: 12 months	No difference was seen between prophylaxis regimens in any of the studies. Thrice-weekly higher dose prophylaxis regimen compared to a twice-weekly lower dose regimen, MD -1.70 (95% CI -5.06 to 1.66) (LEOPOLD II 2015). PK-guided prophylaxis targeting trough levels of 8% to 12% compared to targeting trough levels of 1% to 3%, MD -1.50 (95% CI -3.54 to 0.54) (n = 115 participants) (PROPEL III 2020). Low frequency prophylaxis (100 IU / kg once a week) compared to standard frequency regimen (50 IU / kg twice a week, MD of 1.70 (95% CI -1.09 to 4.49) (Valentino 2014).		N/A	219 participants (3 trials)	⊕⊕⊖⊖ **low**[a]	We were unable to combine results in a meta-analysis due to the different prophylaxis regimens used in each trial.
Number of total bleeds per year (ABR) Follow-up: 12 months	There was no difference in total number of bleeds between prophylactic regimens in five trials (Aronstam 1977; LEOPOLD II 2015; PROPEL III 2020; Valentino 2012; Valentino 2014). A twice-a-week regimen (7.5 IU/kg) was favoured over a once-a-week regimen (15 IU/kg), MD 11.20 (5.81 to 16.59) (Morfini 1976) and a prophylaxis group with dosing producing at least 0.25 IU/mL of factor VIII showed a significant reduction in overall bleeding frequency compared to a dosing regimen producing at least 0.01IU/mL once weekly, MD 3.44 (95% CI 2.42 to 4.46) (Aronstam 1976).		N/A	310 participants (7 trials)	⊕⊖⊖⊖ **low**[b,c]	Due to heterogeneity of intervention and design, none of the trials we were unable to combine data from any of the trials (LEOPOLD II 2015).
Treatment-related adverse events Follow-up: 32 weeks to 12 months	One trial reported no difference in total treatment-emergent adverse events, MD 1.00 (95% CI 0.54 to 1.84) at 32 weeks (Valentino 2014). A further trial reported no difference between treatment regimens in mean rates of adverse events (Valentino 2012). In the study targeting different trough levels , no serious adverse event was treatment-related in the arm targeting trough levels of of 1% to -3%, and in the arm targeting trough levels of 8% to -12%, one serious adverse event was estimated to be treatment-related (PROPEL III 2020).		N/A	223 participants (3 trials)	⊕⊖⊖⊖ **very low** [a,d]	Three trials did not report the rate of adverse events by treatment groups (Aronstam 1977; LEOPOLD II 2015; Morfini 1976). The LEOPOLD II trial reported three treatment related adverse events but gave no further detail (LEOPOLD II 2015). There was no reported inhibitor development reported in six of the trials in this comparison (Aronstam 1976; Aronstam 1977; LEOPOLD II 2015; Morfini 1976; Valentino 2012; Valentino 2014).

*The basis for the assumed risk (e.g. the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).
ABR: annualised bleed rate; **AJBR**: annualised joint bleed rate; **CI**: confidence interval; **FIX**: factor IX; **RR**: risk ratio; **MD**: mean difference.

[a] Downgraded twice due to risk of bias in the included trials, particularly across the domains of randomisation and allocation concealment. The trials were also considererd at high risk of bias due to lack of blinding
[b] Downgraded once due to imprecision as a result of small sample sizes. Although the total number of participants included in this outcome is 390, none of the studies could be combined and so we have based our assessment on the numbers in individual trials. The two trials that showed a difference between regimens included nine and 10 participants.
[c] Downgraded twice due to an unclear or high risk of bias across many of the domains with particular concern around randomisation procedures, allocation concealment and blinding.

[d] Downgraded once due to imprecision from small sample size and low event rates. Although the total number of participants is reasonable, none of the trials could be combined and so we have based our judgement on the numbers in the individual trials.

