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On outcomes for hemophilia

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CHAPTER 1

**General introduction, aims and outline,
and study populations**



Once known as the ‘royal disease’, hemophilia is a condition that affects approximately 1,125,000 individuals worldwide.[1] Advancements in medical science in the second half of the 20th century have led to efficacious treatment and improvements in life expectancy and health outcomes for persons with hemophilia.[2, 3] However, outcomes assessment for hemophilia is complex, due to the heterogeneity in disease characteristics and co-morbidities, types of outcomes and methods to measure such outcomes. This thesis aims to define, measure and quantify relevant health outcomes for persons with hemophilia, with the overall goal to improve care for this group of people.

Hemophilia

Persons with congenital hemophilia have a lack of either functional protein coagulation factor VIII (hemophilia A, 80-85 percent of cases) or IX (hemophilia B, 15-20 percent of cases), preventing the formation of stable fibrin blood clot.[1, 4] As a result, persons with hemophilia have an increased bleeding tendency. In severe hemophilia, coagulation factor VIII or IX concentrations are below 0.01 IU/mL (<1 percent of normal), this often manifests itself as spontaneous bleeding into joints (hemarthrosis), muscles, and internal organs. Intracranial hemorrhage, gastrointestinal bleeding and bleeding in the neck and throat area can be life-threatening.[5] Approximately 70 to 80 percent of bleeding occurs in the synovial joints: ankles, knees, elbows, shoulders, hips and wrists. The number of bleeds is often expressed as the annualized bleeding rate (ABR) and annualized joint bleeding rate (AJBR).[3, 6, 7]

In moderate hemophilia, coagulation factor concentrations are between 0.01 and 0.05 IU/mL (or 1-5 percent of normal). This leads to occasional spontaneous bleeding and prolonged bleeding after minor trauma or surgery. Persons with mild hemophilia have coagulation factor concentrations of 0.05-0.40 IU/mL (5-40 percent of normal), and generally only experience bleeding after major trauma or surgery. They may not experience prolonged bleeding until triggered by such events [5] and may remain undiagnosed until later in life.[8] Coagulation factor concentrations generally correlate well with bleeding phenotype, although individuals with the same concentrations may still have different bleeding phenotypes due to differences in genetics, joint health status and behavior (e.g. with activities that increase the chance of a bleed), but also due to yet unknown causes.[5, 9]

Joint bleeds are mainly triggered by mechanical stress such as weightbearing or trauma.[10] Clinically, a joint bleed results in swelling, pain and a loss in range of motion. [5] When a bleed occurs, blood accumulates in the synovium and synovial cavity (Figure 1).[10] Iron present in erythrocytes causes inflammation of the synovium, which then becomes more susceptible to mechanical damage and subsequent bleeding. Recurrent joint bleeding results in cartilage degeneration and structural changes through synovitis

and oxidative stress. In later stages the underlying bone is also affected. The result is hemophilic arthropathy,[10] with disability and pain.

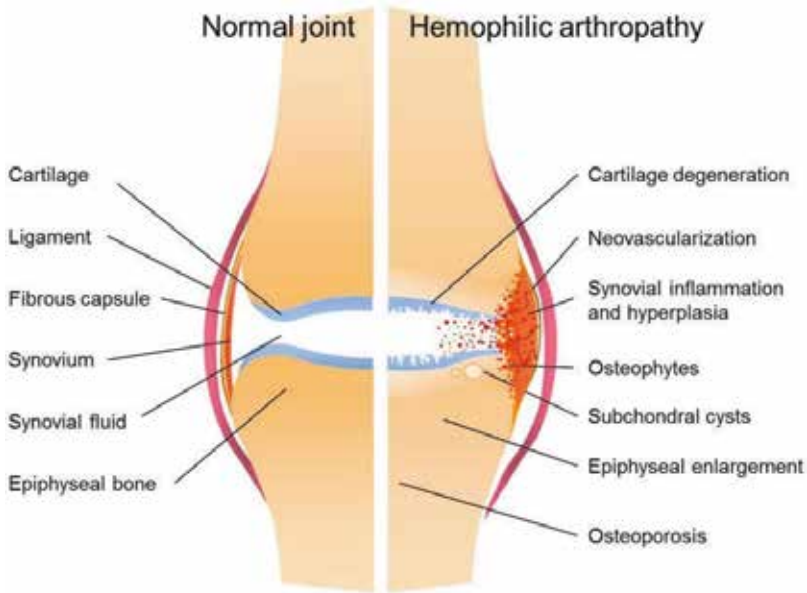


Figure 1: Schematic representation of a healthy joint (left) and hemophilic arthropathy (right). Reprinted from Pulles et al (2017)[10], with permission from Elsevier.

