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KAISA VEPSÄLÄINEN

FVIII PROPHYLAXIS IN CHILDREN WITH SEVERE HAEMOPHILIA A

A nationwide survey of outcome and costs in Finland

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ABSTRACT:

Haemophilia is an X-linked congenital bleeding disorder caused by a partial or complete lack of coagulation factor VIII (FVIII) in haemophilia A (HA) or factor IX (FIX) in haemophilia B (HB), both mainly occurring in males. Severe haemophilia (FVIII or FIX activity < 0.01 IU mL^{-1}) is characterized by serious bleeding episodes, often by spontaneous bleeds in soft tissue, especially in joints, sometimes progressing to chronic arthropathy. Full prophylaxis, which means regular coagulation factor infusions, offers almost complete protection against traditional haemophilia-associated complications such as intracranial haemorrhage, prevents joint damage, and gives patients a near-normal life with a life expectancy similar to that in the general population. In Finland, the standard practice for nearly two decades has been early primary prophylaxis, started before the age of one and before even the onset of the first joint bleed, mainly via surgically inserted central venous access devices (CVADs). These ports secure long-term and reliable venous access, enabling early home treatment. The most serious and costly complication in the treatment of severe HA is the development of FVIII-neutralizing antibodies, called inhibitors, suddenly rendering the treatment ineffective.

In this retrospective nationwide study, we investigated the effects of early primary prophylaxis in Finnish paediatric haemophilia patients during the past two decades. We evaluated the incidence of, and risk factors for, complications associated with CVAD usage; we also examined the incidence of, and risk factors for, inhibitor development (ID) in previously untreated patients (PUPs) with severe HA. The long-term clinical and economic outcomes of regular high-dose prophylaxis were evaluated. We provide real-world data on total treatment costs per body weight in non-inhibitor and inhibitor patients, representing nearly 700 patient-years of follow-up.

Regular high-dose primary prophylaxis of PUPs with severe HA leads to excellent long-term joint health, annualised bleeding rates being near zero. The CVAD-related bloodstream infection rate was lower, and port duration (median of 3.2 years) longer, than earlier described. The cumulative incidence of ID was low (21%) despite the majority having a high-risk genotype. ID incidence was 30-40% lower than the incidence internationally where prophylaxis is mainly started as secondary prophylaxis and administered via peripheral veins. ID risk significantly increased in patients who experienced major bleeds. Rapid immune tolerance induction therapy during early childhood was successful and cost-neutral due to its relatively short expected payback period.

In conclusion, our results emphasize the importance of early primary prophylaxis via ports to prevent bleeds and thereby to decrease inhibitor incidence. This prophylaxis management leads to excellent long-term clinical outcomes and may reduce the health care costs of bleeding events and their long-term complications in the future.

National Library of Medicine Classification: QW 575, WH 325
Medical Subject Headings: Haemophilia A; Haemorrhage; Primary Prevention; Antibodies, Neutralizing; Treatment Outcome; Health Care Costs; Child

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Hyytymistekijäkorvaushoito vaikeaa A-hemofiliaa sairastavilla lapsilla. Valtakunnallinen tutkimus hoidon vaikuttavuudesta ja kustannuksista Suomessa
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TIIVISTELMÄ:

Hemofilia on X-kromosomiin kytketty perinnöllinen verenvuototauti, joka ilmenee miehillä. Hemofilia A johtuu hyytymistekijä VIII:n (FVIII), ja hemofilia B hyytymistekijä IX:n (FIX) vajeesta tai täydellisestä puuttumisesta. Vaikeaan hemofiliaan (FVIII tai FIX-pitoisuus < 0.01 IU mL^{-1}) liittyy taipumus spontaaneihin pehmytkudosvuotoihin sekä henkeä uhkaavien vuotokomplikaatioiden vaara. Toistuvat nivelvuodot voivat johtaa krooniseen nivelvaurioon. Hemofiliahoidon kulmakivi on elinikäinen ennaltaehkäisevä hyytymistekijäkorvaushoito, joka ehkäisee aivoverenvuotoja, estää nivelvaurioiden kehittymisen ja mahdollistaa normaalin elinaikaennusteen. Suomalaisille vaikeaa hemofiliaa sairastaville lapsille on viimeisten 20 vuoden kuluessa aloitettu pysyvä korvaushoito varhaislapsuudessa, ennen yhden vuoden ikää ja ensimmäisen nivelvuodon ilmaantumista. Keskuslaskimoportit ovat mahdollistaneet tehokkaan hoidon, jonka perheet voivat toteuttaa kotihoidossa varhaislapsuudesta saakka. Hemofiliahoidon vakavin ja kallein komplikaatio on vasta-aineiden kehittyminen, mikä johtaa hyytymistekijähoidon tehon nopeaan menettämiseen.

Tässä retrospektiivisessä valtakunnallisessa tutkimuksessa selvitimme 19 vuoden seuranta-ajalla vaikeaa A-hemofiliaa sairastavien lasten (n=62) varhaisen ennaltaehkäisevän hyytymistekijäkorvaushoidon pitkäaikaisvaikutuksia, vasta-aineiden kehittymistaipumusta sekä hoidon yhteiskunnalle aiheuttamia kokonaiskustannuksia. Analysoimme myös keskuslaskimoporttien käyttöön liittyvät komplikaatiot.

Tutkimus osoitti, että varhainen hyytymistekijäkorvaushoito johtaa pitkäaikaiseen erinomaiseen nivelterveyteen, vuosittaisten verenvuotojen ollessa lähellä nollaa. Tulostemme perusteella keskuslaskimoporttien käyttö on pienilläkin lapsilla turvallista: katetri-infektioiden ilmaantuminen oli vähäistä ja laskimoportin käyttöikä pitkä, keskimäärin 3.2 vuotta. Vasta-aineita hyytymistekijähoidolle kehittyi harvemmin kuin aiemmin on raportoitu, niitä todettiin vain 21% lapsista vaikka suurin osa heistä oli geneettisesti suuren riskin potilaita. Tämä on n. 30-40% vähäisempi määrä kuin kansainvälisesti, jolloin hoito toteutetaan perifeeriseen laskimoon ja aloitetaan useammin sekundaariprofylaksina. Vaikeat verenvuodot lisäsivät, mutta ennalta ehkäisevä korvaushoito vähensi tämän vakavan, ja erittäin kalliin komplikaation riskiä. Vasta-aineiden siedätyshoito oli lapsuusiällä toteutettuna tehokasta, ja kalleudestaan huolimatta maksaa itsensä takaisin jo verraten lyhyessä ajassa.

Yhteenvetona voidaan todeta, että nykyisellä suomalaisella hoitokäytännöllä, varhaislapsuudessa aloitettavalla, keskuslaskimoportin kautta toteutettavalla hyytymistekijäkorvaushoidolla estetään tehokkaasti verenvuotoja, samalla vähentäen vasta-aineiden kehittymisriskiä, ja saavutetaan erittäin hyvät pitkäaikaishoitotulokset.

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Kuopio, September 2018

Kaisa Vepsäläinen

List of the original publications

This dissertation is based on the following original publications:

I Vepsäläinen, K., Lassila, R., Arola, M., Lähteenmäki, P., Möttönen, M., Mäkipernaa, A. & Riikonen, P. 2015, "Complications associated with central venous access device in children with haemophilia: a nationwide multicentre study in Finland", *Haemophilia: the official journal of the World Federation of Hemophilia,* vol. 21, no. 6, pp. 747-753.

II Vepsäläinen, K., Lassila, R., Arola, M., Huttunen, P., Koskinen, S., Ljung, R., Lähteenmäki, P., Möttönen, M. & Riikonen, P. 2016, "Inhibitor development in previously untreated patients with severe haemophilia A: a nationwide multicentre study in Finland", *Haemophilia: the official journal of the World Federation of Hemophilia,* vol. 22, no. 5, pp. 721-729.

III Vepsäläinen, K., Riikonen, P., Lassila, R., Arola, M., Huttunen, P., Lähteenmäki, P., Möttönen, M., Selander, T. & Martikainen, J. 2018, "Long-term clinical and economic outcomes in previously untreated paediatric patients with severe haemophilia A: A nationwide real-world study with 700 person-years", *Haemophilia : the official journal of the World Federation of Hemophilia,*vol. 24, no. 3, pp. 436-444.

Contents

Abbreviations

ABR	Annualised bleeding rate
aHR	Adjusted hazard ratio
AJBR	Annualised joint bleeding rate
aPCC	Activated prothrombin complex concentrates
CI	Confidence interval
CR	Complication rate
CRBSI	Catheter-related blood stream infection
CVAD	Central venous access device
DVT	Deep venous thrombosis
ED	Exposure day
EHL	Enhanced half-life
EPIC	Early Prophylaxis Immunological Challenge
FV	Factor V
FVa	Activated factor V
FVII	Factor VII
FVIIa	Activated factor VII
FVIII	Factor VIII
FVIIIa	Activated factor VIII
FVIII:C	FVIII coagulation activity
FIX	Factor IX
FIXa	Activated factor IX
FIX:C	FIX coagulation activity
FX	Factor X
FXa	Activated factor X
FXI	Factor X
FXIa	Activated factor X
HA	Haemophilia A
HB	Haemophilia B
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
HR	High responder
ICH	Intracranial haemorrhage
ICU	Intensive care unit
ID	Inhibitor development
IQR	Interquartile range
ISTH	International Society on Thrombosis and Haemostasis
ITI	Immune tolerance induction
LR	Low responder
MRI	Magnetic resonance imaging
nICU	Neonatal intensive care unit
PCR	Polymerase chain reaction
pd	Plasma-derived
pd-aPCC	Plasma-derived activated prothrombin complex concentrate
pdFVIII	Plasma-derived FVIII
Pednet	European Paediatric Network for Haemophilia Management
PK	Pharmacokinetic
PTP	Previously treated patient
PUP	Previously untreated patient
rFVIIa	Recombinant activated FVII
rFVIII	Recombinant FVIII
rFIX	Recombinant FIX
RWD	Real-world data
SD	Standard deviation
SSC	Scientific and Standardization Committee
SII	Social Insurance Institution
TF	Tissue factor
vCJD	Variant Creutzfeldt-Jakob disease
vWF	von Willebrand factor
WFH	World Federation of Haemophilia

1 Introduction

Haemophilias are congenital bleeding disorders caused by a partial or total lack of coagulation factor VIII (FVIII) in haemophilia A (HA) or factor IX (FIX) in haemophilia B (HB). The disease is the result of mutations in the respective clotting factor genes, resulting in a reduced ability to develop stable blood clots. Since these disorders are X-linked recessive inherited disorders, they mainly occur in males. The bleeding tendency is related to the coagulation factor concentration in blood according to the residual FVIII:C or FIX:C in circulating blood; the disease is clinically classified as severe (<1%), moderate (1-5%), and mild (>5-40%). Severe haemophilia (FVIII:C or FIX:C < 0.01 IU mL^{-1}) is characterized by prolonged bleeding after trauma and surgery and by spontaneous bleeds in soft tissue, muscles and joints, with some patients developing severe chronic arthropathy. The primary aim of haemophilia care is to prevent and treat bleeds by replacing the deficient clotting factor. Prophylaxis, i.e. regular FVIII/FIX intravenous infusions, is aimed at preventing bleeds and joint damage by correcting the bleeding condition to that of a moderate phenotype. Children with severe forms of haemophilia often require surgically inserted central venous access devices (CVADs) to secure long-term and reliable venous access. Unfortunately, these devices have been associated with infectious and non-infectious complications.

The most serious and costly complication in the treatment of severe HA is the development of neutralizing anti-FVIII antibodies, called inhibitors. Consequences of inhibitor development (ID) include not only the reduced efficacy of FVIII replacement therapy and increased morbidity but also increased mortality, with intracranial bleed being the most common cause of death (Walsh et al. 2015). The highest risk for ID is encountered among previously untreated patients (PUPs) during the first 50 exposure days (EDs). Approximately one third of these children develop inhibitors (Gouw et al. 2013, Gouw et al. 2013, Calvez et al. 2014, Collins et al. 2014, Marcucci et al. 2015, Peyvandi et al. 2016). This complication is an unresolved, multifactorial complex process, influenced by patient- (genetic) and potentially modifiable treatment-related factors (Peyvandi et al. 2017b).

Haemophilia is a rare disorder, but its management imposes a high psychosocial and economic burden on patient care. High-dose prophylactic coagulation factor replacement therapy is among the most expensive treatments, and clotting factor consumption accounts more than 94% of total annual treatment costs (Fischer et al. 2013, Zhou et al. 2015). Paediatric health-economic studies with real-world data (RWD) are few. One prospective study with RWD during a short follow-up (two years) reported the total annual treatment costs for non-inhibitor children as US$ 160 000, though a third of the patients included had non-severe haemophilia (Zhou et al. 2015). Most studies report treatment costs per patient and usually not per body weight; this feature challenges cost comparisons among different paediatric studies, where both patient body weight varies to a great extent and dosing is mainly based on weight.

The general aim of this retrospective nationwide study was to investigate the effects of early primary prophylaxis in Finnish paediatric haemophilia patients during the past two decades. The incidence of, and risk factors for, complications associated with CVAD usage were

evaluated. We examined the incidence of, and risk factors for, ID in PUPs with severe HA. We evaluated the long-term costs (with RWD) and clinical outcomes of treatment with early high-dose FVIII prophylaxis.

2 *Review of the literature*

2.1 OVERVIEW OF HAEMOSTASIS

The delicate process of haemostasis balances procoagulant, anticoagulant, and fibrinolytic, activities in the blood and tissues. The coagulation system is triggered in response to rupture of the endothelium and protects against blood loss in the case of vascular damage. The first part of the process is the formation of the platelet plug aiming to occlude and initiate healing of the vascular lesion (primary haemostasis). Secondary haemostasis stabilizes the existing plug by the activation of coagulation plasma proteins into a fibrin clot. The fibrinolytic process is activated by thrombin, formed during the end of coagulation, with the goal of dissolving the fibrin clot and finalizing vascular healing. Anticoagulant mechanisms ensure careful control of coagulation so that the activated procoagulant process remains localized only to the site of injury. Disturbances of the natural balance between the procoagulant and anticoagulant systems due to genetic or acquired factors may result in bleeding or thrombotic events (Dahlback 2000).

2.1.1 Blood coagulation

The coagulation process is a cascade in which the activation of each clotting factor leads to the activation of another, finally resulting in a burst of thrombin generation and the conversion of fibrinogen to a fibrin clot (Dahlback 2000, Hoffman 2003). In this process, some clotting factors are proenzymes that can be converted to an active enzyme, while others are cofactors without enzymatic activity. The clotting sequences are divided into so-called extrinsic and intrinsic pathways (Fig. 1). The "extrinsic" pathway, also called tissue factor pathway, is initiated *in vivo* by tissue injury that activates tissue factor (TF) and factor VII (FVII) to its active form, FVIIa. By contrast, the factors in the "intrinsic" pathway have been thought to be intravascular, started only with the contact system (*in vitro* process), and thus not having a significant role in *in vivo* or trauma-initiated coagulation. Instead, the intrinsic pathway acts mainly as a positive feedback route to maintain ongoing coagulation. Both the extrinsic and the intrinsic pathways can activate factor X: the extrinsic pathway by FVIIa, and the intrinsic pathway by bringing activated factor VIII (FVIIIa) to act as a cofactor for the FIXa-mediated activation of FX. In the common pathway, factor Xa (FXa), in complex with its cofactor Va, converts prothrombin to thrombin and thereafter generates fibrin from fibrinogen.