1 Prophylaxis with standard therapeutic factor concentrate compared to pegylated liposome FVIII formulation

Prophylaxis with standard clotting factor concentrate compared with pegylated liposome FVIII formulation for previously treated individuals with haemophilia A						
Patient or population: children or adults with hemophilia A **Settings**: outpatient **Intervention**: prophylaxis using investigational BAY 79-4980 **Comparison**: standard secondary prophylaxis						
Outcomes	**Illustrative comparative risks* (95% CI)**		**Relative effect (95% CI)**	**No of Participants (studies)**	**Certainty of the evidence (GRADE)**	**Comments**
	Assumed risk	**Corresponding risk**				
	Prophylaxis using investigational BAY 79-4980	**Standard prophylaxis**				
AJBR Follow-up: 12 months	The mean number of joint bleeding in the prophylaxis arm using investigational drug BAY 79-4980 was 12.2.	The mean number of joint bleeding in the standard prophylaxis regimen (5.0), was 7.20 lower (11.01 lower to 3.39 lower)	MD -7.20 (-11.01 to -3.39)	143 participants (1 trial)	⊕⊕⊖⊖ **low**[a,b]	More participants withdrew consent in the investigational drug arm. The trial was prematurely discontinued by the sponsor based on the recommendation of an independent data and safety monitoring board.
ABR Follow-up: 12 months	The mean number of total bleeds in the prophylaxis arm using investigational drug BAY 79-4980 was 15.	The mean number of total bleeds in the standard prophylaxis regimen (5.8), was 9.20 lower (13.07 lower to 5.33 lower)	MD -7.20 (-13.07 to -5.33)	143 participants (1 trial)	⊕⊕⊖⊖ **low**[a,b]	More participants withdrew consent in the investigational drug arm. The trial was prematurely discontinued by the sponsor based on the recommendation of an independent data and safety monitoring board.
Any reported adverse effects Follow-up: 12 months	No specific information was given about the presence/absence of adverse events in the BAY 70-4980 group.	One participant in the prophylaxis group reported three serious adverse events, which were deemed to be drug related.	Not estimable	143 participants (1 trial)	⊕⊕⊖⊖ **low**[a,b]	
*The basis for the assumed risk (e.g. the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). **ABR**: annualised bleed rate; **AJBR**: annualised joint bleed rate; **CI**: confidence interval; **MD**: mean difference.						

GRADE Working Group grades of evidence
High certainty: further research is very unlikely to change our confidence in the estimate of effect.
Moderate certainty: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low certainty: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low certainty: we are very uncertain about the estimate.

a. Downgraded once due to high risk of bias due to attrition bias from incomplete outcome data.
b. Downgraded once due to premature study discontinuation

