

# Treatment of Hemophilia A and B and von Willebrand Disease

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A Systematic Review

May 2011



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Swedish Council on Health Technology Assessment  
*SBU • Statens beredning för medicinsk utvärdering*

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# Treatment of Hemophilia A and B and von Willebrand Disease

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## A Systematic Review

### Project Group

Erik Berntorp (Chair)	Bengt Ljungberg Tore Nilstun (Ethical aspect)	From SBU: Juliette Säwe (Project Director)
Jan Astermark	Anders Norlund (Health Economics)	Jonas Lindblom (Literature Search)
Fariba Baghaei	Jan Palmblad	Anneth Syversson (Project Assistant)
David Bergqvist	Pia Petrini	
Margareta Holmström	Lennart Stigendal	
Rolf Ljung (Section 3.1.1)		

### Scientific Reviewers

Anders Anell	Geir E Tjønnfjord
Christine A Lee	Anders Wahlin
Michael Makris	

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# SBU's Summary and Conclusions

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# SBU's Summary and Conclusions

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In hemophilia A and B and von Willebrand disease, coagulation factors are absent or deficient. This impairs the capacity of the blood to coagulate and increases the risk of bleeding. The diseases are hereditary. If inadequately treated, hemophilia causes painful bleeding in joints and leads to disability. Bleeds can also occur in internal organs, e.g., the brain.

Hemophilia can be treated by replacing missing coagulation factors. The availability of coagulation factors has drastically reduced morbidity, and since the 1950s survival has increased from 15 years to nearly normal life expectancy.

In the past, patients were exposed to high risk of HIV infection and Hepatitis C transmitted via blood and blood products. Since the mid 1980s, concentrated coagulation factors have been produced by methods that have practically eliminated the infection risks. Nevertheless, several questions remain concerning optimum treatment, e.g., selecting the most appropriate dose and dosing strategy. Another question concerns the treatment of bleeding episodes (bleeds) in patients that have developed antibodies (inhibitors) that counteract the effects of factor concentrates.

- ❑ Concentrates of coagulation factors VIII and IX have good hemostatic effects on acute bleeding and during surgical intervention in patients with hemophilia A and B. As scientific evidence is limited, firm conclusions cannot be drawn about possible differences in the effects of different dosing strategies for acute bleeding and surgery. More studies of sufficient quality are needed to investigate the short-term and long-term effects of the different dosage strategies.
- ❑ Preventive treatment (prophylaxis) initiated at a young age, i.e., before articular (joint) bleeding starts to appear, can prevent future joint damage. Due to a lack of studies, firm conclusions cannot be drawn regarding the optimum time to start treatment during infancy, or the optimum dose and dose interval. Another uncertainty

is whether treatment should be discontinued or modified during adulthood in some patients. Such studies are difficult since the numbers of patients are small, and many years of follow-up are required to evaluate the progression of joint damage.

- ❑ In patients that have developed high levels of antibodies (inhibitors) against factor concentrates, acute bleeding can be inhibited by administering bypass agents, but it is difficult to predict the effectiveness of such treatment in individual cases. Prophylaxis with bypass agents probably has a favourable effect. When the antibody level has decreased, immunotolerance induction treatment – which usually involves daily administration of relatively high doses of factor concentrate – can halt the production of inhibitors. This means that patients can then be given normal prophylaxis and can be treated for bleeding by using normal factor doses. Treating inhibitor development is extremely demanding and costly. The available treatment options have been insufficiently assessed due to the limited group of patients and the subsequent difficulties in conducting appropriate studies.
- ❑ Patients with the more severe types of von Willebrand disease must be treated with factor concentrates that contain von Willebrand factor, and often factor VIII. The effects on acute bleeding and during surgery are good. At times, preventive treatment is necessary. Doses, dose intervals, and indications for factor concentrate treatment in von Willebrand disease have not been sufficiently studied, particularly as regards prophylaxis.
- ❑ Treating hemophilia and von Willebrand disease is expensive. The economic consequences of various treatment strategies have been insufficiently analysed due to the lack of studies on clinical effects.
- ❑ It is essential to create a national treatment register that includes defined quality indicators. Regarding the future, there is an obvious need for systematic and centralised follow-up of patients with hemophilia A and B and von Willebrand disease within the context of a national quality register aimed at documenting the short-term and long-term treatment effects.

# Summary

## Aim

This review aims to assess – from medical, economic, and ethical perspectives – different dosing strategies for replacement therapy using coagulation factor concentrates to treat patients with hemophilia A and B and von Willebrand disease.

The systematic literature review does not cover the safety aspects related to transmission of infections, or the risks for developing inhibitors (neutralising antibodies). The methods currently used for virus inactivation and virus reduction in producing plasma-based factor concentrates have been approved by European and U.S. drug authorities, and the products are considered to have a wide margin of safety. The transition to products manufactured by recombinant DNA methods has favourably altered the risks of blood contamination. An international debate is under way concerning the risks of inhibitor development, but evidence supporting the various opinions is deficient. Even a minor difference could have considerable medical and economic consequences.

## Questions

The overriding questions have been:

- What are the short-term and long-term effects of different treatment strategies?
- What methods are available to treat hemophilia patients that have developed inhibitors against factor concentrates?

## Background

### The disease and its prevalence

Hemophilia results from an inherited deficiency in coagulation factor VIII (hemophilia A) or coagulation factor IX (hemophilia B). Hemophilia A and B are gender-related, hereditary, and affect males almost exclusively. One in 5 000 boys are born with the disease. In Sweden, approximately 1 000 patients have hemophilia, whereof approximately 300 receive regular treatment.

Coagulation factors are proteins produced in the liver. Deficiency in a coagulation factor means that the blood coagulates poorly, or barely at all. Hemophilia A and B has three grades of severity: severe, moderate, and mild. Bleeding risk is associated with the degree of severity. Usually, the first bleeds appear at 5 to 6 months of age with the severe type, and at 1 to 2 years of age with the moderate type. The bleeds can appear spontaneously, or following minimum trauma. In mild hemophilia, bleeding problems usually occur in conjunction with surgery and major injuries, and therefore some patients are diagnosed late in life.

Symptoms in severe and moderate hemophilia are more or less spontaneous bleeds in joints and muscles. Untreated, articular (joint) bleeding leads to an acute increase in pressure in the joints, accompanied by severe pain. Later, patients develop chronic joint inflammation and degradation of articular cartilage, leading to stiffness, impaired motion, and chronic pain. Without adequate medication, hemophilia can result in serious mobility-related disabilities. Patients with hemophilia are also at risk for other types of serious bleeding, e.g., cerebral or gastric hemorrhage.

Von Willebrand disease (VWD) is also hereditary and can affect both men and women since the gene is not in the sex chromosomes. The disease results from deficient or impaired function in a protein called von Willebrand factor (VWF), which is produced in the vascular walls. Von Willebrand disease presents mainly as bleeding in the mucus membranes. Approximately 1 000 patients in Sweden have von Willebrand disease. The few patients that have the severe type also suffer from articular bleeding, leading to chronic joint damage and disability similar to that in patients with severe/moderate hemophilia.

## **Treatment**

Patients with hemophilia and the more severe types of von Willebrand disease are treated with the coagulation factor or factors they lack. This treatment approach is usually referred to as replacement therapy. The implication is that patients can become symptom free, similar to the situation with other diseases involving deficiency-related symptoms (e.g., insulin dependent diabetes, vitamin B12 deficiency, hypothyroidism).

With the introduction of highly purified concentrates in the 1970s, treatment of hemophilia patients became easier and more common, but in the 1980s the new concentrates were found to transmit HIV and hepatitis C. These two catastrophic situations shifted the focus toward the care of affected patients and the development of safe products, weakening the momentum for the other types of treatment studies. New studies began after year 2000, but many of them have yet to be completed.

Two types of factor concentrates are currently used to treat hemophilia A and B, plasma-derived or recombinant coagulation factor concentrates. Optimum dosing of factor concentrate is an important question. Internationally, practices vary widely due to tradition, costs, and limitations in the scientific data. The comparison between prophylaxis and on-demand treatment is also important, particularly as regards the long-term outcomes in hemophilia patients. For many years, all patients in Sweden with severe hemophilia have been offered preventive treatment. From an international perspective, however, definitions and perceptions vary regarding dosing practices and when to start prophylactic treatment. Hence, this is another matter that must be analysed. Mild hemophilia A can be treated with desmopressin, a synthetically produced hormone-like (vasopressin) agent that affects blood coagulation by quickly and briefly increasing the concentration of factor VIII and von Willebrand factor in blood.

Most patients with the mild form of von Willebrand disease do not need treatment except in cases of surgery and trauma. An exception would be untreated women with von Willebrand disease, since blood loss associated with menstruation can lead to blood deficiency. The primary treatment for mild von Willebrand disease is tranexamic acid, which reduces blood loss from menstruation and bleeding problems after minor surgery. Another drug is desmopressin, which can temporarily increase the amount of von Willebrand factor and is occasionally used to complement tranexamic acid in surgery and profuse menstruation.

With more severe forms, concentrates containing von Willebrand factor, and usually factor VIII, must be administered in addition to tranexamic acid.