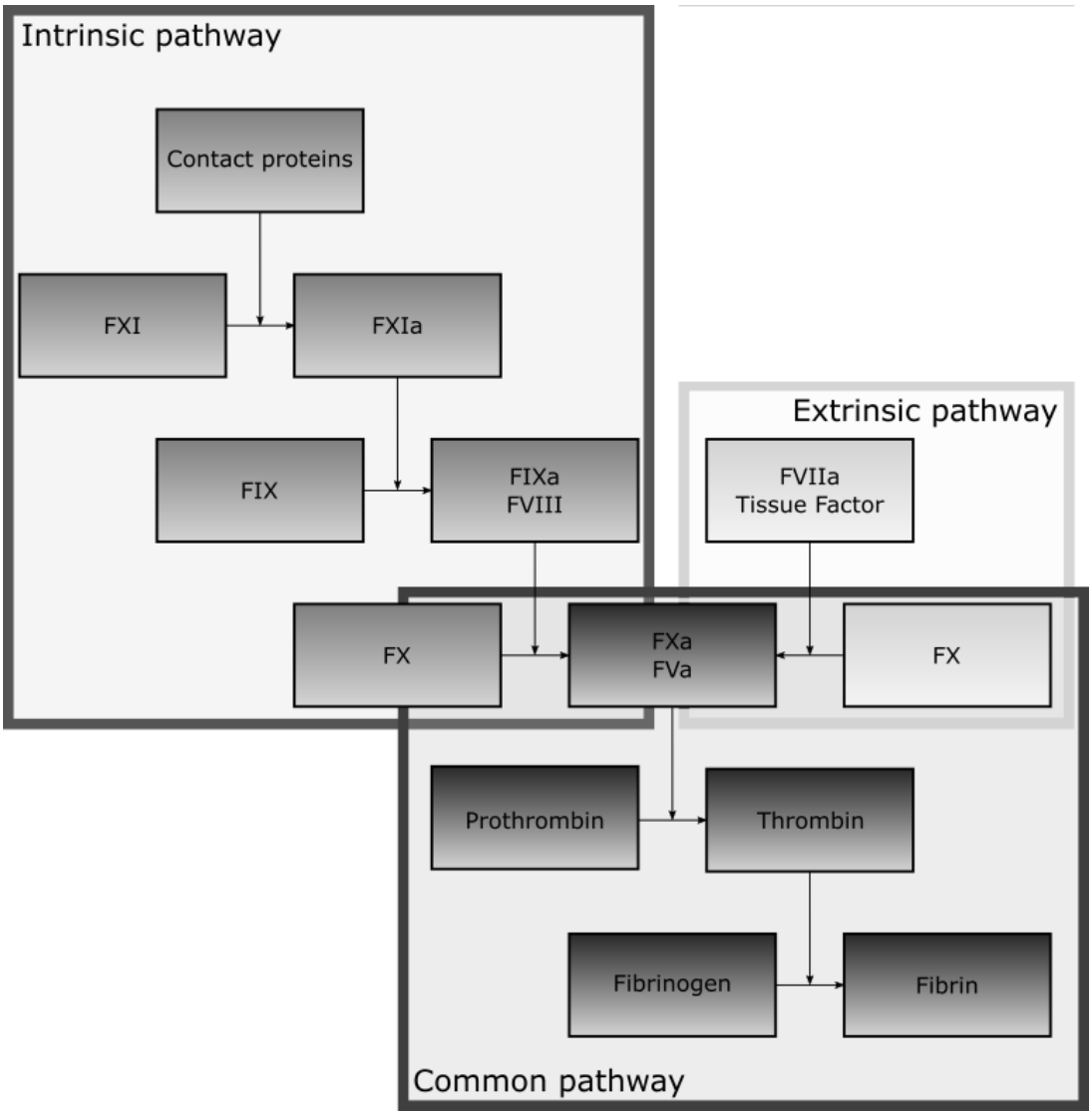

Figure 1. The overview of the coagulation cascade. Abbreviations are found in the section Abbreviations.

The coagulation process described above, however, has flaws as a model of the haemostasis process *in vivo*. For example, it cannot explain why an intact FVIIa/tissue factor (extrinsic) pathway cannot compensate for the lack of the factor IXa/VIIIa complex. Components of the intrinsic pathway must play an important role in haemostasis since patients deficient in FVIII or FIX have a serious bleeding tendency. A revision of the traditional way of looking at coagulation in the last decade pinpoints the mechanism where the required coagulant factors are assembled and react with one another on cell surfaces (Hoffman 2003). In this cell-based model, two cell types are involved, TF-bearing cells and platelets; the process of coagulation is regulated by the properties of these cell surfaces. The intrinsic and extrinsic pathways are not redundant systems; they operate in parallel on different cell surfaces, which better explains bleeding and thrombosis *in vivo*. Firstly, the initiation of coagulation occurs due to vascular injury, with TF activating FVII. Secondly, the amplification phase begins; during

this stage, platelets and co-factors prepare for large-scale thrombin production. Thirdly, propagation occurs on the surface of activated platelets; this process involves both FVIIIa and FIXa, with the main goal of producing more thrombin. For effective thrombin generation and haemostasis, FXa must be directly generated on the activated platelet surface; FXa generated by the extrinsic pathway on the surface of a TF-bearing cell does not do the same job as FXa generated on the activated platelet surface by the intrinsic FVIIIa/FIXa complex (Hoffman 2003). This explains why an individual with a lack of either FVIII or FIX, despite having an intact extrinsic pathway has a serious bleeding tendency.

2.2 HAEMOPHILIA

2.2.1 Background

Haemophilias are X-linked congenital bleeding disorders caused by a partial or complete lack of coagulation FVIII (in HA) or FIX (in HB). The disease is the result of mutations within the respective clotting factor genes. Since these disorders are X-linked recessive inherited disorders, they mainly occur in males; all daughters of an affected male will be carriers, whereas all sons will be healthy. A female carrier will pass the mutation to half of her sons who will have haemophilia and to half of her daughters who will be carriers. About half of all new cases arise from spontaneous mutation, with no previous family history of haemophilia (Kasper, Lin 2007). The incidence of HA is one in 5000 male live births, and that of HB is one in 30 000 (Franchini, Mannucci 2012).

2.2.2 Historical aspects

The earliest writings on haemophilia date back to the second century; the Talmud, a collection of Jewish rabbinical writings, stated that male babies should not be circumcised if brothers or cousins on the maternal side had already died from excessive bleeds after the procedure. The first modern description of haemophilia is from J.C. Otto, a physician from Philadelphia, who in 1803, discovered an inherited bleeding tendency in males. Haemophilia is also well known for its effects on the royal family houses of Europe. Victoria, Queen of England from 1837-1901, a clinically normal carrier of haemophilia B, passed on the disease to her youngest son, Leopold, who suffered frequent haemorrhages and died of brain haemorrhage at age 31. Two of her daughters, Alice and Beatrice, were carriers who, in turn, transmitted the disease to the Russian, German, and Spanish royal families (Franchini, Mannucci 2012).

The bleeding tendency in haemophilia was originally believed to be caused by a fragility of the blood vessels or by defective platelets. In 1944, the Argentinian physician, Pavlosky, showed that blood from one haemophiliac could correct the coagulation defect of another haemophiliac, and vice versa. This finding laid the foundation for the modern therapy of this disease. The two previously clinically indistinguishable bleeding disorders were distinguished and named haemophilia A and haemophilia B in 1952; it was found that HA was caused by a partial or complete lack of FVIII and HB by that of FIX (Franchini, Mannucci 2012).

2.2.3 Clinical disease of haemophilia

The bleeding tendency is related to coagulation factor concentration in blood, according to the residual FVIII:C or FIX:C; the disease is clinically classified as severe (<1%), moderate (1-5%), and mild (>5-40%) (Blanchette et al. 2014). Severe haemophilia is characterized by

spontaneous bleeds in the joints, muscles, and other soft tissues. The first bleeding symptoms, easy bruising and abnormal bleeding, occur when a child with haemophilia starts to walk. Repeated joint bleeds, mostly occurring in the elbows, knees, and ankles, can lead to the development of painful and disabling haemophilic arthropathy (Srivastava et al. 2013). Spontaneous bleeds are most often present in patients with the severe form of the disease. Before the introduction of coagulation factor concentrates, the life expectancy of persons with severe haemophilia was very short (<30 years). Most patients died in childhood or early adulthood, from haemorrhages in the vital organs (mainly in the brain) after surgery or trauma (Franchini, Mannucci 2012). Intracranial haemorrhage (ICH) has accounted for a third of all deaths by haemophilia before the era of prophylaxis (Andersson et al. 2017).

2.3 TREATMENT OF HAEMOPHILIA

2.3.1 Principles of care

The primary aim of haemophilia care is to prevent and treat bleeding with the help of the deficient clotting factor. In the 1950s and early 1960s, the only treatment was transfusion with whole blood or fresh plasma; these, however, do not include enough FVIII or FIX proteins to stop severe bleeds. Modern management with plasma concentrates of coagulation factors started in the 1970s. In the early 1980s, serious treatment complications occurred; 60-70% of people with severe haemophilia became infected with the human immunodeficiency virus (HIV) that had contaminated plasma-derived (pd) concentrates (Franchini, Mannucci 2014). Almost all patients treated were also infected with hepatitis C (HCV). The first recombinant FVIII (rFVIII) products became available in the early 1990s, and the first recombinant FIX (rFIX) in the late 1990s (Franchini, Mannucci 2012). Nowadays, with dual virus inactivation procedures in the manufacturing process, both viral-inactivated pd and recombinant products are considered safe from infections by viruses associated with significant pathogenicity (Norja et al. 2012). Despite this, at least a theoretical risk of transmission of infection through pd products still exists. Currently available viral inactivation methods are unable to eradicate the variant Creutzfeldt-Jakob disease (vCJD) prion or parvovirus B19. This problem is currently being handled by excluding plasma from all donors perceived to be at risk and by testing products by using minipool polymerase chain reaction (PCR) screening (Srivastava et al. 2013, Norja et al. 2012).

2.3.2 Primary prophylaxis – standard of treatment

Prophylaxis refers to regular FVIII/FIX intravenous infusions aimed at preventing bleeds and joint damage by correcting the bleeding condition to that of phenotypically moderate; it was conceived from the observation that patients with a clotting factor level >1% of the normal level seldom experience spontaneous bleeds. It was first introduced in Sweden and then adopted by other countries (Nilsson, Hedner & Ahlberg 1976). Clinical experience over decades, numerous cohort studies, and recent randomised controlled trials, clearly demonstrate that regular prophylactic treatment is superior to on-demand treatment in preventing the development of haemophilic arthropathy (Manco-Johnson et al. 2007, Gringeri et al. 2011). Full prophylaxis offers almost complete protection against ICH (Andersson et al. 2017) and gives patients a near-normal life with a life expectancy similar to that of males in the general population (Tagliaferri et al. 2010). Prophylactic FVIII treatment also associates with a decreased ID risk (Gouw et al. 2013). Hence, early primary prophylaxis

is the current standard of care in children with severe haemophilia. Early primary prophylaxis refers to regular continuous replacement therapy started in the absence of documented joint disease, and before the second clinically evident joint bleed and three years (Blanchette et al. 2014, Srivastava et al. 2013, Fischer et al. 2016, Fischer, Ljung 2017).
Opinions about the timing of starting prophylaxis vary widely between countries but, in general, the trend is towards an even earlier start, i.e. primary prophylaxis before the first joint bleed. This is justified after findings that the best long-term joint outcome is achieved by starting prophylaxis at an earlier age (Fischer et al. 2016, Astermark et al. 1999, Fischer et al. 2002) and before the first joint bleed, compared to starting after one or more joint bleeds. The number of joint bleeds before starting prophylaxis has a stronger association with outcome than the age at which prophylaxis starts (Nijdam et al. 2016). After an intracranial bleed, prophylaxis needs to be immediately initiated (Fischer et al. 2016).
Dose and dose interval in primary prophylaxis are still a matter of discussion and depend on several factors: the goal of treatment, the bleeding tendency, the patient's daily activities, economic resources, available sizes of coagulation factor vials, and venous access. Due to the lack of evidence for an optimal prophylactic regimen, no strict recommendations exist. However a standard recommendation is that primary prophylaxis should be started with 250IU (for HA) or 500IU (for HB) vials, with the child 10-17 kg at the start, and continued with infusions either once weekly or more frequent, up to every second day (Fischer et al. 2016). A large multicentre study compared three different prophylaxis regimens: 1) full early prophylaxis, starting with prophylactic infusions at least thrice weekly before age three, 2) early initiation, with increasing frequency as soon as possible, and 3) starting and increasing frequency according to bleeding phenotype. It showed full early prophylaxis to be the most effective in the prevention of joint bleeds before age four (32% full vs. 27% as soon as possible and 8% phenotype) (Nijdam et al. 2015).

2.3.3 Use of central venous access devices

When starting prophylaxis in very young children, repeated peripheral punctures can be technically problematic and lead to subcutaneous exposure of the concentrate. Surgically inserted ports are required to secure long-term and reliable venous access in the majority of patients with prophylaxis. Of the children with full early prophylaxis in the Pednet (European Paediatric Network for Haemophilia Management) cohort, 88% required a port (Nijdam et al. 2015). However, these devices have been associated with infectious, thrombotic, and mechanical, complications, with infections being the primary complication. Valentino and colleagues performed a large meta-analysis with 2704 haemophilia patients and 2973 CVADs (Valentino et al. 2004); they reported infection as the most common reason for removal (in 69.9% of cases) and the incidence of infection as 0.66/1000 catheter days. Other reports have described a wide variety of higher infection rates (0.2–3.4 infections/1000 CVAD days) (Ljung 2007, Titapiwatanakun et al. 2009, Yeoh et al. 2013, Mancuso et al. 2008, Van Dijk et al. 2004, Bollard et al. 2000, McMahon et al. 2000, Tarantino et al. 2003).
Especially due to the infection risk, port implantation has been avoided in many countries. The Canadian tailored ("dose escalation") prophylactic strategy allows up to two bleeds per joint in three months before intensifying prophylaxis and aims to avoid a CVAD. However, this strategy has proved to be inferior to full-dose prophylaxis for the prevention of early structural joint changes (Kraft et al. 2012). In magnetic resonance imaging (MRI), in 50% of patients at age 8.8, tailored primary prophylaxis resulted in osteochondral changes. Thus, a

more rapid escalation is now recommended, often requiring the use of a CVAD. The decision to use a central venous port is often a compromise between the medical goal, the bleeding tendency, and familiarity with the use of these devices at a particular treatment centre.

2.3.4 Management of Finnish paediatric patients with severe haemophilia

In Finland, the treatment of all children with severe haemophilia is centralized in the departments of paediatric haematology in university hospitals and follows a uniformly agreed protocol. All paediatric patients are on regular prophylaxis. Here, it has been a standard practice for nearly two decades to start primary prophylaxis very early, before age one and the onset of the first joint bleed, mainly with a rFVIII and via a CVAD. Parents start the education and training program during the first postoperative days and become competent to use ports with aseptic infusion techniques soon after port implantation. Ports enable an early start in home treatment, during the first weeks after CVAD insertion and prophylaxis onset, even for patients living at a long distance from the treatment centre.

2.4 INHIBITOR DEVELOPMENT IN CHILDREN WITH SEVERE HAEMOPHILIA A

2.4.1 Overview of inhibitor development

Currently, the most serious and costly complication of the treatment of severe HA (FVIII:C $<0.01 mL^{-1}$) is inhibitor development. Inhibitory antibodies neutralize the factor infused, rendering patients resistant to conventional FVIII replacement therapy. The highest risk for ID is encountered among PUPs during the first 50 EDs. Approximately a third of these children develop inhibitors (Gouw et al. 2013, Wight, Paisley 2003, Gouw et al. 2013, Calvez et al. 2014, Collins et al. 2014, Marcucci et al. 2015, Peyvandi et al. 2016). This complication is an unresolved, multifactorial complex process, influenced by patient- (genetic) and potentially modifiable treatment-related factors (Peyvandi et al. 2017b).

Patients with inhibitors can be low responders (LR), with an FVIII inhibitor titre <5 BU mL^{-1}; or high responders (HR), with an inhibitor titre ≥ 5 BU mL^{-1}.

Consequences of ID include not only reduced efficacy of FVIII replacement therapy and increased morbidity but also higher mortality. A retrospective analysis with 7386 males with severe HA during a 13-year period reported an association between the current inhibitor and death (Walsh et al. 2015). The odds of death were 70% higher among patients with a current inhibitor compared with those without an inhibitor ($p<0.01$). Haemophilia-related bleeding complications (mainly intracranial bleeds) as the cause of death were significantly more frequent among patients with active inhibitors (42%) than among those without (12%; $p<0.0001$).