3 Prophylaxis regimen versus on-demand treatment

Prophylaxis regimen compared with on-demand treatment for previously treated individuals with haemophilia A or B						
Patient or population: children and adults with haemophilia A or B **Settings**: outpatient **Intervention**: secondary prophylaxis **Comparison**: on-demand treatment						
Outcomes	**Illustrative comparative risks* (95% CI)**		**Relative effect (95% CI)**	**No of Participants (studies)**	**Certainty of the evidence (GRADE)**	**Comments**
	Assumed risk	**Corresponding risk**				
	On-demand treatment	**Prophylaxis regimen**				
Number of joint bleeding episodes or joint bleeding frequency Follow-up: 12 months	The mean number of joint bleeding episodes in the on-demand treatment group was 34	The mean number of joint bleeding episodes in the prophylaxis regimen group was 30.34 lower (46.95 lower to 13.73 lower)	MD -30.34 (-46.95 to -13.73)	164 (2 trials)	⊕⊕⊖⊖ **low**[a,b]	The data from the A-LONG trial suggests the same; however, these data were reported with medians, hence could not be included in the analysis.
Number of total bleeds per year or bleeding frequency Follow-up: 12 months	The mean number of total bleeds in the on-demand treatment group was 44	The mean number of total bleeds in the prophylaxis regimen group was 40.24 lower (64.04 lower to 16.44 lower)	MD -40.24 (-64.04 to -16.44)	164 (2 trials)	⊕⊕⊖⊖ **low**[a,b]	The data from the A-LONG trial suggests the same effect; however, these data were reported with medians, hence could not be included in the analysis (A-LONG 2014). When comparing the overall bleeding frequency in 9 participants in the Aronstam cross-over trial, there was a significant reduction in the overall bleeding frequency in the prophylaxis group
Any reported adverse events Follow-up: 12 months	415 per 1000 (27 per 65)	712 per 1000 (47 per 66) The number of participants with adverse events in the prophylaxis regimen group was 1.71 times higher (1.24 times higher to 2.37 times higher)	RR 1.71 (1.24 to 2.37)	131 (2 trials)	⊕⊕⊕⊖ **moderate**[a]	The 2 trials were open-label trials with unclear risk of bias for randomised sequence generation (A-LONG 2014; SPINART 2013). The LEOPOLD II trial did not give the distribution of adverse events across groups, but there were 3 reported treatment-related adverse events while no participant developed an inhibitor during the course of treatment (LEOPOLD II 2015). In the 1976 Aronstam trial, one participant developed antigen-negative hepatitis and was removed from the remaining duration of the trial (Aronstam 1976).
*The basis for the assumed risk (e.g. the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). **CI**: confidence interval; **RR**: risk ratio; **MD**: mean difference						

GRADE Working Group grades of evidence
High certainty: further research is very unlikely to change our confidence in the estimate of effect.
Moderate certainty: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low certainty: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low certainty: we are very uncertain about the estimate.

a. Downgraded once due to high risk of bias due to performance and detection bias attributed to open-label studies.
b. Downgraded once due to high levels of heterogeneity across trials