## **Inhibitors (neutralizing antibodies) against factor concentrate**

Treatment of hemophilia can become more complicated with the development of inhibitors against factor concentrates, which in most cases neutralise the effects of factor VIII and factor IX agents. Inhibitors appear in 20 to 30 percent of the patients. In approximately half the number of patients, the levels are low and the inhibitors usually disappear after a period of “enhanced” prophylactic treatment. Others have high levels of inhibitors (high titres) that completely neutralise the administered factor concentrates, and they have no effect. The inhibitors usually appear within the first 10 to 30 treatment doses. To inhibit bleeding, these patients are administered treatment with recombinant factor VIIa (rFVIIa) or activated prothrombin complex concentrate (aPCC), so-called “bypass products”. Without these agents, even minor bleeds could become life-threatening. The treatment goal in these patients is to eliminate the formation of inhibitors through immunotolerance induction, which involves daily administration of relatively high doses of factor concentrate. This treatment method has been used in Germany and Sweden for approximately 30 years with apparently good effects in most cases, but at a very high cost. Studies in this area are difficult to conduct, but a couple is in progress. Acute hemorrhaging causes severe pain and must be treated.

Only recently have randomised trials been published on treatment in patients with inhibitors. Prophylaxis to prevent acute hemorrhaging in inhibitor patients is in its early stages, but several smaller studies have been published, and others are under way.

## **Method for Systematic Review of the Literature**

SBU’s assessment methods include a systematic review of scientific studies in the subject area. In this context, systematic refers to identifying and assessing the quality of all relevant scientific studies that address the question.

The literature reviews cover several phases: identifying, selecting, and assessing the quality of studies, and finally synthesising the information and rendering a collective judgement. This report has been com-

piled by a panel of 10 experts representing different specialties. Five external experts and the SBU Scientific Advisory Committee reviewed the final report.

Based on the questions addressed by the project, a systematic database search was conducted in PubMed, NHSEED, Cochrane Library, EMBASE, and other relevant databases. The literature search covered all studies in the field published from 1985 up to the spring of 2010, with a supplementary search in October 2010 (reported separately).

### **Inclusion criteria**

In the initial phase of the review, the following criteria were used to select relevant publications:

- The study must address patients with hemophilia A and B, with and without inhibitors, and patients with von Willebrand disease (VWD) of all ages treated with recombinant or plasma-derived factor VIII or factor IX concentrates, recombinant coagulation factor VIIa, activated prothrombin complex concentrate or factor concentrate containing von Willebrand factor (VWF) and factor VIII (FVIII).
- The study must report on one or more of the following effects: quality of life, articular bleeding, number of factor concentrate infusions for hemostasis, life-threatening hemorrhages, other bleeding, tolerance development (measured as the absence of inhibitors), inpatient days, resource utilisation (orthopaedics, surgery, sick leave/disability pension, school absenteeism).
- Primarily, treatment studies should be randomised controlled trials (RCT), or secondarily, controlled prospective studies. If studies of this type are not available, non-randomised studies without controls may be reviewed.
- At least 5 to 20 patients per study group (trial groups and control groups) depending on diagnosis.

- Health economic studies must address both costs and effects, be relevant to Swedish conditions, and include comparisons with the best alternative. Preferably, effects should be measured in quality-adjusted life-years.
- The article must be written in English, Swedish, Danish, or Norwegian.

### **Quality appraisal**

At least two individuals in the project group, independently, evaluated the structured abstracts of articles found in the database search. The inclusion criteria listed above were used in evaluation. All articles that any of the reviewers found to be relevant were retrieved in full text format. Using the inclusion criteria, the same individuals (independent of one another) reviewed the articles. Articles that none of the reviewers found relevant were excluded. The included articles were carefully reviewed using SBU's standard checklists to determine the extent to which the studies met the quality criteria, e.g., study design, study population, outcome measures, and the analytical methods used. Based on this information, the reviewers rated study quality and relevance as high, medium, or low.

### **Study quality, evidence grading, and conclusions**

Outcome data from studies that met the basic quality requirements were compiled for each of the questions. The quality ratings of the scientific literature were then compiled as a basis for grading the strength of the evidence (Facts 1). In each chapter, appraisal of the evidence is based solely on studies found to have high or medium quality and relevance. Hence, the strength of the evidence expresses the collective scientific support for a conclusion, i.e., how many studies of medium or high quality support the conclusion. The strength of the evidence is indicated within parenthesis in the text below.

## Facts 1 Study Quality, Relevance and Evidence Grading.

**Study quality** refers to the scientific quality of an individual study and its capacity to answer a specific question in a reliable way.

**Evidence grade** refers to the appraised strength of the collective body of scientific evidence and its capacity to answer a specific question in a reliable way. SBU uses an international evidence grading system called GRADE. Study design is the primary factor considered in the overall appraisal of each outcome measure. Secondary factors that can increase or decrease the strength of the evidence include: study quality, relevance, consistency, transferability, effect size, data precision, risk of publication bias, and other aspects, e.g. the dose-response relationship.

Evidence grades – four levels

### **Strong scientific evidence (⊕⊕⊕⊕)**

Based on high or medium quality studies with no factors that weaken the overall assessment.

### **Moderately strong scientific evidence (⊕⊕⊕○)**

Based on high or medium quality studies with isolated factors that weaken the overall assessment.

### **Limited scientific evidence (⊕⊕○○)**

Based on high or medium quality studies having factors that weaken the overall assessment.

### **Insufficient scientific evidence (⊕○○○)**

Scientific evidence is deemed insufficient when scientific findings are absent, the quality of available studies is low, or studies of similar quality present conflicting findings.

The stronger the evidence, the lower the likelihood that new research findings would affect the documented results within the foreseeable future.

### **Conclusions**

SBU's conclusions present an overall assessment of benefits, risks, and cost effectiveness.

Obviously, the grades chosen to indicate the strength of the conclusions cannot be interpreted as ultimate truth. Nevertheless, conclusions based on strong scientific evidence should provide more concrete guidance than conclusions based on weaker evidence. It is important to note that when the scientific evidence is graded as being insufficient, this does not necessarily mean that a given method has no effect.

## **Basic Conditions for Treatment**

In Sweden, treatment with coagulation factor concentrate has increased survival of patients with severe hemophilia from approximately 15 years to nearly normal life expectancy. Knowledge of the molecular biological mechanisms and the pathophysiology underlying hemophilia forms the foundation for clinical treatment. Clinical outcomes show that treatment has marked effects and extends survival. However, since these positive results have not been documented in scientific studies, it is difficult to grade the evidence in accordance with SBU's standard methodology. It seems logical to assume that treatment of hemophilia and von Willebrand disease is effective since it involves replacement of a single, deficient factor.

Presented below is a summary of treatment methods that are based on clinical experience and involve the use of coagulation factor concentrates.

### **Treatment with coagulation factor concentrate**

Using factor VIII to treat bleeding resulting from hemophilia A has the following effects: hemostasis, reduced pain, and improved mobility. The improvements appear within a few hours. Usually a single treatment is sufficient to achieve a lasting effect. Side effects from current factor concentrates are few and mild, apart from inhibitor development.

Using factor IX concentrate to treat acute bleeding resulting from hemophilia B is effective, and similar to the situation in treating hemophilia A. Occasionally, treatment of hemophilia B can lead to an allergic reaction, particularly if inhibitors are present at the time.

Regular administration of factor VIII concentrate for severe hemophilia A – starting at an early age before the first episode of articular bleeding – has good protective effects against articular bleeding and development of joint damage later in life. Since hemophilia B is less prevalent than hemophilia A, the scientific evidence is even more limited as regards regular replacement therapy. However, available studies suggest a similar, positive effect.

Clinical experience and observational studies suggest that replacement therapy with coagulation factor concentrate has effects that enable surgical intervention. Common procedures include knee and hip arthroplasty.

Treatment with recombinant factor VIIa and activated prothrombin complex concentrate (bypass therapy), has effects on acute bleeding and enables surgical intervention in hemophilia A and B patients with inhibitors. Retrospective observational studies have shown good effects. Nevertheless, therapeutic failure is possible. Clinical data suggest that response to treatment can vary among individuals and between the two agents available on the market. Although the scientific evidence is based mainly on retrospective clinical studies without controls, the reported effects are pronounced and clinically relevant.

Results from case series show that immunotolerance induction treatment with factor concentrates can be effective in up to 80 percent of hemophilia A patients with inhibitors, and in most cases the results are permanent. Clinical experience indicates that treatment should be started early in childhood, when a child with hemophilia develops inhibitors. The situation regarding hemophilia B is less certain.

Treatment with factor concentrate containing von Willebrand factor (VWF) and factor VIII has effects on acute bleeding in patients with von Willebrand disease who do not respond adequately to desmopressin, and in patients with type 3 von Willebrand disease. Similar effects have also been observed with concentrates mainly containing von Willebrand factor alone.

Clinical experience and observational studies suggest that replacement therapy with coagulation factor concentrate containing von Willebrand factor (VWF) and factor VIII has effects that enable surgical intervention in patients that do not respond to desmopressin. Similar effects have also been observed with concentrates mainly containing von Willebrand factor alone. Often in acute situations, however, extra factor VIII has also been administered.

## **Evidence Graded Results**

This report aims to present the scientific evidence underlying different dosing strategies for coagulation factor concentrate in treating patients with hemophilia A, hemophilia B, and von Willebrand disease.

Summarised below are the results from studies that meet the inclusion criteria. In most instances the studies are non-randomised and do not include control groups.

### **Treatment of hemophilia A and B**

- The scientific evidence is insufficient to determine if there are any differences in effects between recombinant and plasma-derived factor concentrates in replacement therapy for hemophilia A and B.
- The scientific evidence is insufficient to determine if there are any differences in effects between different dosing strategies in replacement therapy with coagulation factor concentrates. Results from one randomised trial, supported by results from several non-randomised studies, suggest fewer joint bleeds and fewer major bleeds in prophylactic replacement therapy compared to on-demand treatment. Furthermore, regular administration of factor VIII starting from early childhood, before the onset of joint bleeds, in patients with severe hemophilia has protective effects against joint damage.
- The scientific evidence is insufficient to determine whether the risk of developing inhibitors against coagulation factors is more, or possibly less, for the prophylactic treatment compared with that seen in the treatment only when necessary on-demand.