2.4.2 Genetic risk factors for inhibitor development

Well-known patient-related (genetic) risk factors are a high-risk genotype (severe null mutation defects in the FVIII gene, with a lack of endogenous FVIII production), African ethnicity, a family history of an inhibitor, and polymorphisms within immune response genes (Astermark 2012, Gouw et al. 2012, Bardi, Astermark 2015, Astermark et al. 2013).

2.4.3 Non-genetic risk factors for inhibitor development

Several FVIII treatment characteristics influence ID, including intensity of treatment at first exposure and FVIII product type (Gouw et al. 2013, Gouw, van der Bom & Marijke van den

Berg 2007, Astermark et al. 2010, Gouw, Fijnvandraat 2013, Alvarez, Soto & Astermark 2015, Iorio, Fischer & Makris 2017). These modifiable environmental risk factors stimulate the immune system and in the presence of immunological danger signals (i.e. severe bleeds, trauma, or surgery with major tissue injury), the foreign FVIII protein is intensively presented, especially during high-dose, prolonged therapy at the start of FVIII treatment, and activates T and B lymphocyte responses (Astermark et al. 2010, Alvarez, Soto & Astermark 2015, Lovgren et al. 2016).
Until we understand key ID mechanisms, minimizing the risk of ID by acting on these modifiable risk factors remains a sensible goal for optimizing haemophilia treatment.

2.4.3.1 Prophylaxis

One strategy for inhibitor prevention could be to avoid these potential danger signals, such as major bleeds, by starting prophylaxis early. The CANAL study (Gouw, van der Bom & Marijke van den Berg 2007) found a 60% decreased risk of ID in patients on regular prophylaxis. In another large observational cohort, the RODIN study (Gouw et al. 2013), confirmed the protection provided by regular prophylaxis in patients with low-risk FVIII genotypes.

2.4.3.2 Products

Different concentrates may be associated with a different potential immunogenicity in PUPs. Since 2013, the effect of specific FVIII concentrates on ID has been evaluated in several large epidemiological cohort studies (Gouw et al. 2013, Gouw et al. 2013, Calvez et al. 2014, Collins et al. 2014, Marcucci et al. 2015, Fischer et al. 2015) and in a randomized controlled trial (Peyvandi et al. 2016). Two large multicentre observational cohort studies, the RODIN study with 574 PUPs and the EUHASS project with 417 PUPs, observed no difference in inhibitor incidences between plasma-derived FVIII (pdFVIII) and rFVIII products (Gouw et al. 2013, Fischer et al. 2015). The Survey of Inhibitors in Plasma-Product Exposed Toddlers (SIPPET) was the first randomized study comparing the class effect between pdFVIII concentrates containing von Willebrand factor (vWF) and rFVIII products; it showed increase in the inhibitor rate in rFVIII versus pdFVIII products (hazard ratio, 1.87; 95% CI, 1.17-2.96) (Peyvandi et al. 2016). The immune response against rFVIII products was also faster and stronger: inhibitors with rFVIII developed earlier, and were more severe (higher titre) than with pdFVIII (Peyvandi et al. 2017a). Patients with a low genetic risk suffered the highest increment in risk when treated with rFVIII; no inhibitors occurred in those with a low genetic risk when treated with pdFVIII; the cumulative incidence was 43% when patients were treated with rFVIII ($p<.01$) (Rosendaal et al. 2017). This example of gene-environment interaction, in addition to the finding of the protective effect provided by regular prophylaxis in low-risk patients (Gouw et al. 2013), shows that patients with a low genetic risk may potentially benefit more than high risk by acting on these modifiable risk factors in order to minimize the risk of ID.
However, the external validity of the SIPPET study has been largely criticized (Iorio, Fischer & Makris 2017); especially because of its population characteristics (selection of very high-risk patients), it is not easy to apply the difference observed directly to Western patients. In addition, the residual rate of inhibitors is still high, and pdFVIII concentrates still have a higher theoretical risk of transmission of virus- or prion-related blood-borne infections. These factors may restrict widespread use of pd factors in PUPs.

Concerning the differences in immunogenicity between specific rFVIII products, the use of a second-generation full-length rFVIII product (Kogenate Bayer/Helixate Next Gen) in PUPS associates with an increased inhibitor rate compared to Advate, a third-generation rFVIII product. The difference is significant [(aHR 1.6; 95% CI, 1.08-2.37) and aHR 1.75; 95% CI, 1.11-2.76)] (Gouw et al. 2013, Collins et al. 2014) or borderline (aHR 1.55; 95% CI, 0.97-2.49) (Calvez et al. 2014). Even though this observation has not been corroborated by other studies (Marcucci et al. 2015, Fischer et al. 2015), it has been suggested that physicians consider the use of Advate rather than Kogenate Bayer in PUPs (Iorio, Fischer & Makris 2017).

2.4.3.3 Treatment intensity

Many studies have evaluated intensive FVIII treatment mainly on the basis of peak treatment moments, defined as episodes of treatment with FVIII for bleeding or surgery on at least three, five, or ten, consecutive days (Gouw et al. 2013, Gouw, van der Bom & Marijke van den Berg 2007). During the first exposure to FVIII, intense FVIII treatment on at least five consecutive days is a clear risk factor for ID (Gouw et al. 2013, Gouw, van der Bom & Marijke van den Berg 2007). Yet, major peak treatment moments of at least five days later during the first 75 EDs result in no significant increase in inhibitor risk (Gouw et al. 2013).

In the CANAL study, patients first treated for a surgical procedure had a higher risk of ID than patients treated for a bleed or prophylaxis (Gouw, van der Bom & Marijke van den Berg 2007). In more recent studies, a major surgical procedure during first exposure resulted in no increase in the risk by itself; the same held true if it was performed later during the first 75 EDs (Gouw et al. 2013, Maclean et al. 2011).

2.4.3.4 Treatment-related risk factors without influence on inhibitor risk

Recent studies have shown that age and reason for first exposure have no association with ID (Gouw et al. 2013, Gouw, van der Bom & Marijke van den Berg 2007); neither does switching the FVIII product (Gouw et al. 2013, Santagostino et al. 2015). A higher dose or frequency of prophylaxis does not increase ID risk (Gouw et al. 2013). A recent retrospective investigation with 375 PUPs reported no association between ID and vaccinations, even if administered close to FVIII exposure (48h before to 24h after) (Hashemi et al. 2015).

2.4.4 Management of inhibitor patients - immune tolerance induction

Haemophilia patients with neutralizing antibodies experience poor bleeding control and higher levels of morbidity and mortality (Walsh et al. 2015). The management of inhibitor patients requires on-demand or prophylaxis treatment with bypassing agents, immune tolerance induction (ITI), or both. If patients are LRs, high doses of FVIII can be useful in the case of bleeds. In HRs, high doses of FVIII are ineffective, and bypassing agents (activated prothrombin complex concentrates [aPCC], recombinant activated FVII [rFVIIa]) are required for the management of acute bleeds. ITI, a method meant to eliminate inhibitors through long-term daily treatment with large doses of coagulation factors, is the only proven therapy to eradicate inhibitors and thus to enable regular FVIII treatment (Franchini, Mannucci 2012). ITI success rates vary but usual quoted rates are 60-80% (Peyvandi et al. 2017b). In patients refractory to standard ITI therapy, rituximab (a humanized chimeric anti-CD20 monoclonal antibody) alone, or sometimes concomitant with other immunosuppressive agents, has helped to achieve successful inhibitor eradication in occasional cases (Franchini, Mannucci 2014). However, these treatments are very costly, and inflict a burden on patients, their family, and society.

A promising novel treatment to prevent bleeds in haemophilia A is emicizumab (ACE910), a recombinant humanized bispecific monoclonal antibody that acts as an FVIII mimetic by binding simultaneously to activated FIXa and FX (Shima et al. 2016, Shima et al. 2017). Because of its unique structure, emicizumab has demonstrated not only a favourable safety profile including no neutralizing antibody development to date but it also enhances efficacy in bleeding control in patients with FVIII inhibitors (Oldenburg et al. 2017). It may provide a weekly, subcutaneously administered, prophylactic therapeutic option for patients with inhibitors, and thus decrease the burden of the disease. To date, it is too early to say how the costs of emicizumab and the standard ITI therapy will compare.

2.5 LONG-TERM CLINICAL AND ECONOMIC OUTCOME

2.5.1 Costs for non-inhibitor patients

Haemophilia is a rare disorder, but its management imposes a high psychosocial and economic burden on patients, caregivers, and society. High-dose prophylactic coagulation factor replacement therapy is among the most expensive treatments, and clotting factor consumption accounts for 94.0-99.6% of total annual treatment costs (Fischer et al. 2013, Zhou et al. 2015). The annual total treatment costs for an adult non-inhibitor patient with high-dose prophylaxis exceed US$ 298 000 (Fischer et al. 2013). Paediatric health economic studies with RWD are few; the average total annual costs of treating paediatric patients have been estimated to be US$ 21 600 for young children and US$ 124 000 for teenagers (Smith et al. 1996, Valentino et al. 2012). One prospective study used RWD during a short follow-up (two years) and reported total annual treatment costs for 110 non-inhibitor children as high as US$ 160 000, though a third of the patients included had non-severe haemophilia (Zhou et al. 2015). Most studies report treatment costs per patient and usually not per body weight, which challenges cost comparisons. This is typical among different paediatric studies where patient body weight varies to a great extent, and yet dosing is based mainly on weight.

A recent publication compared the costs and outcomes between the most well-known prophylaxis regimens for adult HA, the Swedish high-dose regimen (2000 IU 3 times a week or 1500 IU every other day) and the Dutch intermediate-dosing regimen (1000 IU thrice a week) (Fischer et al. 2013). The overall annual FVIII consumption was 2150 IU/kg per year (95% CI, 1600-2700), lower for the intermediate dose regimen (median, 2100 vs 4000 IU/kg per year, $p < .01$). Annual total costs were 66% higher for high-dose prophylaxis, with a mean of US$ 298 000 for Swedish high-dose prophylaxis vs. US$ 180 000 for Dutch intermediate-dose prophylaxis. Overall, in both cohorts, physical activity was high, and bleeding frequencies were low. However, compared to the 'intermediate dose' group, the Swedish patients had less annual joint bleeds and a greater proportion of patients who experienced no joint bleeds and those whose status of the joints was excellent.

Early prophylaxis is beneficial from a health economic perspective (Shrestha et al. 2017). Among children (n=319), overall haemophilia and bleeding complication-related non-pharmacy costs were substantially lower for patients receiving prophylaxis compared to those who did not; these savings fully offset the incremental pharmacy costs caused by prophylaxis.

2.5.2 Costs of managing inhibitor patients

Inhibitors are not only very challenging to manage but extremely costly in terms of financial resources. The cost of immune tolerance therapy has been estimated to range from 70 290€ for an LR paediatric patient (ITI duration of 2 months) to 3 812 400€ for an HR (24 months of ITI with aPCC) (Auerswald et al. 2004). In addition, during ITI, for treatment of bleeding episodes on demand with FVIII or bypassing agents, the average annual cost per paediatric patient amounts to 77 000€. For an adult patient, ITI costs are estimated to account from 287 500€ (6 months; LR) to 17 253 000€ (36 months; HR); for treating an average of 12.5 acute bleeds, mean annual costs were €354 000€. A recent study with the RWD of 71 inhibitor patients (median age at ITI start of 3.8 years) reported mean clotting factor costs of 60 078.5€ per patient-month during ITI (2203€ per kg patient-month) (Rocino et al. 2016). Assuming an average two-year ITI treatment duration, the total costs of ITI amount to approximately 53 000€ per kg body weight.

3 *Aims of the study*

The general aim of this retrospective nationwide study was to investigate the effects of early primary prophylaxis, started mainly via a CVAD, in Finnish paediatric haemophilia patients during the past two decades. Their treatment has followed national recommendations among paediatric haematologists; the management has been uniform, including early prophylaxis with port insertions and the objective of early inhibitor eradication.

Specifically, the aims were the following:

1) To evaluate the incidence of, and risk factors for, complications associated with CVAD usage (Study I)

2) To examine the incidence of, and risk factors for, inhibitor development in PUPs with severe haemophilia A (Study II)

3) To evaluate the long-term clinical outcomes and costs of treatment with high-dose FVIII prophylaxis in PUPs from birth to adolescence, including immune tolerance induction (Study III).

4 Materials and methods

4.1 STUDY DESIGN

In Finland, the treatment of all children with severe haemophilia in the departments of paediatric haematology in university hospitals follows a uniformly agreed protocol. Here, it has been a standard practice for nearly two decades to start primary prophylaxis with an rFVIII for all patients below age one, mainly via a CVAD. Routine implantation of ports has facilitated not only prompt primary prophylaxis but also ITI therapy even in the youngest patients, ensuring reliable venous access and enabling early home treatment.
We designed a retrospective multicentre study to evaluate the incidence of, and risk factors for, CVAD complications; the nationwide incidence of, and risk factors for, ID; and the clinical outcomes and direct medical costs of haemophilia treatment, during the 19-year study period. The study was performed in five Finnish paediatric Haematology-Oncology centres (Kuopio, Oulu, Turku, Tampere, and Helsinki, University Hospitals).

4.2 PATIENTS

4.2.1 Patients using a port (study I)

In study I, which evaluating the incidence of, and risk factors for, CVAD complications, all children with the following criteria were eligible: severe (FVIII or FIX coagulation activity <0.01 IU mL^{-1}) or moderate (FVIII:C or FIX:C 0.01–0.05 IU mL^{-1}) HA or HB born between June 1994 and May 2012 and treated in the participating centres, and who required CVAD insertion by the end of the follow-up in September 2013.
Sixty-six provided written informed consent for this study. Eight of these 66 children did not require a port before the end of follow-up. Totally, 58 patients were included in this study. Of them, 51 had severe HA and two children had severe HB. Three patients with moderate HA and two patients with moderate HB were included. Eleven patients (19%) of this cohort had an inhibitor, all of them with severe HA.

4.2.2 Previously untreated patients with severe haemophilia A (studies II-III)

The study populations in studies II and III were identical. All PUPs with severe HA, born between June 1994 and May 2013 who had at least 75 EDs of concentrate use by the end of the follow-up in September 2013, were included. Over this 19-year period, 69 children with severe HA were treated in the participating centres. We excluded seven patients: four immigrants were PTPs, previously treated patients with an unknown amount of an unidentified factor concentrate and blood components for bleeds; and three children had less than 75 EDs. In total 62 PUPs were included, analysed, and followed up for up to 19 years.
One child with a severe immunodeficiency, a chronic granulomatous disease, was included in these studies. The other patients were not diagnosed with any other severe conditions or bleeding disorders.

4.3 DATA COLLECTION

From the medical records of all patients, the principal investigator (KV) collected detailed data on patients and treatment history.

4.3.1 Data on CVAD-related complications (Study I)

4.3.1.1 Register data

Register data included date of birth, type of bleeding disorder, ID, onset and reason for prophylaxis, date of CVAD insertion and removal, indication for port insertion and removal, and incidence of complications associated with CVAD, age at transition to peripheral veins, and the use of heparinised/non-heparinised saline solution to flush and/or lock the CVAD.
For each CVAD, the total number of catheter days was calculated as the total number of days from CVAD insertion to removal or to the date of the last follow-up day, for those whose CVAD remained in place. Port infusion days before CVAD removal, registered as exposure days (EDs), were estimated based on the administration frequency of the coagulation factor concentrates. The incidence rate for any complication per 1000 CVAD days was calculated as 1000 times the number of complications divided by the total number of CVAD days.

4.3.1.2 CVAD management

In the operating theatre, using strict aseptic techniques, an experienced anaesthesiologist inserted ports through the subclavian or the internal jugular. Port access was most often started immediately after implantation. Catheters were flushed with heparin or saline after use. No antibiotic prophylaxis was used in the catheter lock. In febrile episode cases, parents were advised to contact the hospital immediately. Patients were examined and, in the absence of common symptoms and signs of respiratory infection as a cause of fever, blood samples were drawn and cultured before initiation of antimicrobial therapy. Most centres obtained paired blood cultures from a port and a peripheral vein; in some centres, blood cultures were collected only from the port. Where blood cultures were not percutaneously obtained but the culture from the CVAD was positive, blood samples were collected again from the CVAD and cultured. Every time the port was accessed, CVADs were flushed with a heparinised saline solution or with only non-heparinised saline.