FIGURES

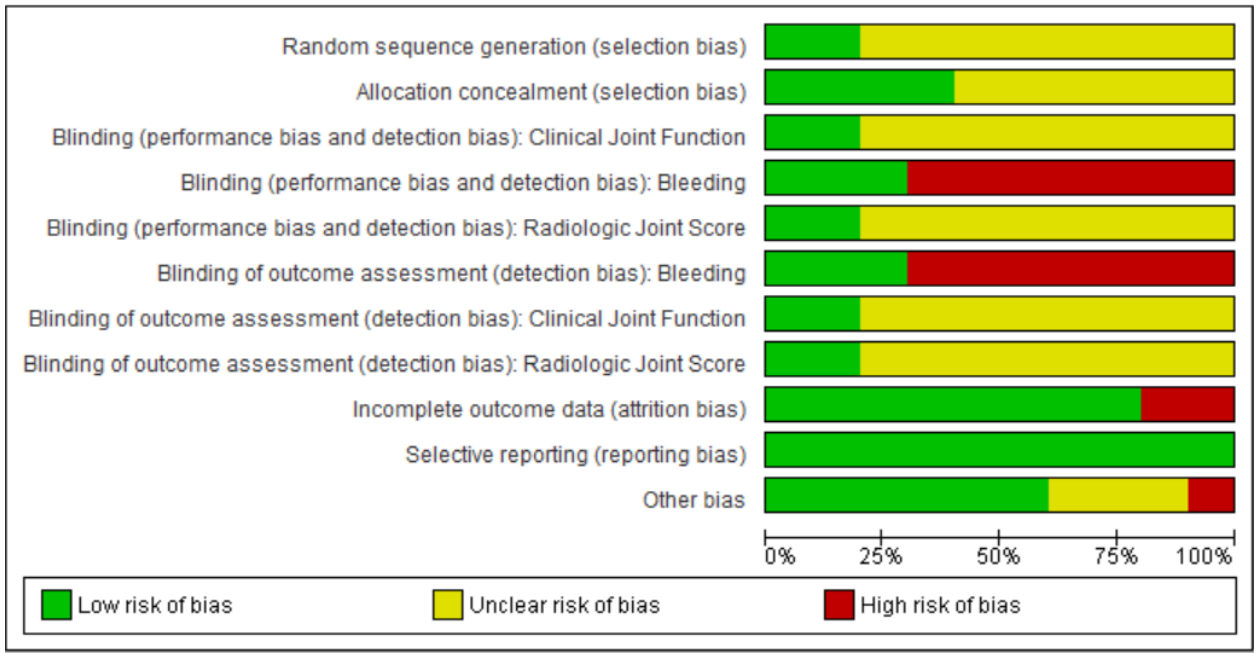

Figure 1: Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

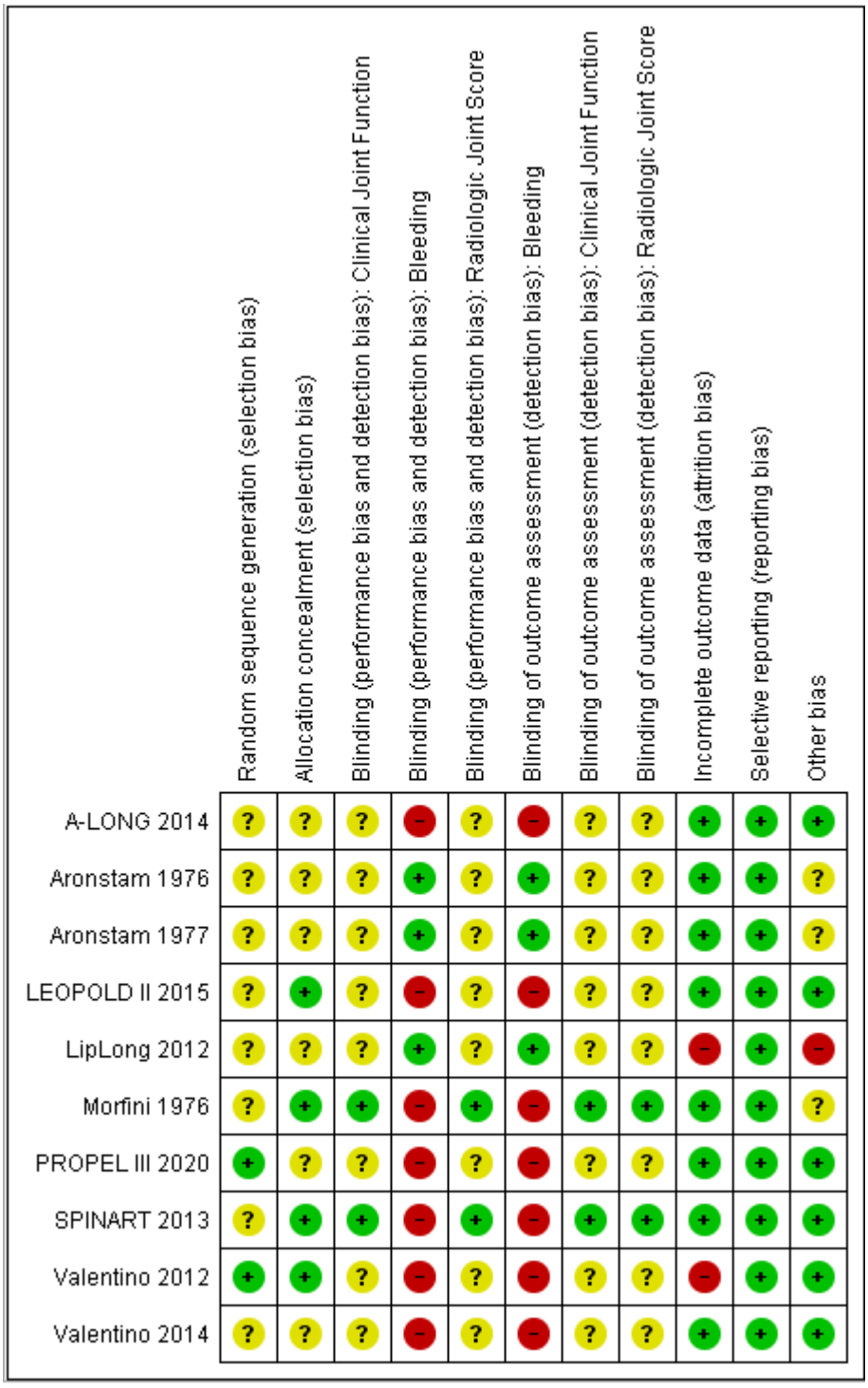

Figure 2: Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

CHAPTER 5: DISCUSSION

In this thesis, challenges with insufficient data in rare bleeding disorders were addressed through the (i) development and description of the IHTC surgical database, (ii) the assessment of perioperative hemostasis, complications, and surgical plan deviations, and (iii) the methodological review of RCTs to make recommendations for future assessment of perioperative outcomes. In this chapter, key findings, strengths and limitations of the research, and future research directions are highlighted.

5.1 Evidence review of perioperative outcomes in the IHTC-surgical database (1998-2019)

Within the 21-year study period covered in the initial data extraction from the IHTC-SD, 3,246 procedures were conducted in 1,413 unique patients with a rare bleeding disorder.[1] Majority of the procedures were minor (63.3%), and the median number of surgeries per patient was 1 (range: 1–22). Adequate perioperative hemostasis was achieved in 90.9%, complications occurred in 13.6%, and surgical plan deviations occurred in 31.3% of procedures.

In our analysis reported in **Chapter 2**, patients with hemophilia B were found to record the **highest frequency of inadequate hemostasis and surgical plan deviations** compared with other bleeding disorders. Complications were not significantly different across bleeding disorders ($p = .164$). Deviations from initial surgical plans were highly heterogenous in nature with some deviations being administrative in nature such as a change in surgical date or time (re-scheduling), while others are dose optimization. Therefore, not all deviations are equal and not all may be detrimental to surgical outcomes.

To the best of our knowledge, there are no studies comparing the rate of perioperative hemostasis or complications in Hemophilia B with other rare bleeding disorders i.e., across the