Diagnosis of hemophilia is based on clinical features (bleeding without an apparent trigger, easy bruising, excessive bleeding after trauma or surgery), family history, coagulation screening tests (prothrombin time (PT) and activated partial thromboplastin time (APTT)), and coagulation factor activity assays. Comprehensive laboratory testing is important to rule out other bleeding disorders and to start appropriate treatment as soon as possible.[5]

The deficiency in coagulation factor VIII or IX in congenital hemophilia originates from mutations in the F8 and F9 coagulation genes.[5] For severe hemophilia A the most common causative mutation is an intron 22 inversion, which is present in 30–45 percent of cases. Both the F8 and F9 genes are located on the long arm of the X-chromosome.[5] The inheritance is X-linked, meaning that hemophilia occurs mostly in men.[5] However, women may also have hemophilia, with a diagnosis based on a combination of personal bleeding history and baseline plasma FVIII or IX concentrations.[11] The most prominent hemophilia symptom in women is excessive bleeding during menstruations.[5]

Hemophilia is a rare disease, which is defined as a disease with a prevalence of less than 5 in 10,000 in the population.[12] In the Netherlands, the prevalence of hemophilia

was estimated at 1.6 per 10,000 males,[13] and the prevalence at birth was estimated at 2.06 per 10,000 male live births in 1986.[14] Based on these estimates, the Dutch hemophilia population was expected to consist of 1364-1756 individuals in 2018. More recent international estimates based on national patient registries in 6 high-income countries, however, indicate that the prevalence of hemophilia is 2.46 and 0.5 per 10,000 male live births for hemophilia A and B, respectively, and 1.71 and 0.38 per 10,000 live males.[1] These higher estimates likely result from better diagnostic techniques, completeness of population testing, and the precision in case reporting.[1] The updated estimates of prevalence means that the number of persons with hemophilia in the Netherlands may amount to 2500 to 2600 individuals.

Treatment of hemophilia

Prior to the 1960s, the only treatment available for hemophilia consisted of whole blood or plasma transfusions.[15] The discovery of high amounts of FVIII in fresh-frozen plasma precipitate (cryoprecipitate) in the mid-1960s was the first step towards modern hemophilia treatment products.[16] Next, FVIII products were extracted from human plasma. Nowadays, FVIII and FIX products may either be derived from human plasma obtained from blood donors, or, more commonly, produced using recombinant techniques.[5]

Coagulation factor replacement is by intravenous infusion, either as episodic (on-demand) treatment to treat a bleed, or as prophylaxis to prevent bleeds. Prophylaxis may be initiated as primary, secondary or tertiary prophylaxis, depending on starting age and on whether joint disease is present or not.[5] Prophylaxis does not prevent all bleeds, but it is recommended for persons with a severe bleeding phenotype, as is often the case for persons with severe hemophilia and for some persons with moderate hemophilia.[5, 17] Non-severe hemophilia A may also be managed with desmopressin.[8, 18]

Both recombinant and plasma-derived treatment products are currently on the market for hemophilia A and B in the Netherlands.[19] Dosing is based on bodyweight and depends on the goal of treatment, cost, bleeding phenotype, daily activities, venous access and vial volume of the treatment product.[20] Dosing regimens applied in high-income countries such as the Netherlands are intermediate-dose or high-dose prophylaxis: 15-25 IU/kg or 25-40 IU/kg 3 times a week for hemophilia A and 20-40 IU/kg or 40-60 IU/kg twice a week for hemophilia B.[5, 20] In the past few years, innovations have led to alternative forms of treatment: coagulation factor products with a prolonged half-life reduce the burden of treatment because they allow for fewer injections.[5, 15] In addition, a non-coagulation factor based product (emicizumab) has been developed for treatment of hemophilia A that mimics the function of FVIII and that can be administered subcutaneously as prophylaxis. It initially became available for persons who develop inhibitors against infused coagulation factor VIII,[21] but as of 2020 it may also be used in persons without inhibitors.[22]