4.3.1.3 CVAD-related complications

Complications were defined as any complication requiring CVAD removal: malfunction, mechanical complication, symptomatic deep venous thrombosis (DVT), catheter-related blood stream infection (CRBSI), or a local infection such as skin or tunnel infection.
A CRBSI was defined according to the guidelines of the Infectious Diseases Society of America (Mermel et al. 2009). A definitive diagnosis required one of two conditions. The same organism would grow from at least one percutaneous blood culture and from a culture of the catheter tip if a port had been removed for suspected CRBSI. The second condition was that two positive blood cultures were drawn: one from a catheter and the other from a peripheral vein. In this study, we define a presumed CVAD-related infection as involving clinical symptoms of infection (fever, chills, or hypotension) and a recognized pathogen cultured from at least two blood samples (collected from a CVAD on separate occasions). Additionally, the recognized pathogens had to be unrelated to an infection at some other site. Thus, this study excluded febrile episodes not fulfilling the definition of either confirmed or

presumed CVAD-related infection. Two infections were excluded: Staphylococcus aureus-sepsis and multiple abscesses in a patient with concomitant severe congenital immunodeficiency, and Klebsiella pneumonia and Acinetobacter-bacteraemia in another patient who had pneumonia and osteomyelitis.
Malfunction was defined as a blockade or an occlusion (difficulties in drawing blood, infusing fluids through the catheter, or both) in the absence of documented thrombosis. Mechanical complication was defined as a displacement (i.e. malposition of the catheter tip), disconnection, split, or skin erosion requiring port removal.
CVAD-related thrombosis was defined as a thrombosis with clinical symptoms or signs of venous thrombosis diagnosed using venography or ultrasound.
Early complications were those resulting from the catheter insertion procedure. These included pneumothorax, arrhythmias, and major bleeds or CRBSI, within the first 2 weeks after CVAD positioning. A major bleed was defined according to recommendations of the Scientific and Standardization Committee (SSC) of the International Society on Thrombosis and Haemostasis (ISTH) (Schulman et al. 2010).

4.3.2 Data on inhibitor development in PUPs with severe haemophilia A (Study II)

4.3.2.1 Data registered

Data concerning patient-related risk factors for ID included ethnicity, FVIII genotype, and family history of haemophilia and of inhibitors. Treatment data included first exposure to FVIII (age, indication, brand of FVIII, dosage IU kg^{-1}, and duration of the treatment) and prophylaxis (age, number of EDs and previous joint bleeds at prophylaxis onset, type of venous access, type and dosing of FVIII prophylaxis). They also included date of the 75th ED and treatment with FVIII for prophylaxis, bleeds, and surgical procedures up to the first 75 EDs or inhibitor development. ID data comprised the date of inhibitor diagnosis, number of EDs at the time of ID, all available inhibitor tests, and recovery measurements, including dates and body weight.

4.3.2.2 FVIII concentrates

The following rFVIII products were used:
a first-generation full-length rFVIII product (Recombinate®; Baxter AG, Wien, Austria),
a second-generation full-length rFVIII product (Kogenate® Bayer; Bayer Pharma AG, Berlin, Germany),
a third-generation full-length rFVIII (Advate®; Baxter AG, Wien, Austria),
a second-generation B-domain-deleted rFVIII product (ReFacto®; Wyeth, Berkshire, UK), and a third-generation B-domain-deleted rFVIII product (ReFacto AF®; Pfizer, Sandwich, UK).
We used the following pdFVIII products:
Amofil®, a monoclonal antibody-purified FVIII, manufactured by the Finnish Red Cross Blood Service until 2004 and by Sanquin, Amsterdam, Netherlands, since 2005,
Haemate® (human von Willebrand factor and coagulation FVIII; CSL Behring GmbH, Marburg, Germany), and
a cryoprecipitate, a large-pool intermediate purity VIII concentrate; this cryoprecipitate was used until 1995.
Before 1995, Finnish HA patients were almost exclusively treated with domestic plasma products derived from voluntary, non-remunerated donors; since 1995, recombinant

products have been available (Ebeling et al. 2001). Paediatric haemophilia patients were all electively switched from pdFVIII to rFVIII products gradually thereafter, with pdFVIII products replaced by 2008.

4.3.2.3 Definitions of FVIII prophylaxis

"Regular prophylaxis" was defined as long-term uninterrupted administration of an FVIII concentrate at least once a week to prevent bleeds. "Primary prophylaxis" meant regular prophylaxis started before age two and before the onset of any joint bleed. "Secondary prophylaxis" covered all long-term prophylactic regular treatments failing to fulfil the criteria of primary prophylaxis. The definition of primary prophylaxis in our study was stricter compared to those of the World Federation of Haemophilia (WFH) (Srivastava et al. 2013) and to PedNet (Ljung 1999) and ISTH recommendations (Blanchette et al. 2014).

4.3.2.4 Inhibitor development

Clinically significant ID was defined as at least two positive antibody titres combined with decreased *in vivo* FVIII recovery. A transient inhibitor was defined as a positive inhibitor that drops below the detection threshold within six months of initial documentation despite continuing replacement therapy. With high-titre inhibitors, the peak inhibitor titre was at least 5 BU mL^{-1}. FVIII recovery was considered decreased when it was <66% of the expected level at 15–30 min after infusion of FVIII. The expected level of FVIII activity was calculated according to the criteria of Lee et al. (Lee, Gomperts & Kingdon 1993).

Inhibitor testing was conducted using the Bethesda assay without the Nijmegen modification, in the same national coagulation laboratory of the Finnish Red Cross Blood Service. The inhibitor detection limit was 0.7 Bethesda BU mL^{-1} until October 13, 2013. Since then, however, the cut-off level has been 0.5 BU mL^{-1}. The cut-off level changed upon the revalidation of the method and stayed the same throughout the study.

Most centres routinely performed recovery tests half-yearly and, in addition, preoperatively; however, in some centres, recovery and inhibitors were tested only upon clinical suspicion of ID. Since the diagnosis, we closely followed up the condition of all our patients for signs of a bleed or of ID; a haemophilia expert team was available to the patients and parents even during on-call hours. Thus, we recorded every major bleed and clinically significant inhibitor.

4.3.2.5 Definitions of risk factors for inhibitor development

Ethnicity was reported as Caucasian or non-Caucasian. High-risk FVIII genotypes included those with large deletions, nonsense mutations, splice-site mutations involving conserved nucleotides, and inversion of introns 1 and 22 (Gouw et al. 2012, Bardi, Astermark 2015). Low-risk FVIII genotypes included those with small deletions and insertions, splice-site mutations at non-conserved sites, and missense mutations. Genotyping was performed at the Malmö Centre for Thrombosis and Haemostasis (Lund University, Malmö, Sweden).

FVIII treatment intensity was evaluated based on 'peak treatment moments' in the RODIN study (Gouw et al. 2013); these were defined as episodes of FVIII replacement for a bleeding event or a surgery on at least three, five, or ten, consecutive days. We defined a major surgery as a surgical procedure for which replacement therapy was required at least for three consecutive days. A major bleed was defined according to ISTH recommendations (Schulman, Kearon & Subcommittee on Control of Anticoagulation of the Scientific and

Standardization Committee of the International Society on Thrombosis and Haemostasis 2005).

4.3.3 Data on long-term clinical and economic outcomes (Study III)

4.3.3.1 Prophylaxis

We recorded detailed individual prophylaxis data, the annual prophylactic regimen for every patient, including body weight and the dosage and frequency of prophylactic FVIII administrations, and whether trough levels of FVIII were served to guide prophylactic treatment. The definitions of prophylaxis were identical to those in study II (see 4.3.2.3).

4.3.3.2 Bleeding data and long-term clinical outcomes

We recorded all major and minor bleeds requiring hospitalization. We based our definition of a major bleed in surgical and non-surgical settings on ISTH recommendations (Schulman et al. 2010, Schulman, Kearon & Subcommittee on Control of Anticoagulation of the Scientific and Standardization Committee of the International Society on Thrombosis and Haemostasis 2005). We registered the annualised bleeding rate (ABR) and the annualised joint bleeding rate (AJBR), as well as the number of patients with a target joint or an arthropathy. A joint bleed meant an episode characterized by an unusual sensation or "aura" in the joint in combination with any of the following three signs. These were (a) increasing swelling or warmth of the skin over the joint, (b) increasing pain, and (c) progressive loss of range or difficulty in using the limb compared with the baseline (Blanchette et al. 2014, Blanchette, Srivastava 2015). In infants and young children, a joint bleed meant reluctance to use the limb accompanied with pain, swelling, or warmth of the skin over the joint. A target joint was defined as a single joint having three or more spontaneous bleeds within six consecutive months (Blanchette et al. 2014, Blanchette, Srivastava 2015). In this study, a chronic haemophilic arthropathy meant a target joint with clinical or radiological evidence of significant synovitis (Blanchette, Srivastava 2015).

4.3.3.3 Inhibitor development and immune tolerance induction

The definitions of ID were identical to those described in study II (see 4.3.2.4). We classified as LRs patients with inhibitor titres persistently ≤5 BU/mL despite repeated challenges with FVIII; HRs referred to patients with inhibitor titres >5 BU/mL at any time (Blanchette et al. 2014). For ITI, LRs received 50-150 IU FVIII kg^{-1} daily, or thrice a week; HRs received 100 IU FVIII kg^{-1} every 12 h, or 100-200 IU FVIII kg^{-1} daily. For ITI success in terms of successful tolerance and partial response, we based our definition on the criteria of the International ITI (I-ITI) study and US guidelines for ITI (Hay, DiMichele & International Immune Tolerance Study 2012, Valentino et al. 2015).

4.3.3.4 Health care resource use and costs

To evaluate the long-term costs of treatment, we recorded the use of all clotting factor concentrates and health care services. The former included FVIII, rFVIIa, and pd-aPCC, use for prophylaxis, bleeds, and for surgical procedures; and FVIII use for ITI. The latter comprised the number of hospitalization for bleeding episodes or surgical procedures and the length of stay for each hospitalization, including the number of days in the intensive care unit (ICU). We also recorded the numbers of outpatient visits, CVAD insertions and removals, and CVAD-related infections. The unit costs of the services utilized (Table 1) were

obtained from the national health care unit cost list (Kapiainen, Väisänen & Haula 2014), and all costs were assessed at real values (€) in 2014. The estimated costs are convertible to US$ by using the European Central Bank annual bilateral exchange rates in 2014, available at sdw.ecb.europa.eu. We report all costs by weight adjustment, i.e. per kg of body weight, to describe and compare costs between patients of different ages and weight.

Table 1. Unit costs

Recourse use	Price in €	Source
FVIII product (per IU)	0.69	Market share weighted price per IU (excluding VAT)
rFVIIa (per µg)	0.64	Market share weighted price per IU (excluding VAT)
pd-aPCC (per IU)	0.85	Market share weighted price per IU (excluding VAT)
Hospital day/ Ward day	931	*
ICU day	3803	*
nICU day	2716	*
Visit to outpatient clinic	294	*
CVAD insertion	963	Kuopio University Hospital tariff
CVAD removal	813	Kuopio University Hospital tariff

rFVIIa, recombinant activated factor VII; pd-aPCC, plasma-derived activated prothrombin complex concentrate; ICU, intensive care unit; nICU, neonatal intensive care unit; CVAD, central venous access device
*(Kapiainen, Väisänen & Haula 2014)

4.3.3.5 Validation of the cost data

In order to validate the FVIII consumption data extracted from the medical records, we acquired a patient-specific validation sample from the Finnish Prescription Register maintained by the Social Insurance Institution (SII). This database of nationwide electronic pharmacy reimbursement claims became available in 1994, and it includes outpatient records of all medication dispensations reimbursed to community-dwelling residents in Finland. The register keeps no record of non-reimbursed medications or medications dispensed during a hospital stay (Furu et al. 2010). Our validation data sample included all study patients, except children living in the area of the hospital district of Helsinki and Uusimaa.

4.4 STATISTICAL METHODS

Descriptive statistics are presented (a) as either mean and standard deviation (SD) or (b) as median and either ranges or an interquartile range (IQR). Categorical variables are reported as frequencies and proportions.

In study I, groups were compared using the log-rank test, and 95% confidence intervals (CIs) for incidence rates were calculated.

In study II, Cox proportional hazard models were used to estimate crude and adjusted hazard ratios with 95% CIs. In the Cox models, ID was the index event, and the cumulative number of EDs was the time variable. In our multivariate analysis, all associations were adjusted for the FVIII genotype categorized based on high-risk and low-risk mutations, as well as for the FVIII product type (a pdFVIII or rFVIII), family history of ID, and ethnicity.

In study III, longitudinal outcome data was analysed by using a linear mixed model for repeated measures. The hurdle modelling approach was applied to right-skewed cost data, including excess zero values. Furthermore, non-parametric bootstrapping was applied to define 95% CIs for mean cost estimates and for the payback period estimate.
To demonstrate the potential economic value of ITI, an expected payback period estimate in years was provided to indicate the period of cost savings (after the completing of ITI) needed to equal the overall cost of ITI. To estimate the expected length of the payback period, the average costs of ITI were compared with the costs of an expected alternative treatment strategy without ITI, i.e. a treatment with prophylaxis or on-demand therapy with bypassing agents. The payback analysis included all patients who completed ITI, except one with ID recurrence, to describe the average costs for ITI performed during early childhood.
A $P < 0.05$ was considered statistically significant. All analyses in studies I-II were performed using SPSS software version 21.0; SPSS Inc. (IBM Corp., Armonk, NY, USA). In study III, a linear mixed model for repeated measures was performed with SPSS software version 21.0; hurdle regression analysis with bootstrapping was executed by R statistical software version 3.1.1 by using function hurdle in R package pscl. All statistical analyses performed with SPSS were made by K.V. and Hurdle regression analysis with R software by a statistician (T.S.) in Kuopio University Hospital.

4.5 ETHICAL CONSIDERATIONS

The Research Ethics committee of Northern Savo, Finland, provided a favourable opinion for the study (26//2010). We obtained permissions to use the register data from each organization concerned. In addition, for study I, and prior to SII data collection for study III, all patients, their parents, or both, provided written informed consent.

5 Results

5.1 COMPLICATIONS ASSOCIATED WITH CVAD (STUDY I)

5.1.1 Patients and CVADs

This study included 58 patients with 106 CVADs, and 137 971 CVAD follow-up days. These included 122 053 CVAD days for patients without inhibitors and 15 918 CVAD days for patients with inhibitors. The majority (53/58; 91%) of the patients had severe haemophilia (51 with HA, and two with HB). Of this cohort, 11 (19%) children had an inhibitor. Eight of them were successfully immunotolerized, and three children had ongoing ITI therapy.

The median age at first CVAD implantation was one year (range 0.1–9.1 years). The main reason for the first CVAD insertion was the start of prophylaxis (88% of initial implantations). Additional indications were the initiation of ITI therapy (10.3% of initial implantations) and difficult venous access (1.7% of initial implantations). Port access was frequent immediately after the first port insertion: six patients (10%) were using the port daily for ITI, 30 non-inhibitor patients (52%) every second day or three times per week, and 13 patients (22%) two times per week for prophylaxis. Most children (48/58; 83%) were managed with a single CVAD only or with a maximum of two ports. The median age at transition to peripheral veins was 8.2 (range 2.6–16.2). After the use of the device, heparin flushing was performed with the majority of CVADs (90/106; 85%); the rest were flushed with only saline. Table 2 presents detailed data on patients with CVADs.