different bleeding disorders. However, the role of recombinant coagulation factor IX (FIX) albumin fusion protein (rIX-FP) in has been evaluated in surgical procedures in people with hemophilia B undergoing surgical procedures. [2,3] In this study, perioperative hemostasis was achieved and was excellent or good in 87.5% (7/8) of minor surgeries and 95.5%(21/22) of major surgeries. [2,3] The rate of perioperative hemostasis obtained in our analysis falls within the range observed in the study by Curtin et al. (87.5% - 95.5%).[3]

Implications for practice: This study suggests a need for more comparative effectiveness studies focusing on hemophilia B, and its perioperative care to improve perioperative outcomes.

The **nature of data collection** i.e., prospective vs retrospective data collection, which is a function of the historical and time variations in the database structure, was identified to be associated with reported perioperative hemostasis, complications, and surgical plan deviations. The more recent prospective data collection period, which coincides with a period of technological advancements (2006-2019), was associated with higher rates of hemostatic efficacy (92.4% vs. 88.3%; $p < .001$), complications (14.3% vs. 12.3%; $p < .001$), and plan deviations (34.2% vs. 25.1%; $p<.001$) compared with the retrospective data collection period (1998-2006).

In comparison with existing literature, in a population of emergency department patients admitted with chest pain, retrospectively collected data is estimated to be less accurate compared with prospectively collected data.[4] However, the retrospective data collection in the IHTC database was dependent on data retrieval from electronic medical records and not on patient recall.

Implications for practice: Our study adds to the evidence to support the improvements in therapy outcomes and surgical options. However, adverse perioperative events and complications were also on the increase. Our analysis helped to identify patterns which provided basis for hypothesis generation for future studies.