Coagulation factor replacement therapy has some disadvantages. First, blood-borne transmission of pathogens made persons with hemophilia vulnerable for infections with the human immune deficiency virus (hiv) between 1982 and 1985 and with hepatitis C virus until 1992. Approximately 17 percent of Dutch persons with hemophilia were hiv-positive in 1988 [23] and 68 percent were infected with the hepatitis C virus (hcv; at the time known as non-A non-B hepatitis).[24] Acquired immune deficiency syndrome (aids) was the cause of death for 26 percent of deaths among Dutch persons with hemophilia between 1992-2001,[2] and for two percent between 2001-2018.[25] Of those with hcv, approximately 20 percent of infected persons cleared the virus spontaneously,[24, 26, 27] the others developed chronic hcv infection. Of them, 13 percent developed end-stage-liver disease and 3 percent developed hepatocellular carcinoma. [27] Complications of hcv were the cause of death for 22 percent of deaths among Dutch persons with hemophilia between 1992-2001 [2] and for 40 percent between 2001-2018.[25] Improved selection of healthy blood and plasma donors, screening of donations and pathogen inactivation and removal techniques have virtually eliminated transmission of hiv and hcv and other pathogens of concern.[28]

A second complication of treatment with coagulation factor replacement therapy is the development of neutralizing antibodies (inhibitors) against infused coagulation factor VIII or IX. In these cases, coagulation factor replacement therapy is no longer effective in preventing or treating bleeds. It is estimated that one third of persons with severe hemophilia A develop inhibitors during their lifetime, and that this risk is higher in those using recombinant products than in those using plasma-derived products.[29] Inhibitor development occurs only rarely in hemophilia B.[5]

Finally, hemophilia treatment is costly. Several studies have assessed the cost of annual coagulation factor replacement product for persons with severe hemophilia in the Netherlands [7] and Europe.[30] The cost of the Dutch intermediate-dosing prophylaxis regimen was estimated at a mean of US\$179,600 (€135,210) per patient per year,[7] and on average €199,541 in five European countries in 2014.[30]

Innovations in treatment continue to be developed, including hemostasis-rebalancing agents that target natural anticoagulants in hemostasis, such as reduction of antithrombin production and anti-tissue factor pathway inhibitor (anti-TFPI) monoclonal antibodies. Phase 2/3 studies are currently ongoing for these products.[31] Also, gene therapy for hemophilia is still under study. Using adeno-associated viral vectors, a healthy copy of the F8 or F9 gene can be delivered to hepatocytes, which then start to produce coagulation factor VIII or IX. Trials for both hemophilia A and B have shown FVIII and FIX expression since 2009 for FIX [32] and since 2015 for FVIII. Recent reports show a decline in FVIII expression over time.[33]

In summary, hemophilia may largely be viewed as a medical success story. The missing coagulation function can be replaced with either coagulation factors or by-passing therapies, even for those with inhibitors.[21] Recombinant techniques have limited

transmission of pathogens considerably, and health outcomes have improved tremendously since the 1960s.[2, 13, 25, 34–40] In the near future, gene therapy will become available to correct the coagulation factor deficiency. Yet, hemophilia continues to affect many patient-relevant outcomes, especially for those who grew up without appropriate prophylactic treatment. Long-term follow-up will show the intended and unintended effects of treatment innovations and to further improve health outcomes.

Assessing health outcomes for hemophilia

Improving health outcomes is the goal of clinical care.[41, 42] Appropriate assessment of health outcomes for hemophilia is therefore crucial in efforts to improve quality of care for persons with this condition.

Health outcomes assessment for hemophilia is complex. First, there is a large heterogeneity between patients; those with mild hemophilia are thought to have few health problems, few bleeds and a life expectancy that is near that of the general population. [2, 3] On the other hand, persons with severe hemophilia may still experience bleeding, despite the availability of prophylaxis. Both the ABR and the AJBR have improved over time, but older generations who grew up without appropriate prophylactic treatment developed arthropathy and disability.[3] Persons who contracted hiv or hcv still suffer from the consequences of these infections.[3, 26] Personalized treatment is therefore warranted. Individual patient decision-making about treatment (type of product, dose) will help optimize patient-relevant outcomes.