Table 2. Characteristics of patients with CVADs

Number of patients	58
Bleeding disorder	
Factor VIII deficiency (%)	54 (93)
With inhibitor	11
Factor IX deficiency (%)	4 (7)
With inhibitor	0
Haemophilia severity	
Severe (%)	53 (91)
Moderate (%)	5 (9)
Indication for first CVAD insertion (%)	
Prophylaxis	51 (88)
ITI	6 (10.3)
Difficult venous access	1 (1.7)
Median age at initial CVAD insertion (range), years	1.0 (0.1-9.1)
Age at initial CVAD insertion (%), years	
<2	52 (90)
2-6	2 (3)
>6	4 (7)
Median age at transition to peripheral veins (range), years	8.2 (2.6-16.2)
Number of all CVADS	106
Number of CVADs per patient (%)	
One	25 (43)
Two	23 (40)
Three	6 (10)
Four	4 (7)

CVAD, central venous access device; ITI, immune tolerance induction

5.1.2 Outcome of CVADs

At the end of the follow-up period, 89 of the 106 CVADs (84%) had been removed and 17 CVADs (16%) were still in place (Table 3). The median duration of a CVAD was 1159 days (3.2 years; range 3-3778 days). Port duration in patients without inhibitors was longer (1501 median days) than those with inhibitors (782 days) ($p<.01$). The median ED before CVAD removal was 550 for all patients: 600 EDs for non-inhibitor patients and 365 EDs for patients with inhibitors ($p=0.04$).

Table 3. Outcome of all 106 CVADs

	No. CVADs (non-inhibitor patients), n=86	**No. CVADs (inhibitor patients), n=20**	**Total no. CVADs, n=106**	**Median duration, days**
CVADs Removed	**74**	**15**	**89**	**1227**
Infectious complications				
CVAD-associated bloodstream infection	9	3	12	937
Local skin/tunnel infection	3	2	5	846
Non-infectious complications				
Malfunction	19	2	21	1640
Mechanical	8	2	10	445
Thrombosis *in situ*	1	1	2	831
Uncomplicated removal (improved venous access)	34	5	39	1175
Still in use without any complication	**12**	**5**	**17**	**850**

CVAD, central venous access device

More than half (56/106; 53%) of the CVADs were used without any complication. After a median of 1175 catheter days, because of improved peripheral venous access, 39 ports (37%) were electively removed because they were no longer required. With 850 days of catheter time, 17 ports (16%) were still in use. Fifty of all the 106 CVADs (47%) required removal because of a complication, mostly a malfunction. Figure 2 and Table 4 summarize port survival and complication rates (CRs).

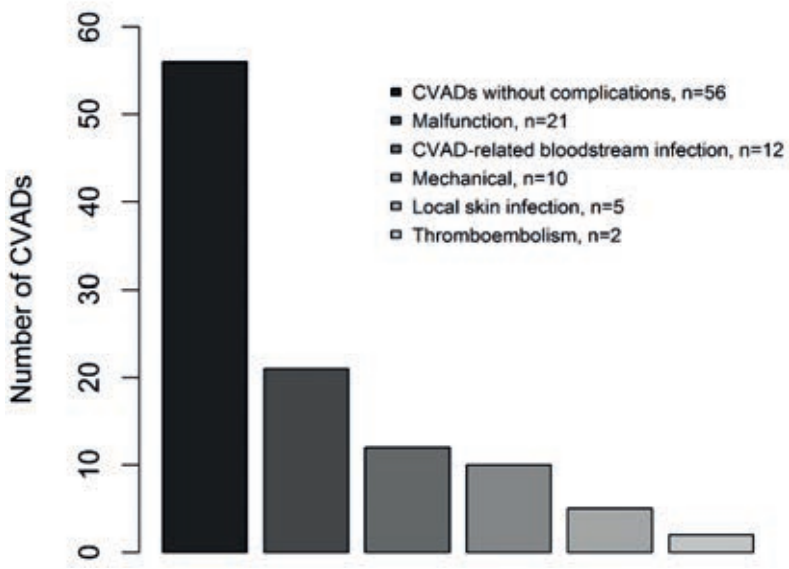

Figure 2. The outcome of all 106 CVADs. CVADs without complications include 39 ports removed after improved venous access (no longer required), and 17 ports still in use.
CVAD, central venous access device

Table 4. Complications associated with CVAD according to inhibitor status

	All patients (n=58)	**Non-inhibitor patients (n=47)**	**Patients with inhibitors (n=11)**	***p***
No. of CVADs	106	86	20	
Total no. of CVAD days	137971	122053	15918	
Median duration of CVAD placement (range), days	1159 (3-3778)	1501 (3-3507)	782 (21-3778)	<.01
Complications	Incidence rate, per 1000 CVAD days (CI)			
Malfunction	0.15 (0.10-0.23)	0.16 (0.10-0.24)	0.13 (0.03-0.50)	.67
CVAD-associated bloodstream infection	0.12 (0.08-0.20)	0.10 (0.06-0.17)	0.31 (0.13-0.75)	<.01
Mechanical	0.07 (0.04-0.13)	0.07 (0.03-0.13)	0.13 (0.03-0.50)	.64
Local skin/tunnel infection	0.03 (0.02-0.09)	0.02 (0.01-0.08)	0.13 (0.03-0.50)	.02
Thrombosis	0.01 (0.00-0.06)	0.01 (0.00-0.06)	0.06 (0.01-0.45)	.06

CVAD, central venous access device; CI, 95% confidence interval per 1000 CVAD days

5.1.2.1 Early complications

Two early complications occurred: one *Staphylococcus aureus* septicaemia within the first two weeks after CVAD positioning and one major bleed in the area of port entry. This bleed was recorded in a patient with an inhibitor, and it required CVAD removal three days after its insertion. No other complications, such as pneumothorax or arrhythmias, occurred as a consequence of the catheter insertion procedure. We detected no mortality due to any CVAD-related complication.

5.1.2.2 Non-infectious complications

The majority (66%; 33/50) of the complications requiring CVAD removal were non-infectious. Malfunction, a catheter blockade, or an occlusion in the absence of documented thrombosis, was associated with 21 of 106 CVADs (20%) after a long survival period, a median of 1640 CVAD days, with a CR 0.15 per 1000 CVAD days. Ten CVADs (9%) were removed because of a mechanical complication (CR 0.07) after a shorter survival period (445 CVAD days, median). Three of the mechanical complications were skin erosion over the port, three CVADs had to be removed after displacement (malpositioning of the catheter tip) and four after disconnection or splitting of the catheter. Two cases of clinically significant CVAD-related thrombosis, with port malfunction as the initial symptom, were recorded. One non-inhibitor patient had a thrombosis in the brachiocephalic vein; and a patient with an inhibitor suffered a thrombosis in the jugular vein during a bleeding episode, while being treated with bypassing agents without concomitant ITI.

5.1.2.3 Infectious complications

In 14 CVADs, 17 CRBSIs were detected, requiring removal in 12; CRBSI was the cause in 13% (12/89) of all port removals. The overall rate of bloodstream infection was very low: 0.12 infections per 1000 CVAD days. Three (18%) cases of 17 CVAD-related infections were detected when the child was under two years, four (23%) between two and six, and the rest (59%) when over six years. Five infections developed in three children with inhibitors (three infections during ITI), and 12 infections occurred in 11 children without inhibitors. Gram-positive organisms were responsible for CVAD-associated bloodstream infections. The most common organisms were *Staphylococcus aureus* (10/17; 59%) and *Staphylococcus epidermidis* (5/17; 29%), the former requiring port removal in 80% (8/10) and the latter in 60% (3/5) cases. *Bacillus cereus* and *Enterococcus faecium* both caused a single bloodstream infection, the former leading to port removal. Local skin or tunnel infections (n=5) requiring CVAD removal were rare.

5.1.2.4 Risk factors for CVAD-related complications

Inhibitors were a three-fold increased risk factor for higher infection rates. The bloodstream infection rate for children with inhibitors was 0.31 per 1000 CVAD days and for children without inhibitors 0.1 per 1000 CVAD days ($p<0.01$). Non-infectious CRs differed little between non-inhibitor and inhibitor patients (Table 5).

No difference existed in infection rate between heparinised and non-heparinised ports. The bloodstream infection rate per 1000 CVAD days was 0.11 for heparinised ports and 0.25 for non-heparinised ones ($p=.30$).

5.2 INCIDENCE OF, AND RISK FACTORS FOR, INHIBITOR DEVELOPMENT (STUDY II)

5.2.1 Patient characteristics

All PUPs with severe HA (n=62) born between June 1994 and May 2013 were included; the follow-up lasted until ID was detected or until they had been administered FVIII for at least 75 EDs by the end of the follow-up in September 2013. The study involved 61 boys and one girl with a baseline FVIII activity <0.01 IU mL^{-1}, clinically severe bleeding history, and a combination of a missense mutation and an inactive FVIII gene in the other X chromosome. Sixty patients (97%) were Caucasians. Only 36 children (58%) had a family history of

haemophilia; among these, five (14%) had a history of ID. Overall, 51 were genotyped; three patients had no mutation found. The mutation in the family was known in another 11 children; a brother with haemophilia or a carrier mother, or both, had been previously genotyped. Thus, 59 patients (95%) had a known FVIII genotype; 46 (74%) had a high-risk mutation, whereas 13 (21%) had a low-risk mutation. Table 5 delineates patient characteristics.

Table 5. Characteristics of patients included in studies II-III

PUPs with severe haemophilia A		62
Caucasian (%)		60 (97)
Median age at diagnosis, months (range)		0.7 (0-14.8)
FVIII genotype (%) according to inhibitor risk		
High-risk		46 (74)
	Intron 22 inversion	24
	Intron 1 inversion	1
	Nonsense mutation	15
	Large deletion	6
Low-risk		13 (21)
	Missense mutation	9
	Small deletion	3
	Small insertion	1
No mutation found		3
Family history of haemophilia (%)		
No		26 (42)
Yes		36 (58)
	Negative for inhibitors	31
	Positive for inhibitors	5

PUPs, previously untreated patients; FVIII, coagulation factor VIII

5.2.2 Treatment history

5.2.2.1 First FVIII exposure

The median age at first exposure to FVIII was nine months (0–16.2 months). The most frequent reason for the first FVIII administration was a bleed (69%). Six children (10%) were first treated for prophylaxis and 12 (19%) natively for a CVAD placement in order to start prophylaxis via a port. One child was treated for another surgical procedure, a tympanoplasty. The initial product was an rFVIII product in 39 patients (63%) and a pdFVIII product in 23 (37%) (Amofil® in 19, Haemate® in three, and a cryoprecipitate in one case in 1994–1995). In 15 (24.2%), the clotting factor concentrate was later switched during the first 75 EDs, following the national strategy to offer children the rFVIII replacement. Table 6 presents more detailed treatment characteristics.

5.2.2.2 Treatment intensity during subsequent exposure days to FVIII

FVIII exposure during the first 75 EDs or before ID was intensive (Table 6). The majority (84%) of the 62 patients were treated for a bleeding event or surgery for at least five consecutive days. Sixty children (97%) had a history of a surgical procedure (mainly port implantation) and 20 (32%) of a major bleed. Nine of the 51 children (17%) with primary prophylaxis, and all 11 (100%) with secondary prophylaxis had a major bleed during the first 75 EDs or before ID ($P < 0.01$).

Table 6. Treatment characteristics of patients (n=62) in studies II and III. Reprinted with the kind permission of Wiley.

	Number (%) or median (range)
First exposure to FVIII	
Indication	
Prophylaxis	6 (10)
Bleeding episodes	43 (69)
Soft tissue	31 (50)
Mucosal	6 (10)
Joint	4 (6)
Intracranial	2 (3)
Surgery	13 (21)
CVAD implantation	12 (19)
Surgical procedure other than a CVAD placement	1 (2)
Age at first exposure to FVIII, months	9.0 (0-16.2)
Type of FVIII product	
pdFVIII products	23 (37)
rFVIII products	39 (63)
1st Generation Full-Length	14 (23)
2nd Generation Full-Length	8 (13)
3rd Generation Full-Length	2 (3)
2nd Generation B-domain deleted	14 (23)
3rd Generation B-domain deleted	1 (1)
Peak treatment moment* at first exposure	
≥3 days	22 (35)
≥5 days	15 (24)
≥10 days	7 (11)
Treatment intensity during the first 75 EDs or before ID	
Peak treatment moments*	
≥3 days	60 (97)
≥5 days	52 (84)
≥10 days	14 (23)
History of a major surgery#	60 (96.8)
History of a major bleed[¥]	20 (32)
Switching of concentrate during the first 75 EDs or before ID	15 (24)

FVIII, factor VIII; CVAD, central venous access device; pdFVIII, plasma-derived FVIII; rFVIII, recombinant FVIII; ED, exposure day. *Peak treatment moment, an episode of FVIII replacement for a bleed or a surgery on at least three consecutive days. #Major surgery, a surgical procedure requiring replacement therapy at least for three consecutive days. [¥]Major bleed (Schulman, Kearon & Subcommittee on Control of Anticoagulation of the Scientific and Standardization Committee of the International Society on Thrombosis and Haemostasis 2005)

5.2.2.3 Prophylaxis

All patients were on regular prophylaxis started after a median of four EDs and almost exclusively (92%) via CVADs. All five (8%) children who started prophylaxis by peripheral intravenous infusion underwent port implantation during the first 75 EDs. Patients started prophylactic FVIII infusions with a median (range) dose of 28 IU kg^{-1} (21–50). 16 children (26%) were infused with a coagulation factor twice weekly and half of the cohort at least thrice weekly. Fifty-one (82%) fulfilled the criterion for primary prophylaxis, while secondary prophylaxis was used in 11 children (18%). Primary prophylaxis was started at

the median age of 11.4 months (0.8–23.6), and after a median of 2ED. Secondary prophylaxis was started at the median age of 15.6 months (7.7–51.2) and after a median of 11ED. Thirty-seven (73%) with primary prophylaxis and nine (82%) with secondary prophylaxis had a high-risk genotype. Table 7 provides more detailed prophylaxis data.

Table 7. Regimen of prophylaxis. Reprinted with the kind permission of Wiley.

	Number (%) or median (range)
Regular prophylaxis†	
Patients	62 (100)
Patients initiating prophylaxis during the first 75 EDs	57 (92)
Age at the onset of prophylaxis, months	11.8 (0.8-51.2)
EDs at the onset of prophylaxis	4 (0-641)
Dose of FVIII at onset (IU/kg)	28 (20.6-50)
Prophylaxis at least thrice a week	34 (55)
Prophylaxis at least twice a week	54 (87)
Type of venous access at onset	
Peripheral veins	5 (8)
CVAD	57 (92)
Primary prophylaxis¶	
Patients	51 (82)
Patients with high-risk genotype	37 (73)
Age at the onset of prophylaxis, months	11.4 (0.8-23.6)
EDs at the onset of prophylaxis	2 (0-146‡)
Type of venous access at onset	
Peripheral veins	5 (10)
CVAD	46 (90)
Secondary prophylaxis§	
Patients	11 (18)
Patients with high-risk genotype	9 (82)
Age at onset, months	15.6 (7.7-51.2)
EDs at the onset of prophylaxis	11 (2-641)
Type of venous access at onset	
CVAD	11 (100)

ED, exposure day; FVIII, factor VIII; CVAD, central venous access device
†Regular prophylaxis, regular and long-term administration of FVIII concentrate at least once a week aimed at preventing bleeds; ¶Primary prophylaxis, regular prophylaxis started before age two and before the onset of the first joint bleed; ‡ The patient with 146 EDs at the onset of primary prophylaxis was a boy who started prophylaxis before age two and before the first joint bleed but after successful immune tolerance induction; §Secondary prophylaxis, regular prophylaxis started later than age two or after the first joint bleed

5.2.3 Inhibitor development

In total 13 (21%) patients developed a clinically significant inhibitor, 10 (16%) of these high titre (Fig. 3). Of the 46 patients with a high-risk genotype, nine (20%) had high-titre inhibitors and two (4%) low-titre ones. Of the 13 children with a low-risk mutation, one (8%) had a high-titre inhibitor and another a low-titre inhibitor. Inhibitors were first detected at the median (range) age of 11.7 months (7.2–27.7) after a median (range) of 19 EDs (10–61). The median (range) peak titre was 14 BU mL^{-1} (1.7–42). None of the detected inhibitors was transient.