In **Chapter 3**, the association between the presence of neutralizing antibodies (inhibitors) and achievement of perioperative hemostasis, development of complications, and pre-surgical plan deviations was examined based on a subset of the procedures (n=1,492 surgeries) which were conducted in 539 unique patients with hemophilia. The presence of inhibitors was linked to adverse perioperative outcomes including reduced rates of hemostasis (65.6% vs 91.4%; adjRR=0.69 [0.51-0.94], p<.001), increased complications (31.7% vs 14.6%; adjRR=1.68 [1.07–2.64]; p=0.024), and increased risk of plan deviations (70.8 vs 39.5%; adjRR= 1.49[1.24–1.79]; p<.001).

Implications for practice: Overall, surgeries involving inhibitors were associated with higher risks of adverse perioperative outcomes compared to those without inhibitors. Therefore, we recommend the prioritization of strategies to prevent or eradicate inhibitors in patients with hemophilia to avoid undesirable treatment outcomes. Adequate genetic profiling and exploration of other contributors to inhibitor incidence and successful inhibitor eradication via immune tolerance induction should be also explored.

5.2 Efficacy of clotting factor concentrates for secondary prophylaxis

In **Chapter 4**, we systematically reviewed the evidence from RCTs examining the efficacy of clotting factor concentrate prophylaxis in managing previously treated patients (PTPs) with hemophilia A or B.[5] Ten studies (n=608 participants) met our inclusion criteria. Eight trials (n=477 participants) compared two or more prophylactic regimens and four trials (n=

258 participants) compared prophylaxis to on-demand therapy. Two trials had multiple arms and were included in both comparisons. In the comparison of two prophylaxis regimens, there was no difference between dosing regimens in the primary outcome which was the frequency of joint bleeding (low-certainty evidence). For the secondary outcome of total bleeding events, prophylaxis with a twice-weekly regimen of FIX likely results in reduced total bleeds compared to a once-a-week regimen of the same dose, mean difference (MD) 11.2 (5.81 to 16.59) (one trial, 10 participants, low-certainty evidence). Transient low-titer anti-FVIII inhibitors were reported in one of the trials, while blood-transmitted infections were not identified. Other adverse events reported include hypersensitivity, oedema, and weight gain. However, these were rare and unrelated to study drugs (very low-certainty evidence).

In the comparison of prophylactic and on-demand therapies, prophylaxis was found to likely result in a large decrease in the number of joint bleeds compared with on-demand treatment, MD -30.34 (95% CI -46.95 to -13.73) (two trials, 164 participants, low-certainty evidence). On the long-term, prophylaxis also showed improved joint function, quality of life, and improvement of pain scores; but no difference between groups in joint structure when assessed by magnetic resonance imaging (MRI). Two trials (n=131 participants) reported that prophylaxis likely results in a slight increase in adverse events, risk ratio 1.71 (1.24 to 2.37) (moderate-certainty evidence). No inhibitor development and blood-transmitted infections were identified. Overall, the certainty of the body of evidence was judged to be low because of different types of bias that could have altered the effect.

Implications for practice: Prevention of bleeding should be considered in patients even when signs of advanced disease progression i.e., joint damage are evident. However, more methodologically rigorous trials are needed to improve the certainty of evidence from RCTs

conducted in PwRBDs. Also, more research is needed to identify the best dosing schemas for the achievement of optimal outcomes.

5.3 Strengths and limitations of this research

The IHTC-surgical database is the first database in PwRBDs which focuses primarily on surgeries, thus bridging the gap in data availability for perioperative outcomes. More than 20 bleeding disorders were captured in the database with unnamed bleeding disorders categorized into an "undefined" category. There is also the advantage of comprising both **retrospective and prospective data collection** across an extended period. Limitation to this research include the inadequacy for use in determining **causality**, which are best studied in randomized controlled trials. However, it offers the advantage of a **large sample size** to study outcomes in association with observable variables. The IHTC database records details in perioperative period and may not capture other elements of the comprehensive care provided; these details can however be sourced from linked medical records at the IHTC. In our exploratory analysis, possible **confounders** such as demographic and clinical characteristics, were not controlled for in the analysis. These will, however, be considered in future analyses.