- The scientific evidence is insufficient to determine if there are any differences in the long-term effects (>6 years of follow-up) of different treatment regimens in hemophilia A and B. Clinical experience and the results from retrospective, observational studies suggest that early prophylactic treatment yields better results than on-demand treatment, but this should be confirmed by prospective, longitudinal studies.
- The scientific evidence is insufficient to determine which doses and dosing intervals are the most effective when using factor concentrates as replacement therapy to inhibit and/or treat bleeding during surgery.

### **Treatment of patients with inhibitors**

- The scientific evidence is insufficient to determine the effects of treating acute bleeds with the bypass agents, recombinant coagulation factor VIIa and activated prothrombin complex concentrate. Observational studies suggest that treatment is superior to no treatment.
- The scientific evidence is insufficient to assess the effects of prophylactic treatment using recombinant coagulation factor VIIa and activated prothrombin complex concentrates to prevent bleeds in patients with hemophilia A and B with inhibitors.
- The scientific evidence is insufficient to appraise the effects of immunotolerance induction using factor VIII or IX concentrates during a given period when the aim is to eliminate antibody formation (inhibitors) against factors VIII and IX in hemophilia patients with inhibitors. Scientific evidence is lacking on immunotolerance induction in treating inhibitors against factor IX.

### **Treatment of von Willebrand Disease**

- The scientific evidence is insufficient to determine if the incidence of bleeds differs between long-term prophylactic therapy compared to treatment only in conjunction with bleeding when concentrates containing von Willebrand factor and factor VIII (FVIII) are used in patients with von Willebrand disease. The scientific documentation consists of retrospective studies. Prophylactic treatment, particularly for type III von Willebrand disease, probably has good effects, and larger studies are under way to address this.

- Experience concerning regular prophylaxis during long-term indicates a reduced incidence of joint damage and improved quality of life. However, the scientific evidence is insufficient, and further studies are needed.
- Scientific studies that illuminate possible differences between various concentrates containing von Willebrand factor and factor VIII (FVIII) are lacking, as regards their effects of treatment on bleeding.
- Scientific studies that illuminate possible differences between dosing strategies for concentrates containing von Willebrand factor and factor VIII are lacking, as regards their effects on bleeding.

### **Economic aspects**

- The scientific evidence is insufficient to determine which dosing strategy, i.e., on-demand or prophylaxis, is the most cost-effective in treating hemophilia.

### **Ethical aspects**

Treatment, particularly for hemophilia, raises a range of ethical issues due to the high costs involved. Previously, the risk of blood contamination was high. Today, this risk is thought to be so low that it is no longer weighed into the indications for administering factor VIII or IX concentrates. Given the widespread use of recombinant products, it is assumed that such risks have been eliminated. To some extent, plasma-based products are still used in treating von Willebrand disease and patients with inhibitors. The risk for developing inhibitors is high, and can constitute an ethical problem in treating small children from families with previous occurrence of inhibitors. Since patients with hemophilia now reach old age, they are also affected by common disorders such as cardiovascular disease, cancer, and dementia. Managing these problems in relation to bleeding disorders has several ethical and medical implications that have not been studied. An ethical analysis is necessary in each individual case to enable well-grounded decisions about treatment and care.

## Summary and Discussion

This therapeutic area is unique since the diseases are rare and the clinical outcomes cannot be fully evaluated for many years, perhaps decades. Because of this situation, and the fact that contemporary regulations for clinical trials create major financial obstacles in comparing products, it becomes difficult to implement studies yielding high-grade evidence. Hence, well-executed studies are lacking.

No longitudinal studies have compared different types of factor concentrates. One of the reasons is that no scientific evidence is available to suggest that it would be possible to show any differences in effects in the comparatively small and heterogeneous group of patients available for study. Moreover, concentrates have advanced rapidly in recent years, which does not allow the decades needed for follow-up studies of individual product brands. Hence, we must rely on observational studies where treatment varies over time.

Studies often use two measures to determine the effects on bleeding, the number of infusions needed to stop articular bleeding, and a subjective rating of effects (where definitions can vary between studies). More recent studies often show how patients or parents rate the effects. For instance, the effects of a factor concentrate injection on articular bleeding could be rated as: *excellent*, *good*, *moderate*, or *no response*. The definition of *excellent* usually includes a combined assessment of pain and swelling. Hence, an *excellent* effect might be greatly reduced pain and swelling, e.g., within eight hours, and one infusion could be sufficient. *Good* response usually signifies that pain and swelling have not subsided substantially within eight hours, and a second infusion is administered, leading to markedly reduced pain and swelling. *Moderate* response could mean that a third injection is required after a further eight hours, and *no response* suggests that the treatment is comparable to no treatment. Evaluation of treatment effects on acute articular bleeding becomes substantially more difficult when the natural course of a bleed is uncertain. Increased pressure during an on-going bleed eventually helps stop the bleeding. Moreover, pain arising from an inflammation can be difficult to distinguish from any concurrent hemorrhaging.

In the absence of objective, generally accepted, evidence-based methods to identify and document treatment effects, most treatment providers accept the method of defining good treatment effects as marked reduction in pain and swelling, combined with the number of infusions needed.

Assessment of treatment effects, expressed as the number of infusions needed to stop a bleed, or subjective ratings such as *excellent*, *good*, etc have limitations when it comes to comparing outcomes of studies in different patient groups – in part, because previously untreated patients, usually small children, do not have joint damage. Hence, the results are not fully comparable to those from studies in older, previously treated, patients. Slightly older patients with joint damage probably have another course of symptoms and are more difficult to treat than patients with bleeds in a structurally normal joint.

Acknowledging these reservations, the method of documenting treatment effects in most studies nevertheless enables the analyst to weigh the studies together. As a general conclusion, we could say that treatments with contemporary factor concentrates, whether recombinant or plasma-derived, have very good effects on pain and swelling from articular bleeds when the doses are adjusted for weight and type of hemorrhage. One or two doses are often sufficient to stop a bleed.

Treatment of acute bleeding in hemophilia A varies by country when it comes to choosing doses and the intervals between doses. Similar variation is found in prophylactic therapy since opinions vary about dosing, the time to start treatment, and the age to which prophylaxis should continue. There is much to suggest that it is good to start prophylaxis early, before the onset of joint damage (primary prophylaxis), i.e., probably before the first or second articular bleed, and it should continue until adulthood. Even in adulthood, the fundamental problem of hemophilia remains (i.e., lack of a factor in blood), making patients prone to bleeding and exposing them to life-long risk of severe and life-threatening hemorrhaging. For this reason, it would be natural to extend prophylactic therapy into adulthood. More studies are needed to optimise and individualise prophylactic treatment, although such studies would require lengthy follow-up and would be difficult to perform.

Observational studies, primarily in Europe (but especially in Sweden and the Netherlands), have addressed the long-term effects that treatment of hemophilia A and B with regular replacement therapy (prophylactic treatment), from childhood to adulthood, has on the development of joint damage. The results show that the treatment has good effects and hence, it would be considered unethical, in Europe today to conduct a study with better design. In North America, where hemophilia treatment with prophylaxis has received less attention, randomized trials were permitted as late as year 2000 which from a European perspective exposed small children to unnecessary harm.

Patients that develop inhibitors are difficult to treat. Acute bleeds can be treated with bypass therapy, and two different products with fundamentally different modes of action are available. Treatment is costly, and the hemostatic response is difficult to predict. Only a few comparative studies are available. They suggest that effects vary by product and individual. Early treatment in the course of hemorrhaging appears to have decisive effects. Better studies are needed to assess the doses, dose intervals, and long-term effects on joint damage. This applies especially to prophylaxis. Studies are under way.

Several different treatment models address immune tolerance, but all are associated with high costs. Most of the models only involve factor administration, although some add immune suppression. Since controlled trials are difficult to implement, the information currently available comes from register studies, observational studies, and case series. Studies in progress should eventually provide some guidance for cost-effective dosing and selection of factor concentrates, depending on the content of factor VIII and von Willebrand factor. Regarding hemophilia B, treatment for immunotolerance has been insufficiently studied and involves further difficulties due to the risk for allergy and development of nephrotic syndrome.

Comparing the studies is difficult because of variations in agents, doses, dose intervals, and definitions of tolerance development. Most of the retrospective analyses independently found that tolerance developed in 70 to 80 percent of the cases, regardless of agent type and dosing.

Basically this coincides with available register data, as described above. The European immunotolerance register also indicates that high daily doses yield relatively better treatment results. Further studies and data are needed to confirm these findings.

A smaller percentage of patients with von Willebrand disease report little or no effect from treatment with desmopressin and are therefore dependent on replacement therapy with concentrate containing von Willebrand factor. Since von Willebrand factor, in addition to thrombocyte activation, is also the carrier protein for factor VIII (FVIII), patients with more severe forms of von Willebrand disease also have low FVIII even though their ability to produce FVIII is intact. Most of the concentrates used in treating von Willebrand disease contain both von Willebrand factor and FVIII, and immediately increase both of these factors in plasma. The ratio between von Willebrand factor and FVIII varies among different products. Since the concentrates have not been compared, it is difficult to document the importance of the different contents in von Willebrand factor. Moreover, qualitatively, von Willebrand factor varies in the products.

The studies described in the report are retrospective or prospective observational studies without controls and present low-grade evidence. Using concentrates to treat von Willebrand disease is relatively new, and concentrates are reported to consistently yield very good results with few side effects.

Some believe that prophylactic treatment of von Willebrand disease is justified, particularly for type 3 von Willebrand disease. International studies of higher quality are in progress.