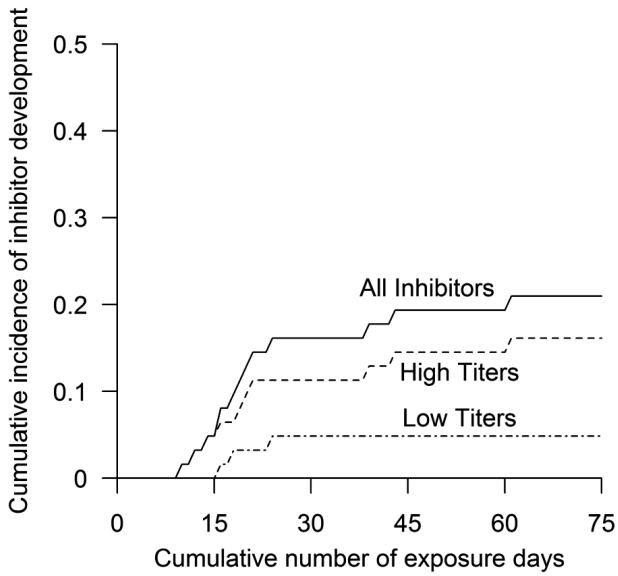

Figure 3. Cumulative incidence of inhibitor development according to cumulative number of factor VIII exposure days for all inhibitors, high-titre, and low-titre inhibitors. Reprinted with the kind permission of Wiley.

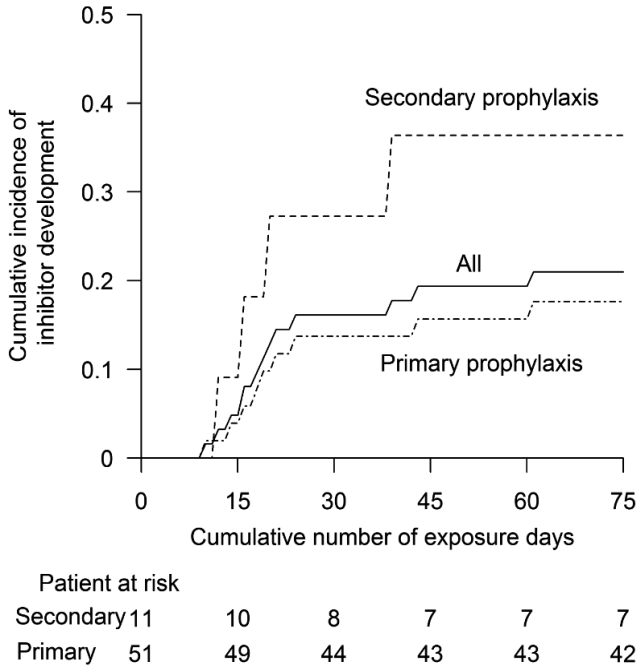

Figure 4. Influence of primary versus secondary prophylaxis on the cumulative incidence of inhibitor development. Reprinted with the kind permission of Wiley.

5.2.4 Patient-related risk factors for inhibitor development

No significant differences existed in patient-related risk factors between patients with and without inhibitors (Table 8). The FVIII genotype had no association with ID risk; inhibitors occurred in 11/46 (23.9%) with high-risk mutations and in 2/13 (15.4%) with low-risk mutations (p=0.67). Neither ethnicity (p=0.68) nor family history (p=0.30) of an inhibitor was a risk factor for ID.

5.2.5 Treatment-related risk factors for inhibitor development

A history of major bleeds during the first 75 EDs was a significant risk factor for ID: inhibitors occurred in 8/20 (40%) patients with a bleeding history and in 5/42 (11.9%) without one [adjusted hazard ratio (aHR), 4.0; 95% CI, 1.2–13.7]. Patients with primary prophylaxis had a 50% lower risk of ID (aHR, 0.5; 95% CI, 0.1-1.6), the incidence of overall ID being 17.6% in primary prophylaxis patients and 36.4% in secondary prophylaxis ones (Fig. 4). The incidence of high-titre inhibitors in primary prophylaxis patients was 13.7%; in secondary prophylaxis patients, it was 27.3%, (p=0.53).

The use of a pdFVIII or an rFVIII product as the first replacement therapy was not a risk factor (P = 0.44); neither were the age at first exposure (P = 0.33) nor a product switching (P = 0.40). Inhibitor incidence presented no association with the indication of the first exposure, FVIII treatment intensity, nor a history of major surgery. A history of a port implantation during the first 75 EDs and of peak treatment moments for at least five days was associated, with lower ID incidence (P < 0.01 and P = 0.04 respectively). aHR for ID according to patient- and treatment-related factors differed little from the crude hazard ratio (Table 8).

Table 8. Patient-related and treatment-related risk factors for ID. Reprinted with the kind permission of Wiley.

	N	N inh (%)	HR (95% CI)	p	aHR (95% CI)	p
Patient-related risk factors						
Ethnicity						
Caucasian	60	12 (20)	1		1	
Non-Caucasian	2	1 (50)	2.6 (0.3-20.0)	.36	3.5 (0.3-36.3)	.30
FVIII genotype						
Low-risk	13	2 (15.4)	1		1	
High-risk	46	11 (23.9)	1.6 (0.4-7.2)	.54	1.4 (0.3-6.5)	.67
Family history of an inhibitor						
No	57	12 (21.1)	1		1	
Yes	5	1 (20.0)	0.9 (0.1-7.3)	.96	0.6 (0.1-5.8)	.68
Treatment-related risk factors						
First exposure to FVIII						
Age at first exposure, months						
Less than 9 months	31	8 (25.8)	1		1	
9 months or more	31	5 (16.1)	0.6 (0.2-1.8)	.34	0.6 (0.2-1.8)	.33
Indication						
Surgery	13	2 (15.4)	1		1	
Prophylaxis	6	0 (0.0)	0.0 (0.0-0.0)	.98	0.0 (0.0-0.0)	.99
Bleed	43	11 (25.6)	1.8 (0.4-8.0)	.46	1.1 (0.2-5.5)	.86
Type of FVIII product						
rFVIII	39	7 (17.9)	1		1	
pdFVIII	23	6 (26.1)	1.5 (0.5-4.5)	.47	1.6 (0.5-5.0)	.44
Peak treatment moment*						
No	40	7 (17.5)	1		1	
Yes	22	6 (27.3)	1.7 (0.6-5.1)	.33	2.4 (0.7-7.6)	.15
Primary Prophylaxis¶						
No	11	4 (36.4)	1		1	
yes	51	9 (17.6)	0.4 (0.1-1.4)	.16	0.5 (0.1-1.6)	.24

Continues

Table 8. (Continues)

Treatment intensity during the first 75 EDs or before ID						
Peak treatment moment						
<5 days	10	5 (50)	1		1	
≥5 days	52	8 (15.4)	0.3 (0.1-0.8)	.02	0.3 (0.1-0.8)	.04
History of a major surgery#						
No	2	2 (100)	1		1	
CVAD implantation	56	8 (14.3)	0.05 (0.0-0.3)	<.01	0.1 (0.1-0.3)	<.01
Surgical procedure other than CVAD placement	4	3 (75.0)	0.6 (0.1-3.7)	.56	1.7 (0.2-15.7)	.63
History of a major bleeding¥						
No	42	5 (11.9)	1		1	
Yes	20	8 (40.0)	3.9 (1.3-11.9)	.02	4.0 (1.2-13.7)	.03
Switching during the first 75 EDs or before ID						
No	47	8 (17.0)	1		1	
Yes	15	5 (33.3)	2.1 (0.7-6.5)	.19	2.0 (0.5-7.9)	.40

All associations were adjusted for FVIII genotype, the type of the FVIII product, family history of inhibitor development, and ethnicity.

N inh, number of inhibitor patients; HR, hazard ratio; aHR, adjusted hazard ratio; ID, inhibitor development; FVIII, factor VIII; rFVIII, recombinant FVIII; pdFVIII, plasma-derived FVIII; ED, exposure day

*Peak treatment moment, an episode of a treatment with FVIII for a bleeding or a surgery on at least three consecutive days; ¶Primary prophylaxis, regular prophylaxis started before age two and before the onset of the first joint bleeding; #Major surgery, a surgical procedure requiring replacement therapy for at least three consecutive days; ¥Major bleeding (Schulman, Kearon & Subcommittee on Control of Anticoagulation of the Scientific and Standardization Committee of the International Society on Thrombosis and Haemostasis 2005)

5.3 LONG-TERM CLINICAL AND ECONOMIC OUTCOMES (STUDY III)

5.3.1 Patients

The patient cohort (62 PUPs with severe HA) was the same as in study II; see Table 5. One child with a severe immunodeficiency, a chronic granulomatous disease, was included in the study; we excluded costs unrelated to haemophilia care, such as costs related to treatment at the stem cell transplantation unit. With the end of the follow-up in September 2013, the median follow-up time was 12.7 years (range 1.2-19.3), with a cumulative follow-up time of 698 person-years. During the follow-up, 13 (21%) children developed a clinically significant inhibitor, 10 (16%) a high-titre one.

5.3.2 Treatment

Treatment characteristics during the first 75 EDs were the same as in study II (Table 6). All our patients were on regular prophylaxis. Fifty-one (82%) fulfilled the criterion of primary prophylaxis, while 11 children (18%) had secondary prophylaxis initiated. The median age of starting home treatment was 1.1 years. During the 19-year follow-up, the median frequency of prophylactic FVIII concentrate infusions was three times a week, with a median dose of 26 IU kg^{-1} (IQR, 22-32). The median annual FVIII used in prophylaxis was 4136 IU kg^{-1} (IQR, 3250-5113). Trough levels of FVIII served to guide prophylactic treatment in 11 patients (18%).

5.3.3 Validation

Comparing the annual prophylactic FVIII consumption data extracted from the medical records with the patient-specific data obtained from the Finnish Prescription Register (2012), we found no significant differences among the patients included in the validation sample. The prophylactic FVIII median consumption observed was 4136 IU kg^{-1} (IQR, 3250-5113) in the medical record data and 4722 IU kg^{-1} (IQR, 3510-5777) in the national register data.

5.3.4 Long-term clinical outcomes

Table 9 displays long-term clinical outcomes. During the follow-up of 19 years, 25 (40%) of our patients experienced no joint bleeds; 71% of those who did had less than three. Median ABR was 0.19 (IQR, 0.07-0.46), and median AJBR was 0.06 (IQR, 0-0.24). Inhibitor development was a significant (three-fold) risk factor for a higher overall bleed rate, but not for a higher joint bleed rate; ABR was 0.16 in non-inhibitor patients; in inhibitor patients, it was 0.49 ($p<0.001$). AJBR was 0.06 in non-inhibitor patients; in inhibitor patients, it was 0.15 ($p= 0.26$).

In contrast, ABR (0.17) and AJBR (0.06) were three- to four-fold lower among primary prophylaxis patients compared with patients who received secondary prophylaxis: ABR 0.52 ($p= 0.04$) and AJBR 0.26 ($p= 0.001$)). Four non-inhibitor patients (6%) had a traumatic intracranial bleed early in their childhood. No deaths occurred during the follow-up. Hospital inpatient days were rarely necessary (2.5 per patient annually), with approximately two routine annual outpatient visits to haemophilia centres.

Table 9. Long-term outcomes of PUPs with severe haemophilia A

	All patients, n=62	**Non-inhibitor patients, n=49**	**Patients with an inhibitor history, n=13**	**p**
ABR, median (IQR)	0.19 (0.07-0.46)	0.16 (0.03-0.33)	0.49 (0.22-0.83)	<0.001
AJBR, median (IQR)	0.06 (0-0.24)	0.06 (0-0.21)	0.15 (0-0.26)	.26
Patients with 0 joint bleed, n (%)	25 (40)	21 (43)	4 (31)	.32
Patients with 1 joint bleed, n (%)	15 (24)	12 (25)	3 (23)	
Patients with 2 joint bleeds, n (%)	4 (7)	3 (6)	1 (8)	
Patients with ≥3 joint bleeds, n (%)	18 (29)	13 (26)	5 (38)	
Patients with a target joint, n (%)	10 (16)	9 (18)	1 (8)	.68
Patients with arthropathy, n (%)	4 (6)	4 (8)	0 (0)	.26
Hospital inpatient days, per year, median (IQR)	2.5 (1.4-4.2)	2.4 (1.3-4)	3.9 (1.9-7.5)	0.09
Visits to outpatient clinic, per year, median (IQR)	2.2 (2.0-3.0)	2.0 (1.9-3)	2.7 (2.4-3.9)	<.01

PUPs, previously untreated patients; ABR, annualised bleeding rate; AJBR, annualised joint bleeding rate; IQR, interquartile range

Ten (16%) patients developed a target joint; four (6%) children developed chronic arthropathy, two of them requiring synovectomy. At the end of the follow-up, in non-inhibitor patients, the incidence of a target joint was 18% and that of an arthropathy was 8%; in inhibitor patients, the incidence was 8% and 0%. These differences were nonsignificant. Children with primary or secondary prophylaxis had the same incidence of a target joint or an arthropathy.

During these 698 patient-years of follow-up, our 62 subjects suffered 23 CVAD-related infections. They had 18 CVAD-associated bloodstream infections and five local tunnel infections, corresponding to 3.3 CVAD-related infections per 100 person-years.

Of the 13 inhibitor patients, 12 (92%) initiated ITI; in one case with a titre drop of 45% to 15 BU/mL 4 months from ID, ITI was postponed. Eleven patients (92%) completed ITI after a median duration of 8.7 months (range 4.1-30.1), all achieving tolerance with either complete success (in 4/11 of children; 36%) or partial success (7/11; 64%). One HR remained in ITI after an 18-month therapy, with the inhibitor declining to 1.9 BU/mL. A recurrence with a peak inhibitor titre of 24 BU/mL occurred in one patient a decade after ITI, at the age of 14; 17 months of re-ITI led to complete success.

5.3.5 Long-term economic outcomes

During the 698 patient-years of follow-up, the mean (SD) annual treatment costs were 97 005€ (65 465) per patient and 4 391€ (3 852) per weight kg. These mean annual weight-adjusted costs were 2.8-fold (95% CI 1.9-4.1) higher in the case of inhibitor patients. For patients

without an inhibitor, they were 3 154€ (95% CI, 2 887-3 446); for patients with an inhibitor, they were 8 691€ (95% CI, 6 142-12 298, p< 0.01).

Figure 5 shows the mean costs per patient, and Figure 6 shows per patient and body weight adjustment, according to the treatment entity and age group. Prophylactic FVIII treatment accounted for the main cost; ages one to three were an exception, with ITI accounting for more than half of the total costs. The mean annual costs for FVIII prophylaxis increased with age until seven, reaching 3 172€ per kg (95% CI 2915-3455). Thereafter, they gradually decreased and reached 2 246€ per kg (95% CI 1717-2857) at the age of 18. Mean annual total costs between prophylactic regimens were about the same: 4 437€ per kg (95% CI 3 431-5 738) for patients with primary prophylaxis and 4 183€ per kg (95% CI 3 170-5 519, p=0.76) for those with secondary prophylaxis. The proportion of costs related to hospitalization and outpatient visits were 51% for age zero and 11% for age one. However, from age two, clotting factor consumption dominated costs, accounting for over 94% of the total costs. The group using trough level guidance (n=11) exhibited a trend towards lower annual prophylactic FVIII consumption (median 3645, IQR 2889-4588) compared to the group with untested trough levels (n=51) (median 4330, IQR 3391-5200, (p=0.12).