Being routinely collected data, another limitation of our research using the IHTC-surgical database is missing data. Therefore, strategies to address missing data are to be considered in all future studies. Also, **ongoing data quality initiatives** are being deployed to ensure accurate data collection in the database.

In our systematic review, the **certainty of the evidence** was judged to be low overall due to biases that could alter the findings. such as selection bias (due to unclear random sequence generation techniques), performance and detection bias (due to lack or unclear blinding of participants and outcome assessors), and attrition bias (due to incomplete outcome data).

Therefore, to ensure valid and reliable outcome assessment in PwRBDs, the following methodological elements should be considered.

5.4 Methodological considerations for perioperative outcome assessment in PwRBDs

Study Designs: For the assessment of treatment outcomes, perioperative outcomes inclusive, observational studies (case-control, cross-sectional, cohort studies) and RCTs are key study designs for the outcomes assessment in patients with rare bleeding disorders.[6] Well-designed RCTs where randomization and allocation concealment is maintained have the advantage of ruling out confounding and selection bias. Other bias to watch out for include performance and detection bias, attrition bias, and selective outcome reporting. Observational studies when properly designed also stand a chance to control for confounding if properly designed with appropriate analytical approaches.

Patient selection: Due to three levels of complexity in assessing perioperative outcomes in PwRBDs i.e., the low prevalence of rare diseases, low prevalence of RBDs, and limited frequency of surgeries in PwRBDs, convenience sampling and observational studies as exemplified in the IHTC database are more resource efficient. Sampling techniques such as random sampling would require a very long time for sufficient patient enrollment with consequences such as obsolete or findings due to the fast pace of technology.[7]

Other databases and registries such as the CBDR, and the EUHASS offer similar disease-specific and contextual data in PwRBDs.[8,9] However, most existing databases and registries are multi-purpose and not specific to surgeries.

Sample Size: Due to the low prevalence of these disorders, sample size considerations are extremely important in outcomes assessment in PwRBDs.[10] Non-completion and non-publication of trials has also been identified as an issue.[11] Potential solutions apart from observational studies include the use of pre-post and self-controlled studies where study participants act as their own controls.[12] For example, in the case where the exposure is a medication (exposure) for the achievement of hemostasis (outcome), effectiveness data can be collected in the pre-exposure period, followed by a sufficient wash-out period, and compared with effectiveness in the post-exposure period. An additional benefit of the pre-post design is the elimination of time-invariant confounding. Time varying confounding can be introduced when values of a variable change over the duration of a study period e.g., age of the participants, weight, and time varying exposures.[13,14] Time invariant variables, however, do not change over the duration of the study period e.g. race and gender. For such time-invariant variables, pre-post and self-controlled designs hold these variables constant between comparison groups across the study period. Sample-size calculation should be based on available epidemiological data assessing the effect of the exposure e.g., presence of inhibitors on the outcome e.g., perioperative hemostasis. The total sample size can be computed to achieve at a power which lowers the risk of a Type II error. A power of least 80% power has been conventionally used to ensure a 1 in 5 chance of having a Type II error.[15] For exploratory analyses to generate hypotheses and for the planning of RCTs, sample size calculations based on power calculations may be waived. (This is because such analyses are exploratory and will help in planning future RCTs)

Privacy and ethical considerations: An extra layer of privacy protection should be considered for epidemiological studies in populations with rare bleeding disorders and rare diseases in

general. Despite data anonymization based on patient-identifying variables, special care must be taken to preserve the participant's privacy as low patient numbers could make the anonymity of no effect. In cases where a patient could still be identified despite anonymization, the need for patient consent is further heightened.