To summarise, the use of concentrates to treat some types of von Willebrand disease is shown to have good clinical effects in relation to acute hemorrhages, surgery, and long-term prophylaxis. The various concentrates now available differ in content and have not been studied comparatively in terms of clinical effects. Evidence-based guidelines are lacking, and the assessments of indications, doses, and dosing intervals need to improve.

## Uncertainties and the need for research

### Greater knowledge and more research is needed on methods for treating hemophilia

Hemophilia and the more serious types of von Willebrand disease are rare disorders. Current treatment strategies are based mainly on more or less well-controlled observational studies. The trends suggested by these studies are easily subject to different interpretations and opinions. Current treatment principles are based mainly on “best clinical practice” and, to a lesser degree, on evidence-based medicine. For several reasons it is difficult, if not impossible, to implement large, well-controlled, prospective, longitudinal studies. Such studies are extremely expensive since often they must be conducted in several countries to recruit a sufficient number of patients.

Several areas can be identified where we lack real knowledge, and where better studies are needed (but nevertheless are difficult to perform).

As regards hemophilia, more research is needed in several areas, including the following:

#### *Prophylaxis in patients that have not developed inhibitors*

- When should treatment be started?
- Should prophylactic treatment be stopped, and if so, when?
- Dose regimen
- Long-term evaluation of joint diseases
- Health economy

#### *Inhibitors*

- Impact of heredity and environment on the risk of developing inhibitors
- Protocols for immunotolerance induction treatment
- Prophylaxis in bypass treatment
- Health economy

### *Factor concentrates*

- Improved pharmacokinetic features with longer biological half-life
- Increased potency
- Development of products or tools to avoid intravenous injections and replace them with alternate routes of administration (subcutaneous, inhaled, oral).

The clinical problems concerning von Willebrand disease are somewhat different. Here, the inhibitor problem is not as great as it is in hemophilia, but also less research is available. Regarding von Willebrand disease, the following areas can be emphasised:

- At what plasma levels of factor VIII and von Willebrand factor is treatment with factor concentrate required, i.e., when is treatment with desmopressin insufficient to achieve hemostasis?
- The clinical importance of heterogeneity in von Willebrand factor concentrate?
- Prophylaxis in von Willebrand disease; indications and dosing?
- Products used to treat von Willebrand disease remain plasma-derived. There is a need for products manufactured via recombinant DNA methods, as is already the case with hemophilia. One such product is undergoing clinical trials, but its utility remains to be proven.

Implementing a national treatment register with defined quality indicators is a high priority. A systematic and centralised means of following up patients with hemophilia A, B, and von Willebrand disease is needed within the context of a national quality register aimed at documenting short- and long-term treatment effects. Potentially, treatment could be improved by optimising dosing in accordance with better evidence on the pharmacokinetics of the agents, which could lower the consumption of factor concentrates while maintaining satisfactory treatment effects.

# Foreword

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This systematic review entitled *Treatment of Hemophilia A and B and von Willebrand Disease* has been written with the aim to evaluate the scientific rationale behind the different strategies regarding therapy in severe forms of hemophilia and von Willebrand disease (VWD). The report tries to reflect the state of the art in the treatment of hemophilia regarding prophylaxis, surgery and inhibitors and regarding von Willebrand disease in need of replacement therapy. Treatment options such as desmopressin and antifibrinolytic agents are not addressed in this report.

Hemophilia and von Willebrand disease are rare bleeding disorders and the medical consequences of the bleeding symptoms cannot be fully assessed until after many years. These circumstances make it difficult to study different treatment regimens in a truly evidenced based way. Studies have also been hampered by the tragic history of transmission of blood-borne (HIV and hepatitis C) agents during the 1970s and 1980s when industry and treaters focussed more on safety than on efficacy. This era now belongs to history in terms of new transmissions and therefore the report does not address this problem more than briefly. However, awareness of future hypothetical transmissions always needs to be kept in mind. Today, the risk of development of inhibitors constitutes the main threat to persons with hemophilia.

As few studies are designed regarding the research question addressed and as treatment effects on bleedings are mainly subjectively assessed, the report does not include evidence grading. Instead, the pathophysiologic rationale for replacing the missing clotting factor together with clinical assessment and judgement from observational studies will remain as the main message from this systematic review. It is clear from several studies and observations that infusion of the missing factor stops the bleeding promptly and relieves pain within hours, symptoms well known to last for days if not treated. Furthermore, the median survival of patients with hemophilia has dramatically increased since the introduction of clotting

factor concentrates during the last 40–50 years and is now approaching that of the general male background population. Therefore, the report does not scrutinise replacement therapy as such but focuses on different modes of factor replacement.

Replacement therapy can eliminate the coagulation defect but the cost is very high compared to treatment for many other diseases. Irrespective of mode of replacement therapy the cost mainly depends on the cost for the factor concentrates used. Survival is nowadays comparable to the other population with any treatment mode but the long-term quality of life differs considerably and the economical and ethical questions raised are discussed in the health economics and ethical aspects part of the report. Patients with inhibitors can usually not be treated just by replacing the missing coagulation factor and treatment efficacy is not easy to predict in the single patient. Inhibitors occur already in the small child and pose a heavy burden on the parent/legal guardian who manages the treatment at home. This raises additional ethical and economical issues as even symptoms not elicited by a bleed may be misinterpreted and render expensive treatment.

Congenital bleeding disorders are rare and therefore well developed international collaboration is a mainstay for clinical research in hemophilia and VWD. The need for substantial industry sponsoring is obvious due to the high cost of studies and therefore hemophilia clinicians often have conflicts of interest in a report dealing with use of clotting factor concentrates. In order to secure the objectivity of this report, the expert group has consequently been enlarged by scientific colleagues not involved in the field but who have great knowledge concerning the issues.

# 1. Hemophilia

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## Background

Coagulation factors are proteins produced in the liver. Deficiency of a coagulation factor causes the blood to coagulate poorly (or almost fail to clot at all).

Hemophilia is caused by a hereditary deficiency in coagulation factor VIII (hemophilia A) or coagulation factor IX (hemophilia B). Hemophilia A and B are inherited, gender-linked disorders that nearly exclusively affect men. The prevalence is 1/5 000 males born. Sweden has approximately 1 000 patients with hemophilia, whereof approximately 300 receive regular treatment.

Hemophilia A and B exhibit three levels of severity: severe, moderate, and mild. It is now possible to identify which part of the factor VIII and IX genes is changed and causes different levels of severity in hemophilia. Further, approximately 50 percent of new cases does not have any previously known heredity. Hence, this means that any family could unexpectedly bear a male child with hemophilia.

The risk for bleeding is linked to the degree of severity. In severe cases, initial hemorrhaging occurs before the age of 1 year, and in moderate cases bleeding more commonly starts later, i.e. at 1 to 2 years of age. Bleeding is spontaneous or occurs after minimal trauma. In mild hemophilia, bleeding problems are often related to surgery and injuries. Hence, mild hemophilia might be diagnosed late in life, in connection with surgery and difficulties to stop a postoperative bleeding.

In severe and moderate hemophilia, the main symptom is hemorrhaging primarily affecting the ankle, knee and elbow joints, and muscles. Normal functioning of these joints is necessary to carry out many normal work and recreation related activities and to achieve good quality of life. Joint

hemorrhages lead to chronic joint inflammation and degradation of articular cartilage, leading to stiffness, limitation in movement, and pain. The disease course and joint damage in patients with undertreated hemophilia show similarities to that observed in rheumatic joint disorders. Without adequate medication with the missing factor, severe and moderate hemophilia lead to serious mobility-related disabilities. Patients with hemophilia are also at risk for other severe, sometimes life-threatening types of hemorrhage, e.g., cerebral or gastric hemorrhage.

## Historical Background

Early on, scientists discovered that the coagulation factors lacking in people with hemophilia were found in the blood of healthy individuals. Hence, in the 1940s physicians began to treat hemorrhaging with blood transfusions and started using blood plasma in the 1940s and 1950s. However, blood or plasma transfusion alone cannot completely normalise blood coagulation in an adult male with hemophilia since 5 litre of blood or 2 to 3 litre of plasma must be given. The treatment was ineffective and did not prevent the onset of joint disorders. Mortality was high, and in 1960 the average length of life was 23 years. Treatment improved during the 1960s with access to products that concentrated the coagulation factors two to three times, and the concept of *factor concentrate* was introduced. During the 1970s and 1980s increasingly, more concentrated products were produced, a prerequisite for effective replacement therapy.

An important consequence of the availability of freeze dried factor concentrates with reduced injection volume compared to plasma was the possibility of home treatment. The patient or care-giver could then easily treat bleedings at home after appropriate training at the hemophilia centre. The combination of factor concentrates and home treatment is also the foundation for the kind of regular substitution therapy commonly called prophylaxis. Taken together, the progress in the treatment and development of hemophilia centres explains the observed improvement in average life expectancy from 16 years in 1930 to 23 years in 1960 and normal or almost normal in 2010. In producing hemophilia concentrate from blood plasma, initially no measures were taken to

select donors or inactivate any viral contamination in the product. Consequently, many hemophiliacs who received plasma therapy during the 1960s and 1970s were infected with hepatitis B (HBV), and a majority treated from 1970 to 1986 were infected with hepatitis C (HCV). From 1975 to 1985, plasma-based factor concentrates transmitted HIV to approximately 90 percent of treated patients with severe hemophilia and AIDS has long been the main cause of death in the hemophilia population. Regarding the longer prognosis, virtually all infected with HBV, some with HCV, and none with HIV cleared the virus. Patients with HCV may be treated with interferon, which clears the virus in approximately 60 percent. Vaccine is available only for HBV. After 1986, plasma-based medications became safer through screening of plasma-donors and virus inactivation steps in production. Nevertheless, patients and care-givers alike remain concerned that the current measures to eliminate viruses will not prevent transmission of new, yet unknown, viruses.