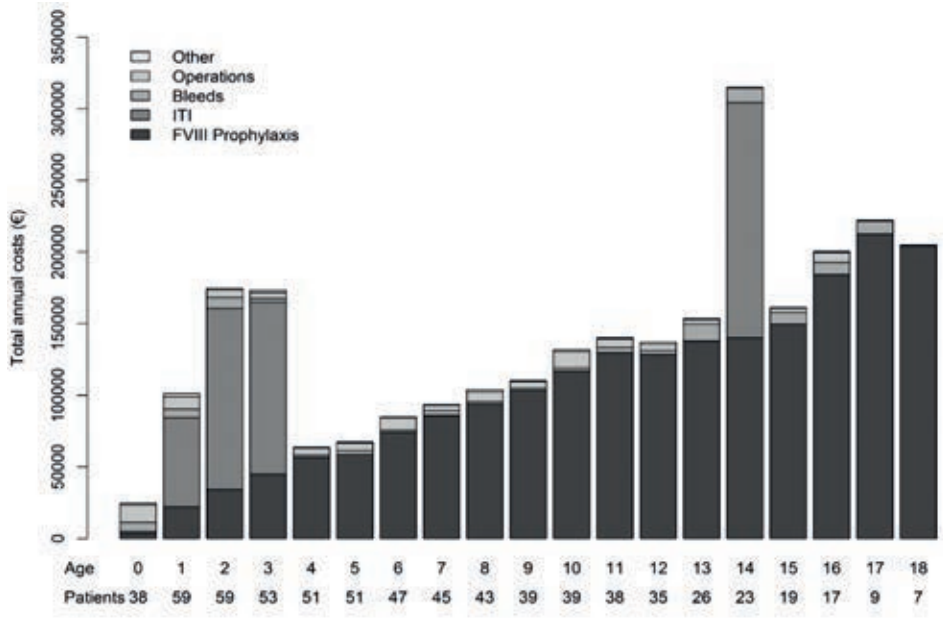

Figure 5. Mean total costs by age group according to a treatment entity. Reprinted with the kind permission of Wiley.

Bleeds: Including costs for visits to outpatient clinic, hospitalization and coagulation factors during the bleeding episode
Operations: Including costs for surgery, hospitalization and coagulation factors
Other: Including costs for regular hospital visits in outpatient clinic, hospitalization for CVAD-related infections, and prophylaxis with rFVIIa in two patients

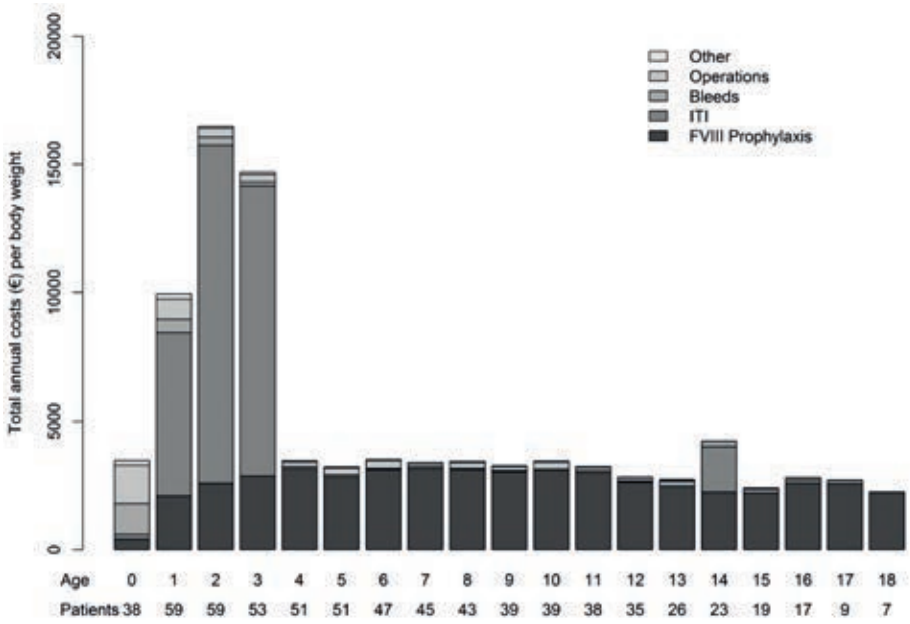

Figure 6. Mean total costs per weight by age group according to a treatment entity. Reprinted with the kind permission of Wiley.

Bleeds: Including costs for visits in outpatient clinic, hospitalization and coagulation factors during the bleeding episode
Operations: Including costs for surgery, hospitalization and coagulation factors
Other: Including costs for regular hospital visits in outpatient clinic, hospitalization for CVAD-related infections, and prophylaxis with rFVIIa in two patients

The mean (SD) cost of ITI was 383 448€ (259 085). In the patient who had an inhibitor recurrence at age 14, the costs of ITI exceeded 3 483 120€. For this boy, the first ITI cost at age three was 352 590€. We calculated the mean total costs per person-month and per weight for inhibitor patients based on the period: before or after ID, and before or after ITI. After inhibitor detection, mean (SD) monthly costs in € kg^{-1} quintupled from 259 (229) up to 1473 (1984); during ITI, they further doubled to 3097 (2039). After ITI completion, the mean monthly € kg^{-1} costs decreased to 316 (97), nearly as low as in non-inhibitor patients (mean, 275, SD, 76). The expected payback period on ITI completion was 1.81 (95%CI 0.62-12.12) years, which indicates a relative short payback period in terms of annual cost savings.

6 Discussion

This is the first nationwide survey of haemophilia treatment in Finland including all PUPs with severe HA (n=62) born between June 1994 and May 2013. Nearly 30 years ago, Rasi et al. reported a 17.3% prevalence of inhibitors and a 22% cumulative risk of inhibitors at age 10 among 60 Finnish patients with severe HA receiving mainly on-demand therapy and only with pdFVIII (Rasi, Ikkala 1990). Since then, early regular prophylaxis via CVADs and more intensive FVIII treatment has been implemented.

We found that the Finnish treatment practice involving early high-dose primary prophylaxis via ports is safe: infectious complication rates were low and port survival long. The incidence of ID was low: 21% (16% of high titre). Clinical outcomes were excellent, annualised bleeding rates being near zero. Undertaking prophylactic factor concentrate administration via ports effectively prevents bleeds and subcutaneous exposure to FVIII and thereby decreases inhibitor incidence. Our experience emphasizes the safety of early primary prophylaxis via ports in very young children, which enables early home treatment.

This population-based study of inhibitor development and the long-term clinical and economic outcomes of treatment of PUPs with severe HA is the first of its kind using RWD and including all treatment data during a 19-year follow-up period. In addition, we report all direct treatment costs per patient and body weight. Reliable national data on long-term treatment costs (with RWD) are now available for future use and support critical decision-making related to new, and potentially more expensive, products.

6.1 COMPLICATIONS ASSOCIATED WITH CVAD (STUDY I)

6.1.1 Infectious complications

This relatively large nationwide study of 106 CVADs in 58 paediatric patients with 137 971 CVAD follow-up days observed a very low CVAD-related bloodstream infection rate: 0.12/1000 CVAD days for all patients and 0.10/1000 for non-inhibitor patients. Infection rates are less than half of those previously reported (Ljung 2007, Titapiwatanakun et al. 2009, Yeoh et al. 2013, Mancuso et al. 2008, Van Dijk et al. 2004, Bollard et al. 2000, McMahon et al. 2000, Tarantino et al. 2003, Valentino et al. 2004). Our median catheter life of 1159 days is twice as long the 578 days in a meta-analysis (Valentino et al. 2004). Only one small single-centre study with 44 CVADs (Upadhyaya et al. 2009) has reported a similar low infection rate (0.13/1000 CVAD days). In our study, bloodstream infection was the cause of removal only in 13% (12) of all removals (n=89), far less than reported earlier (34-70% of all removals) (Valentino et al. 2004, Khair et al. 2017). Our low frequency of complications may reflect meticulous and harmonized techniques, a centralized insertion policy, as well as the specific aseptic training program for and the skilled nursing and strong support of, the parents who maintain these devices at home.

A large meta-analysis showed that young age at insertion significantly increased the risk for infections: patients over six years were 46% less likely to develop infection than younger children (Valentino et al. 2004). Considering our patients' very young age at CVAD insertion

(90% of children were under two at first port implantation), our results with a very low infectious CR are even more remarkable; the data supports our strategy of using ports and maintaining prophylaxis after their implantation.
Inhibitors tripled CVAD-related bloodstream infection rates. This is consistent with other studies, which concluded that inhibitors at insertion significantly increased risk of infection (Valentino et al. 2004, Titapiwatanakun et al. 2009, Mancuso et al. 2008, Van Dijk et al. 2004). The reason is mostly more frequent, usually daily, device usage during ITI.
Many centres recommend the use of heparin to flush CVADs and to prevent catheter occlusion. However, the need for heparin is debatable; data on the benefits of heparin vs. normal saline as a port-locking solution are lacking (Bradford, Edwards & Chan 2015). Heparin flushing may prevent catheter-related infections; thus, our aim was to evaluate whether the use of heparin is related to lower infection rates. A prospective, randomized trial with 203 tunnelled central venous catheters in paediatric patients with cancer observed an increased bacteraemia rate with saline flushing compared with heparin flushing (Cesaro et al. 2009). In our study, heparin flushing after port usage had no influence on bloodstream infection rates.

6.1.2 Non-infectious complications

Non-infectious complications were the most common reason for CVAD removal. Our incidence of mechanical complications is similar to that previously reported (Titapiwatanakun et al. 2009), but the malfunction rate seems to be higher than that in earlier reports (Yeoh et al. 2013, Mancuso et al. 2008, Upadhyaya et al. 2009). Indwelling duration before removal for malfunction was even longer than median catheter life (1640 vs. 1159 CVAD days). Some malfunctions may be due to the increase in the age of the patient and growth; for example, the catheter tip may be dislodged during the growth of the child.
In our cohort, two clinically significant thrombotic complications were observed with a CR of 0.01 per 1000 CVAD days; however, in a large meta-analysis, the CR of thrombosis was 0.06 per 1000 CVAD days (Valentino et al. 2004). Both these incidences reported may be underestimates because most CVAD-related thrombi are probably clinically silent (Kamphuisen, Lee 2012). A recent study investigating 20 children screened by MRI after the removal of a CVAD found a high number of cases of silent DVT; 25% of these patients had abnormal MRI, consistent with DVT (Ranta et al. 2012).

6.2 INCIDENCE OF, AND RISK FACTORS FOR, INHIBITOR DEVELOPMENT (STUDY II)

6.2.1 Incidence of inhibitor development

In the present study among PUPs with severe HA during a long follow-up of 19 years, cumulative ID incidence was only 21% (16% of high titre) despite the majority having high-risk mutations and intensive, mainly rFVIII, exposure. The inhibitor incidence in this nationwide cohort is lower than those from previously published data, in which approximately a third of PUPs developed inhibitors (Gouw et al. 2013, Wight, Paisley 2003, Gouw et al. 2013, Calvez et al. 2014, Collins et al. 2014, Marcucci et al. 2015, Peyvandi et al. 2016). In Finland, the cumulative incidence of ID has remained unaltered for decades. In 1990, Rasi et al. (Rasi, Ikkala 1990) reported a 22% cumulative risk of inhibitors at age 10 among 60 patients with severe HA receiving mainly on-demand therapy and only with pdFVIII. Since

then in Finland, early regular prophylaxis, implantation of ports for all children, and more intensive FVIII treatment mainly with rFVIII, have increased the quality of life as regards joint health and practical prophylaxis via ports at home, but without increasing ID incidence. Due to several confounding treatment-related risk factors for ID and the fact that inhibitors occur mainly in PUPs, previously treated patients (PTPs) were excluded from study II. Including a cohort of all consecutive PUPs avoided selection bias concerning inhibitor incidence.

6.2.2 Patient-related risk factors for inhibitor development

Patient-related risk factors reported earlier, such as high-risk FVIII genotype, African ethnicity, or family history of an inhibitor (Astermark 2012, Gouw et al. 2012, Bardi, Astermark 2015, Astermark et al. 2013), had no association with ID risk in our study. This may be attributable to a small sample size and lack of African ethnicity.

6.2.3 Treatment-related risk factors for inhibitor development

Patients with a history of a major bleed were clearly predisposed to ID. Earlier, clear evidence of the effect of a major bleeding was lacking; it is difficult to separate the independent inhibitor risks caused by the intensive treatment, a bleeding event itself, or both. However, in a single study with 99 PUPs, a history of a haemarthrosis associated with an increased inhibitor risk (Vezina et al. 2014). In addition, intracranial bleeding exhibited a trend towards higher inhibitor incidence (Maclean et al. 2011, Vezina et al. 2014).

Primary prophylaxis reduced the incidence of inhibitor formation: the incidences of overall inhibitors (36.4%) and high-titre inhibitors (27.3%) were twice as high in secondary prophylaxis patients compared to primary prophylaxis ones (17.6% and 13.7%). However, the statistical difference was nonsignificant, likely due to the small number of subjects. Another reason might be the high proportion (74%) of a high-risk FVIII genotype in our survey, which may have precluded our patients from the most protective benefit of early prophylaxis. According to earlier reports, the potential protective effect of prophylaxis is more profound in low-risk FVIII genotype patients (Gouw et al. 2013).

We were unable to dissociate inhibitor incidences between patients treated with rFVIII or pdFVIII products, consistent with previous large cohort studies (Gouw et al. 2013, Fischer et al. 2015). However, our results conflict with a recent randomized study comparing the class effect between pdFVIII and rFVIII products (Peyvandi et al. 2016). In our patients, switching between FVIII product brands posed no increase in ID risk, consistent with other studies (Gouw et al. 2013, Santagostino et al. 2015).

In our study, regular prophylaxis was started almost exclusively (92%) via CVADs; for these port implantations, treatment intensity was initially high, but tapered down to prophylactic doses. At the first FVIII exposure, treatment intensity itself did not increase inhibitor risk; neither did a history of a major surgery or intense FVIII treatment later during the first 75 EDs. The first finding conflicts, but the latter ones are consistent, with previous findings (Gouw et al. 2013, Gouw, van der Bom & Marijke van den Berg 2007, Maclean et al. 2011). A history of a port implantation associated with lower ID incidence, likely due to our small sample size and either ongoing or immediately initiated prophylaxis. In addition, in the RODIN study (Gouw et al. 2013), a major surgical procedure during the first 75 EDs did not enhance ID risk. There, after surgical procedures for reasons other than CVAD, the aHR (95% CI) for ID was 1.4 (0.74–2.6), whereas the aHR for port implantation was 0.84 (0.51–1.4). In

conclusion, our data support the strategy of using ports and maintaining prophylaxis after their implantation.

The association between intensive FVIII treatment and ID may be partially attributable to a reverse causation; major bleeding and subsequent intensive treatment may be due to inhibitors undetected yet, not vice versa (Gouw et al. 2013). In our study, only in one case, the bleeding episode preceded ID by four days; all the others had a major bleed at least three weeks before inhibitor detection.

Kurnik et al. and Auerswald et al. reported promising preliminary results of a very low inhibitor incidence (2.5%) among 40 PUPs treated with an early prophylaxis/FVIII tolerization regimen that introduces low FVIII doses (approximately 25 IU kg^{-1}), administered once weekly upon observation of a bleeding tendency. This strategy avoided immunological danger signals by postponing vaccination and avoiding the use of CVADs and other elective surgery during the early FVIII exposure days (Kurnik et al. 2010, Auerswald, Bidlingmaier & Kurnik 2012, Kurnik, Auerswald & Kreuz 2014). A prospective EPIC (Early Prophylaxis Immunological Challenge) study (Auerswald et al. 2015) was next undertaken, but it had to be terminated prematurely because of excessive ID: in six (31.6%) of all the 19 subjects and three (27.3%) of the 11 PUPs. Notably, among the EPIC study subjects, a large number of bleeding episodes (172 of all 193 bleeds; 89.1%) occurred during a once-weekly prophylaxis, whereas only 14 (7.3%) coincided with a twice-weekly prophylaxis. A frequent history of bleeds in the patients in the EPIC study may have had a potential effect on high inhibitor incidence, corresponding to our results.

Full prophylaxis gives excellent protection against joint bleeds and ICH (Andersson et al. 2017, Nijdam et al. 2015). In addition, our findings on major bleeds increasing inhibitor risk emphasize that we need to avoid the practice of waiting for a first joint or other significant bleed to occur before starting prophylaxis.

6.3 LONG-TERM CLINICAL AND ECONOMIC OUTCOMES (STUDY III)

To the best of our knowledge, our study is the first of its kind using RWD to examine the long-term clinical and economic outcomes of treatment of PUPs with severe HA, representing nearly 700 patient-years of follow-up. We evaluated not only the costs of regular prophylactic FVIII treatment but also other treatment entities, including costs of managing inhibitor patients, providing data on costs per body weight.