Second, there is heterogeneity in what is considered a health outcome. For example, health outcomes may be classified as biological and physiological factors (genotype, coagulation factor VIII or IX concentrations), symptoms (e.g. pain, swelling), functional status (e.g. limitations in self-care, occupational disability), health perceptions (e.g. about the severity of hemophilia, ability to manage treatment) and health-related quality of life [42] (HRQoL, e.g. constructs such as physical functioning, social functioning, psychological functioning and pain).[43, 44] How such health outcomes are defined and which ones are the most relevant from hemophilia patients' perspectives is largely unknown. For example, HRQoL is often poorly defined and conceptualized in research studies [45–47] and the majority of studies fail to describe which domains of HRQoL are measured.[48]

What is considered a relevant health outcome may also depend on the source of information, such as patients, clinicians, or caregivers.[49] For example, 'health outcomes' such as coagulation factor VIII or IX peak and trough concentrations are usually not directly meaningful for persons with hemophilia, but they are useful indicators of disease control for clinicians. Similarly, frequently used process outcomes to evaluate quality of care, such as adherence to guidelines or the number of patients treated,

are not relevant for individual patients.[41] Such biological and process variables are not considered true health outcomes.[41, 42] Examples of health outcomes that are often relevant to patients are physical functioning, pain, mental health and social and economic participation.[36, 50-52] Such health outcomes are called patient-reported outcomes (PROs) because they cannot be measured directly, but can only be reported by patients.[49] There may be different views on the relevance of measured health outcomes among patients and clinicians.

Finally, measuring patient-reported outcomes may be challenging. Patient-reported outcomes are measured with questionnaires (patient-reported outcome measures, or PROMs),[53, 54] that need to be valid, reliable and responsive for use in hemophilia populations.[54] Several PROMs have been developed for hemophilia, each measuring slightly different constructs, and each with different measurement properties and scoring systems.[55-57] This makes it difficult to compare health outcomes over time and between settings.

Heterogeneity among patients and types and measurement of health outcomes makes it difficult to assess the effects of health care and to identify areas for improvement. This may result in suboptimal care that is not aimed at improving the most relevant health outcomes. Calls have therefore been made to standardize health outcomes assessment for hemophilia.[58] Standardized measurement of relevant health outcomes will help optimize individualized treatment, facilitate individual decision-making and allow for comparison of outcomes across settings and over time,[5, 41, 59-61] which will contribute to improved quality of care for persons with hemophilia.

Aim and outline of this thesis

With an overall aim of improving care for persons with hemophilia, this thesis explores hemophilia outcomes and their contexts from several perspectives, using both qualitative and quantitative methods.

Part I of this thesis is about how treatment decisions affect outcomes and part II is about defining, measuring and quantifying relevant outcomes for hemophilia. In part I, **Chapter 2** describes a qualitative study in Vancouver (Canada) that aims to understand patients' experiences with a clinic program designed to encourage independent patient decision-making about dosing and frequency of prophylactic treatment. The clinic team provided personalized treatment information in visual formats to facilitate such decisions. Because these decisions have the potential to affect health outcomes, it is important to gain a better understanding of how hematologists and patients make treatment decisions. In addition to treatment decisions, persons with hemophilia also have the option to choose different types of product (e.g. coagulation factor with an extended half-life). **Chapter 3** therefore reports on a qualitative study in which Dutch persons with hemophilia were interviewed about how they view their current treatment

and, in the light of novel emerging therapies, how they would make decisions about whether or not to switch to a new treatment product.

In part II, **Chapter 4** introduces the concept of value-based health care and how it applies to hemophilia care. One of the first steps in implementing value-based health care is to define a standard set of relevant health outcomes that should be targeted in hemophilia care. The development of such a health outcomes set is described in **Chapter 5**. In this project named 'HaemoValue' an iterative nominal consensus process was performed to define the most relevant health outcomes and to make recommendations for disease-specific as well as generic instruments to measure these health outcomes. **Chapter 6** investigates structural validity, internal consistency, and construct (convergent and discriminative) validity of one of these instruments for use in hemophilia populations: the Dutch-Flemish version of the PROMIS Profile-29. The data for this study were collected as part of the sixth Hemophilia in the Netherlands study. Finally, **Chapter 7** evaluates socio-economic participation of persons with hemophilia. Using internationally recognized standards, the study described in this chapter compares educational outcomes, labor market outcomes and social participation with those in the Dutch general male population.