An important step forward for understanding hemophilia and improving treatment was the publication in 1984 regarding sequencing the factor VIII gene and the expression and production of human factor VIII in cultured mammal cells [1,2].

## **Modern factor concentrates**

In 1992, approval was granted for the first recombinant coagulation factor VIII concentrate produced in cell cultures. Manufacturers were then no longer dependent on blood plasma, apart from the human albumin in the production process. Virus-inactivated human albumin has been used since the 1960s and no cases of infection transmission have been noted since. In 1993 and 1999, two more recombinant factor VIII concentrates were approved, and in 1997 a recombinant factor IX concentrate was approved. The volumes that must be given intravenously to normalise the blood level of, for example, factor VIII, have decreased from 2.5 L to approximately 10 mL. Hence, it is possible to give adequate and safe replacement therapy for the coagulation factors that patients lack. However, the medication must still be administered intravenously.

# Treatment of hemophilia

## Types of replacement therapy in severe and moderate hemophilia A and B

### 1. On-demand treatment

When clinicians began using blood/plasma transfusions in treatment, the aim was to stop the bleeding. Despite the availability of factor concentrates, some clinicians still consider "stop the bleeding" to be the treatment goal. In other words, they treat *on-demand*, i.e., when bleeding occurs. For the best effect, treatment should be given at the slightest symptom of bleeding. If one waits until bleeding in a joint has developed to the point of considerable swelling and severe pain, then treatment results are worse, and more than two doses of factor concentrate are often required to control the bleeding. Early treatment requires home treatment and educating patients and family members. Dosage is determined by body weight and the site and extent of bleeding. Dosing is also based heavily on clinical experience concerning the level of coagulation factor VIII or IX needed to stop the bleeding in different situations involving patients with severe/moderate hemophilia. Common doses for hemophilia A are 20 to 30 IU per kg for minor bleeding, and 40 to 60 IU per kg for major (severe) bleeding. The same dose is usually repeated after 12 to 24 hours. The factor levels achieved in the blood are then 30–60 percent and 60–100 percent of normal, respectively. Even if the bleeding is stopped, pain subsides, and mobility improves, blood remains in the joint, having harmful long-term effects on the articular cartilage. Unnoticed minimal bleeding could occur during on-demand treatment as well as during prophylaxis, causing damage to joints where patients have not had any symptomatic bleeding.

### 2. Prophylactic treatment

As early as the late 1950s, Professor Inga Mari Nilsson and Professor Margareta Blombäck, internationally renowned pioneers in modern hemophilia treatment, recognised that, just as in diabetes, the only medically acceptable treatment must be based on replacing the missing coagulation factors in patients to completely avoid the onset of hemorrhaging. Replacement therapy in reference to hemophilia has been called *prophylactic treatment*.

Experiences from patients with mild hemophilia have indicated that it is unnecessary to replace the “normal” level of the missing coagulation factor except in conjunction with surgery. The goal was, and is, that the factor level should never fall below 1–2 percent. In the Swedish model, replacement therapy is introduced when a boy begins to place load on muscles and joints, i.e., at approximately 1 year of age. The goal is to initiate replacement therapy before the onset of serious hemorrhaging. With some boys, however, serious bleeding can occur in muscles or joints before 1 year of age. In these cases, replacement therapy may be initiated earlier, although it is unusual to start replacement therapy prior to six months of age.

Except at the beginning, parents administer the injections at home three or four times per week. Replacement therapy continues as the children grow, with the goal that they should have healthy joints as adults. Continuous progress is ongoing in replacement therapy aimed at providing optimum treatment that is also cost effective. Studies are under way, for example, providing daily replacement therapy to achieve more stable blood concentration while concurrently reducing the amount of factor concentrate.

The ambitions and goal with modern therapy for severe and moderate hemophilia A/B are: normal schooling, generally free choice of profession, and absence of orthopaedic surgery as a teenager and later as an adult. Also, to avoid the need for wheelchairs, walking aids, personal assistants, and disability allowances as an adult. For a child’s social development it is important not to be overprotective, but allow them normal activities for their age, which would not be possible without prophylactic treatment.

### ***Secondary prophylaxis***

Internationally, other definitions of the prophylaxis concept have emerged. “Late start” or secondary prophylaxis refers to treatment that begins when the child reaches 3 to 4 years of age and has already developed irreversible joint damage. There is a risk for further joint damage despite this kind of prophylactic treatment. Episodic prophylaxis involves giving frequent injections of factor concentrate for several weeks following major hemorrhaging or surgery. None of these prophylactic options aims

at continuously replace the missing factor that would enable the child to be free from joint damage as an adult.

## **Adults and replacement therapy**

The need for continuing regular replacement therapy differs among adults that have had prophylaxis during childhood. Some adults spread out treatment, taking medication only when they plan to do something strenuous that would increase the bleeding risk in joints and muscles.

The question concerning if and when replacement therapy should be discontinued in adults is a topic for further study.

## **Choice of coagulation factor concentrate**

Several aspects (e.g., safety, quality, manageability, access) must be considered in choosing factor concentrates. If possible, one of the modern recombinant concentrates is chosen for children and patients that have not been treated previously with factor concentrate or blood products. Plasma-based concentrates produced from carefully selected donors and virus inactivated according to current regulatory rules are considered to be as safe as recombinant products. Plasma-based products are used in many countries. Older hemophilia patients, parents of children with hemophilia, and even physicians responsible for hemophilia treatment may resist changing medications, due in part to the negative experiences with blood-borne infections during the 1970s and 1980s, and in part to the risk for developing antibodies (inhibitors). Basically, people are generally hesitant to change factor concentrates “without due cause” but the advent of recombinant concentrates has slowly tuned down this aspect.

## Mild hemophilia

In mild hemophilia, the VIII/IX factor concentration exceeds 5 percent, and spontaneous bleeding is unusual. The factor level in individual patients does not vary much during life, but since the concept of mild hemophilia includes patients having factor levels of 6–40 percent, the tendency and risk of bleeding from different interventions varies widely. A patient with mild hemophilia and a factor level of 6 percent bleeds easier and more, for example from playing football, than would a patient whose basal factor level is 20–30 percent. Also, the tendency to bleed at the same factor level varies among individuals with mild hemophilia. Some patients having a coagulation factor level of 6–7 percent need prophylaxis due to repeated joint bleeds, while others have healthy joints and bleed only from serious injuries or if not treated before surgery.

## Treating mild hemophilia

Patients with mild hemophilia A and factor VIII level above 10 percent of normal can have their hemostasis improved temporarily with desmopressin (Octostim<sup>®</sup> or Stimate<sup>®</sup>). The treatment must be individualised. The product increases factor VIII (and the von Willebrand factor level) by two to three times in the blood for 6 to 8 hours. This means that patients with factor levels of 6–10 percent achieve a level of 12–30 percent after receiving desmopressin. This level can be sufficient for mild injuries, but is not sufficient for surgery. Patients whose factor VIII level exceeds 15–20 percent have a sufficient increase in factor VIII after administering desmopressin to achieve effective hemostasis during minor operations and treatment of injuries. Administration of desmopressin is often complemented with tranexamic acid, which can be given for one to two weeks after an intervention. Several patients with mild hemophilia have desmopressin (nasal spray) and tranexamic acid at home, which they can self-administer for minor injuries.

Patients that have factor VIII levels below 15 percent must be treated with factor concentrate for major injuries or surgical procedures. Since desmopressin does not affect the factor IX level, patients with mild hemophilia B must be given factor IX concentrate for surgery or major injuries.

## **Prophylactic treatment for mild hemophilia**

In growing children with mild hemophilia A or B and factor levels of 5–7 percent, prophylactic treatment with factor concentrate is given occasionally, but in lower doses or less frequently than what would be the case for severe/moderate hemophilia. The patient's individual tendency to bleed determines the dosage and the interval.

## **Treatment of hemophilia in Europe**

Primary prophylaxis was started in Sweden in 1958 and is now routinely started in all children with severe hemophilia. A survey by Ljung et al in 2000 [3] showed that primary prophylaxis was routine in 40 percent, secondary prophylaxis in 40 percent, and on-demand treatment in only 20 percent of 20 hemophilia centres from 16 European countries. Nineteen of 20 centres use only recombinant factor concentrate for newly diagnosed cases.

Another survey by Richards et al in 2007 [4], in which 21 hemophilia doctors from different European countries participated, investigated opinion regarding prophylaxis in adolescence. Fifteen of 17 responders had 70 percent of their boys below 5 years on prophylaxis. Two centres had 30 percent of those boys on regular prophylaxis. Eighteen of 19 stated that they advocated modification of prophylaxis at age 16 to 20 years. How this was done varied widely. A questionnaire was answered by 19/21 doctors regarding clinical outcome for patients aged 16 to 22 years whose prophylaxis was modified and results for 218 patients were reported. Thirty percent were able to stop, 22 percent to reduce prophylaxis, and 48 percent restarted or continued prophylaxis.

Thus, it seems that primary prophylaxis is commonly started in newly diagnosed boys with severe hemophilia in Europe. The question regarding when and if to stop prophylaxis in adolescents or adults needs further study.

## Inhibitors against factor concentrates

Genetic and non-genetic factors influence the risk to develop neutralising inhibitory antibodies (inhibitors), and several large studies under way aim to identify these factors. The factors probably interact together in the individual. In some cases from the 1990s, a coagulation factor concentrate caused an increased inhibitor frequency in patients due to changes in the concentrate during the manufacturing process. Otherwise, there is until now no convincing evidence showing that the type of coagulation factor concentrate per se determines the risk of developing inhibiting antibodies. The strongest connection identified to date is the risk associated with the type of genetic mutation in the factor VIII and factor IX genes respectively. Mutations that lead to production in the liver of a substantially changed protein means that the patient's immune defence is more likely to perceive the administered factor concentrate as foreign and would form antibodies against the factor concentrate.