A few long-term outcome studies of adult non-inhibitor patients with regular prophylaxis have reported both clotting factor costs for prophylaxis and other health care costs such as surgery, hospitalization, and health care visits (Fischer et al. 2013, Carlsson et al. 2004). Most paediatric studies report only the costs of prophylaxis (Manco-Johnson et al. 2007, Gringeri et al. 2011); resource utilization and related costs are often estimated with hypothetical patients (Risebrough et al. 2008), without RWD involved. RWD, however, was the basis of our approach. Currently, real-world datasets are being increasingly collected to demonstrate clinical and economic outcomes in real-world health care settings; it is well known that treatment patterns and outcomes differ from those observed in randomized clinical trials. Reliable data about real-world practices provide relevant information to support decision-making related to new, and usually even more expensive, treatments.

6.3.1 Long-term clinical outcomes

Our study demonstrates that regular early high-dose primary prophylaxis of PUPs with severe HA leads to excellent long-term clinical outcomes: both ABR and AJBR are near zero. During the long follow-up (median 12.7 years), 40% of our patients experienced no joint bleed; of those who had breakthrough bleeds, two-thirds experienced fewer than three joint bleeds. Only two (3%) patients required a synovectomy, which was because of a chronic arthropathy. At the end of the follow-up, our patients were relatively young (median age 12.7). However, early childhood in particular is the critical treatment period, affecting long-term joint health in adulthood. In Swedish patients born in 1980 or later, and treated with high-dose prophylaxis from early childhood, no need existed for joint surgery by age 30 (Osooli et al. 2017). In all, with our early prophylaxis strategy and scarce joint bleeds during childhood, we can assume good long-term joint health also in adulthood.

Although only two children developed a chronic arthropathy requiring synovectomy, we need to evaluate whether we could avoid unwanted outcomes in patients in general and completely abolish target joints and arthropathy. Most of our patients (n=46, 74%) had their joint bleeds treated in hospital while a quarter (n=16) had treatment of joint bleeds at home after visiting the outpatient clinic or having informed the haemophilia clinic by phone. ABR and AJBR were lower in patients having treatment for joint bleeds in hospital (0.15 and 0) compared to those with home treatment (0.35 and 0.20), p= < .01). The incidences of a target joint and an arthropathy were also lower (7% and 0%) compared with ones preferring home treatment (44% and 25%), p=<.01 in both. Thus, the management of severe bleeds in a hospital with support and guidance on hand seems to be effective, at least for paediatric patients with severe haemophilia.

There is a need for ongoing follow-up of these patients with severe haemophilia and very expensive prophylactic treatment. A national haemophilia registry is a tool for monitoring costs and clinical outcomes and measuring rates of complications of bleeding disorders, including those related to disease itself and treatment product safety.

6.3.2 Long-term economic outcomes

The median (IQR) annual FVIII consumption in prophylaxis was 4136 IU kg^{-1} (3250-5113), and the mean (SD) overall total annual treatment costs per patient were 4391 € kg^{-1} (3852). The prophylactic FVIII dosing regimen in Finland corresponds to the high-dose Swedish one (Nilsson et al. 1992, Steen Carlsson et al. 2003, Berntorp et al. 2012). Although prophylaxis in Finland mainly employs central venous devices, the need for hospitalization was uncommon (median of only 2.5 hospital inpatient days per year). Costs related to hospitalization and outpatient visits constituted less than 6% of the total costs beyond age one. The quality of life was good as regards joint health and practical prophylaxis via ports at home. In addition, patient age at start of home treatment was low (median, 1.1 years) compared with other western countries: 3.3 years in Sweden (Fischer et al. 2013) and 4.0 in Denmark (Ingerslev et al. 2014).

The development of FVIII-neutralizing antibodies remains the most severe and costly complication of haemophilia therapy. The mean (SD) total costs for ITI were 383 448 € (259085) during early childhood, but they increased ten-fold by age 14 (3 483 120€). Despite the high costs, ITI therapy was highly effective; all patients who completed ITI achieved tolerance with either complete success (36%) or partial success (64%). Early childhood ITI

therapy was successful also in terms of joint bleed rates; no difference existed between non-inhibitor patients and patients with inhibitors.

In our study, after inhibitor detection, direct monthly total costs € kg^{-1} quintupled from 259 € to 1473 €, mainly due to the use of bypassing agents, corresponding to an annual total cost of 1.3 million € for an average-weight (75 kg) adult. During ITI, costs further doubled to 3097 €; but, after successful ITI, FVIII consumption through prophylaxis and total costs decreased to the level of non-inhibitor patients. The expected payback period estimate of less than two years indicates that ITI appears cost-neutral when comparing it with a hypothetical treatment strategy of not starting ITI but continuing with on-demand or prophylactic therapy with bypassing agents. Savings due to successful ITI fully offset the incremental costs due to FVIII used for ITI during the 1.81 years. This estimate is based on the small number of our patients with ITI and, thus, should be interpreted with caution. However, our results with RWD are in line with the findings from a recent health economic modelling study, which reported that the lifetime costs of treating adult patients with inhibitors are lower for ITI compared to on-demand or prophylactic treatment, with bypassing agents (Earnshaw et al. 2015). Without prospective randomized trials to confirm that treatment delay confers benefit, the current practice has been to delay the start of ITI until the inhibitor titre is <10 BU/mL, anticipating a higher success rate. In a retrospective study in two US haemophilia treatment centres, a titre >10 BU/mL at ITI start had no influence on outcome in 58 subjects who had ITI initiation within one month of detection (Nakar et al. 2015). In addition, health economic consequences emphasize the importance of prompt ITI, regardless of the inhibitor titre.

The standard deviation of the mean annual treatment costs was wide, representing the variability in treatment intensity and costs between non-inhibitor patients vs. patients with high-titre inhibitors using high-dose ITI therapy in combination with bypassing clotting agents. The wide variation of cost data between different studies, and even in between patients in the same study, has been found in several previous studies among non-inhibitor patients (Fischer et al. 2013, Valentino et al. 2012, Carlsson et al. 2004) and especially among inhibitor patients (Valentino et al. 2012, Auerswald et al. 2004, Earnshaw et al. 2015). Despite the wide deviation, mean total costs kg^{-1} remained stable during childhood except from ages one to three, and at age 14, when costs rose due to ITI (Fig. 6). Higher variation between mean costs per patient and cost increase by age indicates the natural effect of increasing weight (Fig. 5).

Though the clinical outcomes are favourable, the high total costs of therapy demand continued evaluation on how to reduce prophylactic FVIII doses, at least in certain patients. In a fifth of the cohort, trough levels of FVIII were used in prophylaxis guidance and resulted in 16% lower annual FVIII consumption (median of 3645, vs. 4330 IU kg^{-1}, p=.12) compared to the group with untested trough levels and without a predisposition to target joints or arthropathy. Even though a statistically significant difference was lacking, potential economic savings concerning these highly expensive medications could be remarkable.

Improved understanding of the effect of patients' pharmacokinetic (PK) profile in factor levels will help tailor individualised prophylactic therapy and better protect from bleeding complications; PK-tailored prophylaxis enables more cost-effective use of coagulation factor concentrates, especially in patients with long FVIII half-life (Collins et al. 2011). However, obtaining reliable individual estimates of PK-parameters has been hampered by the demanding sampling schedules and complex calculations. To eliminate barriers to the uptake of individualized PK-tailored haemophilia treatment, web-accessible population

pharmacokinetic solutions have recently became available (Iorio et al. 2017). The services are predicated on the development of validated brand-specific population PK models. By incorporating these tools into routine practice, clinicians can now achieve individual PK forecasting for several concentrates from only a few patient samples, and thus, being implement a more personalised dosing strategy with better bleeding control and at least potential cost reductions.

6.4 STRENGTHS AND LIMITATIONS OF THE STUDY

A strength was that our studies were nationwide multicentre studies, the second and third of them population-based, performed in all five Finnish paediatric Haematology-Oncology centres (Kuopio, Oulu, Turku, Tampere, and Helsinki, University Hospitals). The follow-up time was as long as 19 years in all these studies, from June 1994 until the end of the follow-up in September 2013.

6.4.1 Complications associated with CVAD (Study I)

CVAD care guidelines have been very uniform and congruent in Finland. However, a retrospective survey with a long study period of nearly two decades has its limitations of data integrity and a limited ability to detect all the changes in teaching techniques and training in port handling provided to the parents concerned at different centres during the follow-up period.

One strength of the study is the strictness employed in defining all the complications concerned; another is that, in reporting the infection rate, we included all CRBSIs, not only infections requiring port removal. A third strength was that this was a nationwide multicentre study recruiting all Finnish University hospitals although not all (66 of 90; 73%) patients with severe or moderate haemophilia born during the period of study I were included.

We recorded similar infection rates with heparinised and non-heparinised ports. However, in our study, the use of heparin was left to the discretion of the treating physician and not systemised; so the comparison remains descriptive. Thus, the preventive influence of heparin flushing on catheter-related infections remains unresolved; prospective evaluation of this practice should be conducted in the future. We recorded only two clinically significant thrombotic complications, but this finding may be an underestimate. The reason was that venograms, ultrasound, or MRI-angiography, were not routinely performed; thus, we were unable to assess the prevalence of silent thrombosis.

6.4.2 Incidence of, and risk factors for, inhibitor development (Study II)

Because of the retrospective nature of our study, we may have missed some transient non-significant inhibitors. Our aim, however, was to detect clinically relevant, symptomatic inhibitors. During the follow-up period, we did not systematically control possible inhibitors, contrary to what is suggested nowadays. However, we want to emphasize that our careful follow-up has not missed clinically significant inhibitors. We did perform recovery tests preoperatively, just before CVAD implantations and at the start of prophylaxis, in 63% (39 of 62) of our patients. Among the rest, preoperatively, coagulation factor levels were untested, but postoperative bleeding episodes did not occur. The limitations of the study are its small

sample size and a low-risk ethnic population (97% Caucasian); in contrast, the majority (74%) had a high-risk ID genotype.
Despite the retrospective character, the 19-year study period was a source of strength as were the uniform guidelines in Finnish paediatric haemophilia care (FVIII treatment and prophylaxis) and the consecutive inclusion of all PUPs during this period. Another strength was that, during the whole study period, inhibitor testing was conducted in the same national coagulation laboratory of the Finnish Red Cross Blood Service.

6.4.3 Long-term clinical and economic outcomes (Study III)

The limitations were, again, the retrospective nature of our study and a relatively small sample size, despite including all PUPs born between June 1994 and May 2013. Underreporting of bleeding frequency is possible, especially in the case of soft tissue or minor bleeds; in addition, the diagnosis of a bleeding event is generally subjective. However, both parents and patients were instructed to report and confirm all joint and other significant bleeds with the hospital; the training sessions for parents and patients recommended that treatment be initiated at the hospital and continued at home while maintaining contact with the hospital. This clinical practice may diminish the possible impact of underreporting; the experience of symptoms, conviction in the necessity of treatment, and good relations with the health care provider, are motivators for high adherence (Schrijvers et al. 2013). All bleeding events were entered in patients' medical records by a specialist in haemophilia care. At the time of data collection, all data was registered by the same paediatric haematologist, KV, and not by local personnel, to ensure coherent data collection across centres. We defined a joint bleed according to ISTH recommendations (Schulman et al. 2010, Schulman, Kearon & Subcommittee on Control of Anticoagulation of the Scientific and Standardization Committee of the International Society on Thrombosis and Haemostasis 2005). Theirs is a stricter definition compared to that used by the Pednet group, which defines it as any complaint requiring treatment located in a joint (Fischer et al. 2014).
The present study included only direct medical costs and excluded the loss of caregivers' earnings. However, indirect costs in haemophilia patients, including costs of lost production, account for only 0.07-3% of total annual costs (Fischer et al. 2013, Zhou et al. 2015, O'Hara et al. 2017).
Despite the retrospective character, a strength was the long follow-up; the consecutive inclusion of all PUPs, treated according to uniform guidelines during the whole 19-year study period; and the inclusion of all bleeding events and direct treatment costs from the neonatal period to adolescence. In addition, our study analyses RWD with a top-down costing approach, reporting patient- and body weight-adjusted costs. Our validation exercise strengthened our data by showing that the amount of FVIII dispensed (consumption data obtained from the SII registry) had no deviation from the prescribed doses (data obtained from the medical records). This finding confirms that our patients and their parents adhered well to prophylaxis, in accordance with the clinical experience, including the utilization of the port as the mode of drug administration.
Enhanced half-life (EHL) factor VIII and IX products hold the promise of reducing the frequency of dosing. Today, in the clinic, they are already available. To know the response of an individual child to an agent, pharmacokinetic information is necessary. In the future, prophylactic therapy will undergo a redefinition as the treatment shifts from coagulation factor replacement to alternative mechanisms of action. One of them, emicizumab, is an

antibody that, by binding simultaneously to activated FIXa and FX, mimics the cofactor function of FVIII. Another is peptides that block the function of the inhibitor of the tissue factor pathway to promote haemostasis. A third is an approach that lowers the activity of a natural anticoagulant. Once-weekly subcutaneously administrated emicizumab prophylaxis may decrease the burden of the disease as it has markedly reduced bleeding episodes among patients with HA with or without inhibitors (Shima et al. 2017), and improved health-related quality of life (Oldenburg et al. 2017). However, to date, data on the efficacy and safety of using these new products in PUPs is still limited. These new products are also, at least potentially, more expensive, although the costs of EHL products and emicizumab vary hugely depending on the price of the product in each country. Thus, with its real-world national data on long-term outcome and treatment costs of early FVIII prophylaxis, our national study provides a solid platform for future use, such as for the comparative cost and outcome benefits in the era of novel haemophilia therapies: extended half-life factors, gene therapy and non-factor molecules.

7 Summary and conclusions

The main findings and conclusions of this series of studies are listed below.

Study I
We report a significantly lower CVAD-related bloodstream infection rate (0.12/1000 CVAD days) and longer port duration (median of 1159 days) than previously described. This was despite two factors: the majority (90%) of our patients were very young (≤2 years) at the time of first insertion, and port access was frequent. Our experience of CVAD emphasizes the safety of undertaking prophylactic factor concentrate administration via ports in very young children, which enables early home treatment. The meticulous handling of the insertion as well as the subsequent management with guidance and adherence of the family to instructions appears to be important and favour a good outcome with these types of ports.

Study II
In this nationwide evaluation including all PUPs in Finland, the cumulative incidence of ID was low (21%) despite the majority having high-risk mutations and intensive, mainly rFVIII, exposure. ID risk significantly increased in patients who experienced major bleeds. Therefore, our results emphasize the importance of early primary prophylaxis via ports to prevent bleeds and subcutaneous exposure to FVIII and thereby decrease inhibitor incidence. Despite patient-related risk factors, our management involving early intensive primary prophylaxis via ports helps prevent bleeds and lower the incidence of inhibitors.

Study III
The current study is the first of its kind including all PUPs with severe HA in Finland and using RWD to examine the long-term clinical and economic outcomes of regular prophylactic treatment. We provide data on all direct treatment costs per body weight, representing nearly 700 patient-years of follow-up. Early high-dose prophylaxis leads to excellent long-term clinical outcomes, annualised bleeding rates being near zero; it may thus reduce the health care costs of bleeding events and their long-term complications in the future. Moreover, rapid ITI therapy during early childhood is successful and seems cost-neutral due to its relatively short expected payback period. Reliable national data on long-term outcome and treatment costs (with RWD) are now available for future use and support critical decision-making related to new, and potentially more expensive, products.

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The general aim of this thesis was to investigate the outcome and costs of early primary prophylaxis in Finnish paediatric patients with severe haemophilia A during the past two decades. Regular high-dose primary prophylaxis leads to excellent long-term joint health, annualised bleeding rates being near zero. The cumulative incidence of ID was low (21%) despite the majority having a high-risk genotype. With its real-world national data, our study provides a solid platform for future use, such as for the comparative cost and outcome benefits in the era of novel haemophilia therapies.

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