Study populations

The studies described in this thesis use several sources of data to explore health outcomes for hemophilia: 1) interviews conducted with persons with hemophilia, who were recruited through the Netherlands Hemophilia Society (**Chapter 3**) and through the British Columbia Adult Haemophilia Team (Canada, **Chapter 2**); 2) an international consensus project in which patient representatives, interdisciplinary hemophilia experts and researchers were involved in defining important health outcomes in the HaemoValue project (**Chapter 5**); and 3) the sixth nationwide Hemophilia in the Netherlands (HiN-6) study (**Chapters 6 and 7**), described in more detail below.

The Hemophilia in the Netherlands studies

The Hemophilia in the Netherlands (HiN) studies are a series of cohort studies that were initiated in 1972 (Figure 2). HiN is the oldest still running hemophilia study in the world. The goal of the HiN studies is to evaluate the medical, psychosocial and economic situation of persons with hemophilia in the Netherlands.[2, 13, 34-39] Each edition of HiN consisted of a survey that evaluated important medical aspects of hemophilia, including treatment, bleeds, joint impairment and family history. In addition, each HiN study focused on topics that were relevant at the time the studies were conducted, such as home treatment (1978), hiv (since 1985), psychosocial problems (since 1992), and comprehensive care at specialized hemophilia treatment centers (2001).

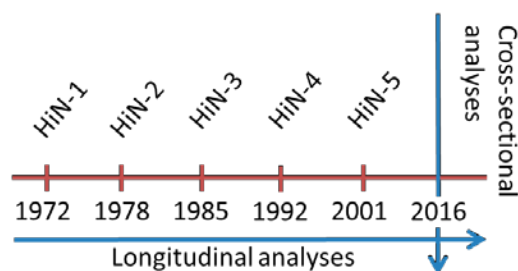


Figure 2: Overview of HiN studies

The sixth Hemophilia in the Netherlands study was initiated in 2015. A steering group was formed that consisted of representatives from all hemophilia treatment centers as well as patient representatives. The steering group was involved in the design and execution of HiN-6. The overall aims of HiN-6 are 1) to describe the health status of the Dutch hemophilia population, with special focus on viral infections, inhibitor development and age-related co-morbidities; 2) to gain insight into HRQoL; 3) to evaluate quality of care; 4) to explain the variability in clinical phenotype and 5) to gain insight into the mechanisms underlying the humoral and cellular immune response to FVIII. This thesis focuses on health outcomes and thereby addresses the second goal of HiN-6: to gain insight into HRQoL.

All male adults and children with mild, moderate or severe congenital hemophilia A or B registered at one of the six Dutch hemophilia treatment centers were invited by letter to participate. They were included during their regular scheduled outpatient clinic appointment. Data collection consisted of a comprehensive questionnaire (online or in hard copy), information collected from electronic medical records, and blood and urine sampling. Part of the blood samples and all urine samples collected were stored in a decentral national biobank to be used for future research.

The questionnaire was based on that of previous HiN surveys, supplemented with additional questionnaires that have become available since previous surveys. Separate versions of questionnaires were available for parents of children aged 0-11, teenagers aged 12-17, and adults of 18 and older. Questionnaires contained questions on demographic characteristics, socio-economic characteristics, clinical characteristics (bleeds, treatment, inhibitors, other medication, joint limitations), hiv and hepatitis C status, medical history (other chronic conditions, hospital admissions, colon cancer screening), sexuality, acute and chronic pain, needle fear, experience with care and novel treatment options. Data on age, type and severity of hemophilia, hcv and hiv status and treatment schedule were verified with data from electronic medical records. In order to ensure comprehensibility of the questionnaire, most questions about the above topics were

tested with cognitive interviews with five adults with hemophilia and with a group of children with hemophilia.

When possible, existing generic and hemophilia-specific questionnaires frequently used in hemophilia research and clinical practice were used to assess PROs. The RAND-36 (generic; health status),[62, 63] PROMIS-29 (generic; several domains of HRQoL),[64] and the Hemophilia Activities List (HAL; hemophilia-specific activities of daily living) [65, 66] were used for this thesis (Chapters 6 and 7).

The data collected as part of the HiN-6 study will provide hemophilia researchers in the Netherlands with insights from a nationally representative sample for years to come.

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