Inhibitors appear in 20–30 percent of the patients. In approximately half of these patients the inhibitor level is low, and the inhibitors usually disappear after a period of enhanced prophylactic treatment. Otherwise, high levels of inhibitors (high titres) neutralise the administered factor concentrate to become ineffective. The inhibitors usually appear within the first 10 to 30 treatment doses. Clinicians usually try to “wear out” the immune defence by immune tolerance induction (ITI), which means administration of factor concentrate daily at high doses (100–200 IU per kg), which can take 6 to 24 months. Immunotolerance treatment (ITI) is initiated as quickly as possible after inhibitors have been detected, but as a rule only after the titres have decreased spontaneously to below 10 inhibitor units, which can take several months. Since factor concentrate is dosed according to body weight, treatment is more cost effective at a young age when body weight is low. Immunotolerance treatment is successful in up to 60–80 percent of the patients, who then become treatable by using standard replacement therapy. This has major benefits in terms of economics, function, and quality of life. Inhibitors remain despite immunotolerance treatment in approximately 10 percent of all patients that developed them, and they must be treated with “bypassing agents” that activate coagulation and stop bleedings despite factor VIII or IX inactivating inhibitors. There are two products available in Sweden

(year 2010), one plasma-derived activated prothrombin complex concentrate, aPCC (FEIBA<sup>®</sup>) which is used mainly for hemophilia A patients, and one recombinant coagulation factor VIIa (rFVII, NovoSeven<sup>®</sup>), which can be used for hemophilia A and B patients. Dosing is complex and response may differ between patients but both agents usually stop bleedings. They are not as effective as factors VIII and IX and the treatment is not easily followed by blood tests and therefore it is essential to achieve immunotolerance if possible.

Since clinical experience suggests that the response to the two products might differ between patients, it is the general opinion today that both agents are needed. Both factor concentrates are usually used for on-demand treatment, which means that the majority of patients by time will experience progressive joint damage. Trials with prophylactic treatment are under way. A key difference is that the treatment effects of factors VIII and IX concentrates can be monitored by blood tests, which is not possible with aPCC or rFVII. To summarise, this treatment can never be as effective as regular replacement therapy using the coagulation factor that the patient lacks.

## **Surgery in hemophilia**

Given access to modern factor concentrates, any type of surgery can be performed on patients with hemophilia, including those with antibodies. All major operations are performed in hospitals that collaborate with the patient's hemophilia centre since it is necessary to follow the factor concentrate treatment with determinations of factor VIII or factor IX. Nurses and physicians, both specially qualified in hemophilia, participate in major surgery and are responsible for administering factor concentrate during the operation. Through qualified expertise at hemophilia centres and ongoing research and development, treatment related to surgery can be optimised for safe procedures and the greatest possible cost effectiveness.

## Gene carriers

Females carry the genetic predisposition for hemophilia since the genes for factors VIII and IX are located on the X chromosomes.

Depending on the interaction between the female's two X chromosomes and type of gene mutation, the factor VIII/IX levels vary among women carrying the gene. Many women with genes for severe/moderate hemophilia have factor VIII/IX levels near or slightly below the normal lower threshold, but some women have factor levels that correspond to mild hemophilia and this may cause considerable bleeding problems at menstruation, and also in conjunction with different surgical procedures. Genetic carriers should therefore be tested for factor VIII/IX levels and given advice on managing bleeding and preparing for surgery to avoid bleeding.

As with mild hemophilia A, carriers of hemophilia A can be treated with desmopressin to temporarily increase factor VIII levels two to three times, which is sufficient for minor surgery and reduces blood loss during menstruation.

Genetic carriers with low factor VIII or IX levels must be given factor concentrate for major surgery to eliminate the risk for bleeding complications, using the same principles that apply to treatment of mild hemophilia. The literature review does not cover management of female carriers.

## Von Willebrand Disease

Von Willebrand disease (VWD) is also hereditary but since the gene is not located in the gender chromosomes, both men and women can have VWD. In Sweden about 1 000 persons are known to have von Willebrand disease according to registries at hemophilia centres.

VWD is caused by insufficient or impaired function of a protein, i.e. von Willebrand factor (VWF), which is produced in the vessel walls and has dual functions. First, it is needed for blood platelets to function normally in hemostasis, and second it is a carrier of coagulation factor VIII in the blood. Von Willebrand disease presents as bleeding in the mucus

membranes, and also as bleeding in joints among the few individuals with a severe form of the disorder.

## **Severe von Willebrand Disease**

In severe VWD, the VWF protein is virtually lacking and factor VIII level is also very low because of high clearance when FVIII is not bound to VWF. The symptoms include bleeding in the mucous membranes, as in mild VWD, but also articular bleeding as in hemophilia A. Since VWF levels are close to 0 percent, a coagulation factor concentrate that contains von Willebrand factor must be administered.

Recent reviews of the health status of Swedish patients with severe VWD have shown them to have chronic joint damage and disabilities, similar to patients with severe/moderate hemophilia. According to the latest practice guidelines for treating hemophilia in Sweden, these patients should also be offered adequate replacement therapy with von Willebrand factor concentrate. International studies evaluating this topic are ongoing.

## **Mild von Willebrand Disease**

Most patients with a mild form of the disease do not need treatment except in conjunction with surgery. The exception is that women with VWD experience increased blood loss during menstruation and become anaemic if not treated. Primary treatment for mild VWD is tranexamic acid. It has been shown to reduce bleeding problems after minor surgery and blood loss from menstruation. Desmopressin can also temporarily increase the VWF level 2 to 3 times. Hence, it is used in surgery and can also be used for profuse menstruation if tranexamic acid is not sufficiently effective.

# Fundamentals of modern comprehensive care for hemophilia

Modern hemophilia care should be centralised at hemophilia centres that provide care for children and adults with hemophilia and von Willebrand disease and also for carriers. Hemophilia centres have treatment teams consisting of physicians and nurses trained in hemophilia care. The teams also include physiotherapists and social workers and have access to dental specialists for children and adults, dental care for HIV patients, genetic counsellors, infection specialists for HIV and hepatitis patients, orthopaedic surgeons (e.g., for prosthetic surgery in elderly people with hemophilia), gynecologic specialists for carriers and patients with von Willebrand disease, and other specialists according to need. The latter can for example include cardiologists since people receiving modern hemophilia treatment and not infected with HIV or HCV have a life expectancy corresponding to the normal population, and cardiovascular diseases also occur in patients with hemophilia.

Hemophilia nurses train patients and family members in home treatment. They visit and inform people at day care centres, preschools, and schools, and when necessary consult with districts nurses in the patient's home district.

In consultation with physicians and hemophilia nurses, physiotherapists provide information on exercise, joint protection, examination of joint function in children, and suitable recreational activities. Physiotherapists also provide training programmes after joint and muscle bleeding or injury.

## Basic treatment principles

1. Replacement treatment with coagulation factor concentrate starting at an early age (primary prophylaxis) to prevent joint and muscle damage and future disability
2. Early initiation of home treatment for good quality of life and to stop bleeding quickly following possible injury

3. A functioning continuum of care
4. National and international collaboration and research
5. Ongoing assessment and quality control of care
6. Secure access to modern factor concentrate  
(e.g., access to several suppliers).

## **Aims**

In the ongoing health technology assessment in Sweden, it seems indicative that the scientific evidence supporting different treatment regimens of hemophilia and VWD with clotting factor concentrates is unclear. Therefore, we undertook the task to systematically review replacement therapy of hemophilia and VWD in order to better elucidate the efficacy of this mode of treatment. We also address health economic and ethical aspects. However, the purpose was not to compare different brands or types of clotting factor concentrates in terms of risk of transmission of blood-borne agents or the risk of inhibitor development.

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## 2. Methodology for the systematic literature review

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### Assignment

The SBU Board assigned the working group to systematically review the scientific evidence on replacement therapy with coagulation factor concentrate in hemophilia A and B and von Willebrand disease. The report is based on a systematic review of the scientific documentation in the field. The assignment did not include comparison of different brands or types of coagulation factor concentrates in terms of risk of transmission of blood-borne agents or the risk of inhibitor development.

### Objectives

The main objectives of this review have been to evaluate:

- the short- and long-term effects (see below) with different treatment strategies in the preventive use of coagulation factor concentrates in patients with hemophilia A or B or von Willebrand disease
- the clinical effectiveness of recombinant FVIIa concentrate and activated prothrombin complex concentrate for the treatment of acute bleeding episodes in patients with hemophilia A and B with inhibitors.

### Criteria for selecting studies

The general inclusion criteria are described below. The respective sections describe in detail the specific requirements concerning the different questions.

## ***Patient***

Patients with hemophilia A and B with and without inhibitors and patients with von Willebrand disease. All ages.

## ***Intervention***

Administration of intravenous recombinant or plasma-derived factor VIII and factor IX concentrates, recombinant coagulation factor VIIa or activated prothrombin complex concentrates and factor concentrates containing von Willebrand factor (VWF) and factor VIII (FVIII).

## ***Outcomes***

- Number of bleeding episodes or bleeding frequency.
  - Joint bleeding (clinic, joint score, x-ray)
  - Number of infusions of factor concentrate to stop bleeding
  - Life-threatening hemorrhages (hospitalisation, need for transfusion)
  - Other bleeding
  - Care days
- Quality of life measurements
- Tolerance development, defined as the absence of measurable inhibitors and, if applicable, normal half-life and recovery.
- Resource use
  - Orthopaedics
  - Surgery
  - Sick leave – disability pension
  - School absenteeism

## ***Study types***

Systematic reviews, meta-analyses, randomised and controlled trials and observational studies.