Longitudinal and contextual data collection in registries and databases: The collection of clinically meaningful variables and outcomes that can contribute to estimation of valid and reliable findings is unnegotiable for the advancement of evidence-based clinical decisions for the perioperative care of PwRBDs. Based on our analyses and experience with the IHTC surgical database, some key variables needed, which could serve as a minimal core data set in RBD registries and databases, especially in the perioperative setting will include:

- *Population-related variables*: demographics (age, race, sex, socio-economic status),
- *Clinical variables* e.g., BMI, co-morbidities, duration of bleeding disorders, inhibitor status in hemophilia (or anti-drug antibodies), duration of bleeding disorder.
- *Surgery/Procedural Characteristics:* type of surgery (major vs. minor, bleeding-disorder related vs. not bleeding-disorder related), physiological system (orthopedic, cardiovascular, neurological)
- *Treatment monitoring*: pharmacokinetics (peak and trough levels of administered clotting factors), dosage and duration of therapies, event timing.
- *Perioperative outcomes tracking (pre-, intra-, and post-surgery)* : Perioperative hemostatic control based on the Scientific and Standardization Committee - International Society on Thrombosis and Hemostasis (SSC-ISTH) criteria e.g., excellent, good, fair, poor/none, blood transfusions required (pre-, intra-, and post-surgery), number of

transfusions, complications, deviations from pre-surgery plans, and HRQoL by validated tools such as Haemophilia Quality of Life Questionnaire for Adults (Haem-A-QoL),[16] Haem-QoL, or the Patient Reported Outcomes, Burdens and Experiences (PROBE)[17] questionnaires.

Perioperative event tracking and follow-up period: Tracking of specified outcomes should be at appropriate times e.g., optimal definitions of the baseline period pre-surgery, adequate event timing intra-operatively, and follow-up period post-operatively.

Analytical considerations: Appropriate statistical analytical techniques which factor in the data distribution (e.g., normal/gaussian, Poisson, binomial, exponential, gamma, or Weibull) should be employed to ensure findings are valid and reliable.[18] In our assessment of surgeries captured in the IHTC surgical database, variables such as age were not normally distributed as seen from the skewness (symmetry) of the data. In such instances, corresponding non-parametric tests such as the Kruskal Wallis test should be used to test for differences across the groups being compared.[19] Data or variable characteristics such as data being presented as continuous or categorical data should also be considered in analytical choices including choice of summary statistics e.g., use of counts and percentages for categorical data and use of summary statistics (mean, median, standard deviation, interquartile range) for continuous data. Confounding adjustment by appropriate variable selection methods should also be considered.

In observational studies, confounding adjustment can also be achieved by propensity score matching which involves the development of a score based on observed covariates to balance

these observed covariates between treated and untreated study population.[20] A prespecified statistical analysis plan is recommended to avoid post-hoc analyses and data dredging.

Considerations for missing data: Missing data can be avoided using standardized data collection templates and utilization of common data elements. The use of drop-down menus for data entry combined with free text options should be explored to avoid missing data and thereby improve the data quality. Steps to handling missing data include description of the frequency (or proportion of missing data), and nature of missingness (e.g., missing completely at random [MCAR], missing at random, and missing not at random). Approaches to address missing data (e.g., complete case analysis, last observation carried forward [LOCF], mean or median substitution, and multiple imputation methods) must take these into consideration before deciding on the method of choice.

5.5 Future research direction

Future studies will include more granular outcomes assessment in relation to **individual surgery types** e.g., orthopedic surgeries which are relatively common in patients with hemophilia due to the joint involvement and associated arthropathy in progressive disease. Increased focus will also be considered regarding (i) **specified population sub-groups** (such as hemophilia B as identified in our exploratory analysis and vWD with the highest prevalence among assessed RBDs) and (ii) **the use of novel therapies** (such as non-clotting factor therapies e.g., emicizumab) for the achievement of perioperative hemostasis.

Identification of **independent risk factors** and development of predictive models for perioperative hemostasis, complications and surgical plan deviations based on data collected in the IHTC-surgical database will also be considered in future research.

5.6 Conclusions

The IHTC- surgical database is an important resource for perioperative outcomes assessment the care of patients with bleeding disorders. Approaches to ensure the validity and reliability of research findings from both observational studies and randomized controlled trials should be implemented to further improve evidence-based decision making in the perioperative care of patients with bleeding disorders.

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