## ***Number of patients***

Hemophilia A, at least 20 patients

Hemophilia B, at least 10 patients

Hemophilia A/B with inhibitors, at least 5 patients

von Willebrand disease, at least 20 patients

## Literature search

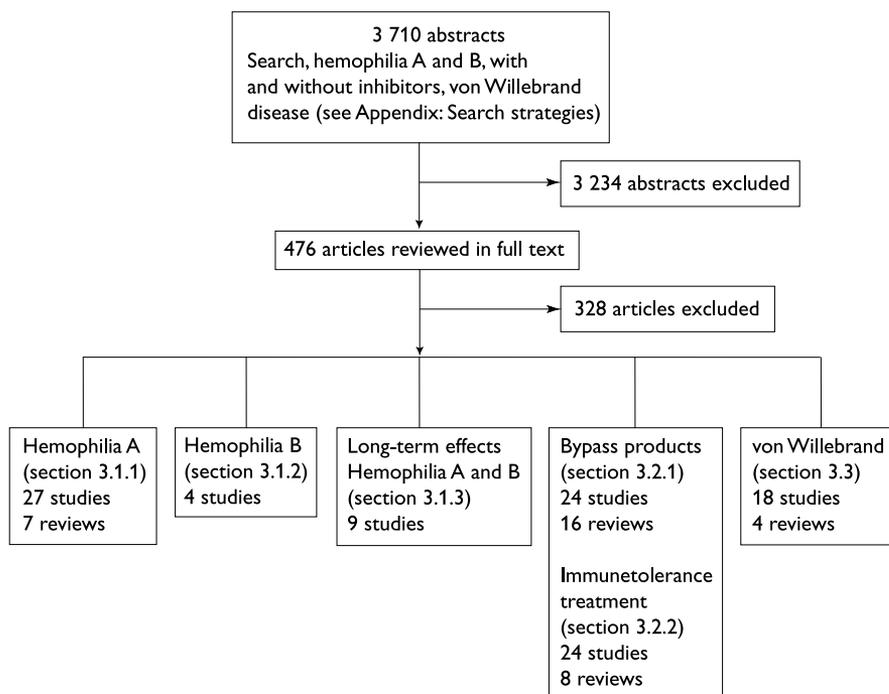
Search strategies were designed based on the questions and the inclusion criteria. Initial searches were conducted in the Cochrane Database of Systematic Reviews (CDSR), the Cochrane Central Register of Controlled Trials, and the NHS Database of Abstracts and Reviews of Effects (DARE) to identify current systematic reviews and meta-analyses. Later searches were conducted in PubMed and Embase. The searches included studies in English, Swedish, Danish, and Norwegian.

The search included literature published from 1985 through spring 2010. In addition to the database searches, reference lists in relevant works were also searched. The literature was later complemented with relevant articles identified from the reference lists in retrieved articles, in documentation from consensus meetings, and reference lists from review articles. (See Appendix “Search strategy” [www.sbu.se/hemophilia](http://www.sbu.se/hemophilia)). Figure 2.1 presents a compilation of the number of abstracts and included studies.

## Study selection

### Relevance to questions

Two individuals independently reviewed the literature search results, presented as abstract lists (brief summaries of the studies). They selected those articles found to meet the established criteria. After examination of the primary selected articles in full text formats, additional articles were excluded since they were found not to meet the inclusion criteria. The selected studies were included in the review.



**Figure 2.1** Flowchart

## Methodological quality

Two independent reviewers evaluated the selected articles (full text) in detail. Members of the group were not allowed to review their own publications.

The review includes evaluation of the studies' subject relevance and methodological quality, with regard to execution and analysis. Reviewers used special review forms to assure objective evaluation of the studies' precision and internal and external validity (see below). The final assessment weighs the studies' quality and clinical relevance to the questions.

Systematic reviews of drug effects should be based primarily on randomised controlled trials (RCT). However, very few randomised trials were identified in this treatment area. Hence, most of the studies included are

observational, i.e., cohort and case control studies, before and after studies or others, and register studies. Many of the studies do not include control groups. The various methodological considerations regarding study design are discussed separately in the individual chapters.

## **Data extraction and presentation**

Following review and evaluation, the relevant outcome data from studies found to meet the established quality requirements was summarised in tables, as was the scientific value of the individual studies. The tables present the study design, patient characteristics, demographic data, type of intervention and control, numbers of included and excluded patients, drop-outs, and treatment effects. Separate reference lists present the studies that met the inclusion criteria, but during review were found not to meet the established quality criteria for inclusion.

## **Assessing the scientific quality of studies**

### **Quality criteria**

The evaluation of study quality and validity is based on a thorough and systematic review of the design, execution, presentation of results, and conclusions of the included studies. Particular emphasis has been placed on the extent to which a study measures what it is intended to measure, i.e., the study's internal validity and precision. Hence, the most critical aspect of the review is evaluating the risk for systematic error due to deficiencies in the design and implementation of a study. To reduce the risk for inter- and intra-evaluator variations, and to more easily summarise the overall quality of the reviewed studies, the reviewers used design-specific review forms for randomised control trials (RCT), observational cohort studies (or non-randomised controlled clinical trials), case control studies (or cross-sectional studies), and systematic reviews (see [www.sbu.se/hemophilia](http://www.sbu.se/hemophilia)).

In assessing a study's quality and clinical relevance, consideration was given to its methodological quality and its ability to provide a valid answer to a particular question. A randomised controlled trial with very

good internal validity is generally viewed to be the study design having the best potential to provide strong scientific evidence in treatment studies. External validity should, as a rule, be at the same level as the internal validity. Extremely well executed cohort studies or controlled studies, where validity is high enough to yield quality comparable to randomisation, can in rare cases be given a high quality rating. This would apply under the condition that allocation to treatment is not related to outcome probability.

## **Study quality and relevance**

A study's scientific quality and relevance, i.e., how well the study answers the question, determines the weight given to the results. The following criteria apply in assessing study quality:

### ***High scientific quality***

High external and internal quality/validity and precision.

All or most of the criteria in the review form are met.

Even if not all criteria are met, this is unlikely to affect the study's quality.

### ***Medium scientific quality***

Medium external and internal quality/validity and precision.

Used if several criteria on the review form are not met and/or the study has not been adequately described. In an overall judgement this is unlikely to affect the study's quality.

### **Low scientific quality**

Low external and internal quality/validity and precision, or if few or no criteria on the review form are met, or if the study description is not satisfactory. In an overall judgement this is very likely to affect the study's scientific quality.

## **SBU's system for grading the evidence of the results**

In grading evidence, SBU uses the international GRADE system to achieve consistency in weighing the scientific evidence.

For each individual question, we compiled the outcome data from studies that met the basic quality requirements. The assessed strength of the evidence, which expresses how certain and lasting the results are judged to be, is based on the study's design and could be affected by various weaknesses or strengths, e.g., in study quality and relevance, consistency, transferability, precision of the data, risk for publication bias, effect size, and the dose-response relationship. An overall judgement of the scientific evidence is then used as a basis for conclusions. The strength of the evidence reflects the overall body of scientific evidence supporting a conclusion, i.e., how many high-quality studies support the conclusion. When the results among studies are heterogeneous and cannot be explained by patient data or study design, the evidence grade is lowered at least one level.

### **Strong scientific evidence**

Based on studies of high-quality and relevance, containing no factors that weaken the overall judgement.

### **Moderately strong scientific evidence**

Based on studies of high-quality and relevance, containing isolated factors that weaken the overall judgement.

### **Limited scientific evidence**

Based on studies of high- or medium-quality and relevance, containing several factors that weaken the overall judgement.

### **Insufficient scientific evidence**

The evidence base is insufficient when scientific evidence is lacking, quality of available studies is poor, or studies of similar quality are contradictory.

## Conclusions

Based on evidence-graded results, SBU's conclusions reflect an overall judgement of the benefits, risks, and cost effectiveness of the methods assessed. The conclusions are based primarily on weighing the findings from high- and medium-quality studies. Conclusions have strong empirical support if they are based on many well-executed studies with high internal validity yielding similar results in terms of effect size and direction. The stronger the evidence, the less likely it is that the results presented will be affected by new research findings within the foreseeable future.

## 3. Systematic Review

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### Sections 3.1.1, 3.1.2, and 3.1.3

The availability of coagulation factor concentrates has dramatically improved morbidity in patients with hemophilia and survival has increased from 16 years to an almost normal life expectancy.

Treatment with factor VIII in association with bleeding in hemophilia A has an effect in terms of improved hemostasis, reduction of pain, and increased mobility. The improvement comes within some hours and usually one single intravenous injection is enough to obtain a lasting effect on bleeding. The side effects of modern factor concentrates are few and mild, except for antibody formation.

Regular administration of factor VIII concentrate from early childhood in patients with severe hemophilia, before joint bleeding has time to occur, has protective effect against joint bleeding and the development of joint damage later in life.

Clinical experiences suggest that replacement therapy with coagulation factor concentrates is effective and enables surgical interventions.

Treatment of acute bleeding in hemophilia B with factor IX concentrate is effective and the situation is similar to that in the treatment of hemophilia A. In the treatment of hemophilia B sometimes allergic reactions are seen, especially with the co-occurrence of an inhibitor.

### Evidence grading of the results

- The scientific evidence is insufficient to determine if there are any differences in effects between recombinant and plasma-derived factor concentrates for substitution treatment of hemophilia A/B.

- The scientific evidence is insufficient to assess if there are differences in effects between different dosage regimens in the replacement therapy with coagulation factor concentrates. Results from one randomised trial, supported by results from observational studies, suggest that prophylactic therapy is associated with fewer joint bleedings and major bleeding episodes compared with “on-demand” treatment and that regular administration of factor VIII concentrate from early childhood in patients with severe hemophilia, before the onset of joint bleedings, has protective effect against joint damage later.
- The scientific evidence is insufficient to determine whether the risk of developing antibodies is more or possibly less for the prophylaxis treatment compared with that seen in the treatment only when necessary “on-demand”.
- The scientific evidence is insufficient to evaluate the long-term effects of different treatment strategies, i.e., prophylactic or “on-demand”. Clinical experience and results from retrospective observational studies suggest that early prophylactic treatment works better than on-demand therapy, but this should be confirmed in prospective longitudinal studies.
- The scientific evidence is insufficient to evaluate what doses and dosing intervals that have proven efficacy in the use of factor concentrate substitution during surgery and to prevent and/or treat bleeding.
- Hemophilia B is less common than hemophilia A and scientific evidence is more limited on regular substitution therapy, but available studies suggest a positive effect.

## Section 3.2

Treatment with recombinant factor VIIa and activated prothrombin complex concentrate, so-called bypass therapy, can arrest bleeding and allows surgical procedures on patients with hemophilia A and B and inhibitors.

## Evidence grading of the results

- The scientific evidence is insufficient to evaluate and to compare the effects of recombinant factor VIIa (rFVIIa) with activated prothrombin complex concentrate (aPCC), so-called bypass therapy, in the treatment of acute bleedings in patients with inhibitors. Results from observational studies indicate that both available bypassing agents can prevent and control bleeding episodes, including surgical settings. Treatment failure occurs. Clinical data suggest that the response may vary between individuals.
- The scientific evidence is insufficient to assess the effect of prophylactic treatment with recombinant factor VIIa and activated prothrombin complex concentrates on the potential to reduce the number of bleeding episodes and to prevent bleedings in patients with inhibitors. More studies are required to appreciate this treatment modality and to elucidate the optimal dosing.
- The scientific evidence is insufficient to evaluate the effect of immune tolerance treatment with factor concentrates for a certain period of time to induce tolerance and to eliminate antibody formation in hemophilia patients with inhibitors. Results from observational studies show that immune tolerance treatment with factor concentrates may be successful in approximately 80 percent of patients with hemophilia A, and in most cases, the result is permanent. Clinical experience suggests that treatment should begin at a young age. Scientific data of immune tolerance therapy for inhibitors to factor IX are scarce and suggest a lower efficacy rate.

### Section 3.3

Treatment with factor concentrates containing von Willebrand factor (VWF) and FVIII is efficacious in acute hemorrhage in patients with von Willebrand disease type 1 and type 2 with insufficient response to desmopressin and in von Willebrand disease type 3. Even if the scientific evidence is based mainly on retrospective clinical studies without controls, published efficacy results are pronounced and clinically relevant.

## **Evidence grading of the results**

- The scientific evidence for the prophylactic treatment with factor VIII/VWF concentrates in patients with von Willebrand disease is insufficient and limited to observational studies. It can be anticipated that prophylaxis, especially in von Willebrand disease type 3, is efficacious and ongoing large prospective studies address this issue. Comparative clinical efficacy studies between concentrate products are lacking. Clinical experience from long-term treatment with regular prophylaxis also indicates reduced occurrence of joint disease and improved quality of life but the scientific evidence is limited and further studies are needed.
- Clinical experience and observational studies suggest that treatment with coagulation factor concentrates containing von Willebrand factor and FVIII as prophylaxis during surgery is efficacious in patients with von Willebrand disease insufficiently responsive to desmopressin.
- The scientific evidence is insufficient to assess if the different factor concentrates differ in their effect on bleeding.
- The scientific evidence is insufficient to permit comparison of the effect of bleeding with different dosage regimens.

## **Section 3.4**

### **Evidence grading of the results**

- The scientific evidence is insufficient to stipulate what strategy of intervention, on-demand or prophylaxis, is cost-effective.

### **3.1 Replacement therapy with factor concentrates in treating severe, moderate, and mild hemophilia A and B**

The availability of coagulation factor concentrates has dramatically improved morbidity in patients with hemophilia and survival has increased from 16 years to an almost normal life expectancy.

Treatment with factor VIII in association with bleeding in hemophilia A has an effect in terms of improved hemostasis, reduction of pain, and increased mobility. The improvement comes within some hours and usually one single intravenous injection is enough to obtain a lasting effect on bleeding. The side effects of modern factor concentrates are few and mild, except for antibody formation.

Regular administration of factor VIII concentrate from early childhood in patients with severe hemophilia, before joint bleeding has time to occur, has protective effect against joint bleeding and the development of joint damage later in life.

Clinical experiences suggest that replacement therapy with coagulation factor concentrates is effective and enables surgical interventions.

Treatment of acute bleeding in hemophilia B with factor IX concentrate is effective and the situation is similar to that in the treatment of hemophilia A. In the treatment of hemophilia B sometimes allergic reactions are seen, especially with the co-occurrence of an inhibitor.

#### **Evidence grading of the results (sections 3.1.1, 3.1.2, and 3.1.3)**

- The scientific evidence is insufficient to determine if there are any differences in effects between recombinant and plasma-derived factor concentrates for substitution treatment of hemophilia A/B.

- The scientific evidence is insufficient to assess if there are differences in effects between different dosage regimens in the replacement therapy with coagulation factor concentrates. Results from one randomised trial, supported by results from observational studies, suggest that prophylactic therapy is associated with fewer joint bleedings and major bleeding episodes compared with “on-demand” treatment and that regular administration of factor VIII concentrate from early childhood in patients with severe hemophilia, before the onset of joint bleedings, has protective effect against joint damage later.
- The scientific evidence is insufficient to determine whether the risk of developing antibodies is more or possibly less for the prophylaxis treatment compared with that seen in the treatment only when necessary “on-demand”.
- The scientific evidence is insufficient to evaluate the long-term effects of different treatment strategies, i.e., prophylactic or “on-demand”. Clinical experience and results from retrospective observational studies suggest that early prophylactic treatment works better than on-demand therapy, but this should be confirmed in prospective longitudinal studies.
- The scientific evidence is insufficient to evaluate what doses and dosing intervals that have proven efficacy in the use of factor concentrate substitution during surgery and to prevent and/or treat bleeding.
- Hemophilia B is less common than hemophilia A and scientific evidence is more limited on regular substitution therapy, but available studies suggest a positive effect.

### **3.1.1 Replacement therapy with factor concentrates in treating severe, moderate, and mild hemophilia A**

#### **Introduction**

Optimal treatment of hemophilia is controversial both regarding choice of type of factor concentrate, i.e., plasma-derived versus recombinant coagulation factor concentrates and dosing. The optimal dosing of factor concentrate is an important issue and it is obvious that there is a relatively large difference between different treatment centres and countries depending on tradition, cost of treatment, and the relatively limited available scientific data. Comparison of prophylactic and on-demand treatment is also important especially regarding long-term results. In Sweden, prophylactic therapy has been offered for many years to all patients with severe hemophilia. However, there may be different definitions and opinions regarding dosing and start of prophylactic therapy in other countries, which is important to analyse, and an important task for this report.

Regarding safety, there is an intense ongoing debate about the risk of developing an inhibitor to FVIII when starting therapy in children with severe hemophilia A, and also if there is a difference in risk comparing recombinant and plasma-derived products.

The questions raised in this report regarding the optimal use of factor concentrates are listed below.

#### **Questions**

- Have effects and safety been shown to differ between recombinant and plasma-derived factor concentrate in replacement therapy for hemophilia A?
- Which doses of factor concentrate and dosing intervals have demonstrated effects in replacement therapy in surgery and in preventing and/or treating bleeding?

- Have effects been shown to differ between replacement therapy with factor concentrate given for prevention (prophylaxis) versus treatment (on-demand) for bleeding episodes?

## **Inclusion criteria**

### ***Patients***

Patients with hemophilia A. All ages.

### ***Interventions***

Replacement therapy with recombinant and plasma-derived factor VIII concentrate for prevention (prophylaxis), or treatment (on-demand) of bleeding, and in surgery.

### ***Effects***

Bleeding

- Joint bleeding (clinical, joint score, x-ray)
- Number of infusions of factor concentrate to stop bleeding (hemostasis)
- Life-threatening bleeding (hospitalisation, transfusion need)
- Other bleeding episodes
- Days in hospital care

Resource utilisation

- Orthopaedics
- Surgery
- School absenteeism

### ***Study type***

Systematic reviews, meta-analyses, randomised and controlled trials, observational studies, narrative reviews and consensus reports.

### ***Number of patients***

Hemophilia A, at least 20 patients.

### *Time frame and language*

Literature published since 1985 to 2010 in English, Norwegian, Danish, and Swedish.

### *Exclusion*

Pharmacokinetic and health economic studies have not been included, with the exception of studies where pharmacokinetics and pharmacodynamics are included as a minor part of a treatment study.

## **Results of the literature search and selection of studies**

The systematic literature search generated 178 abstracts, of which 37 were clinical studies that met the inclusion criteria and seven review articles or consensus reports. After reviewing the articles in fulltext, 10 more studies were excluded as not meeting the criteria. Full search strategies are available on request.

Two tables (Table 3.1.1.1a–e and Table 3.1.1.2) present data from the studies retrieved. Studies not included in the tables are mentioned in notes following the tables.

Table 3.1.1.1a–e contains articles that mainly report on studies of different factor concentrates used to treat hemophilia A. Table 3.1.1.2 presents review articles. Section 3.1.3 presents studies concerning long-term effects of different types of replacement therapy. Articles in the text and tables are reported in chronological order.

In general, very few prospective controlled clinical studies have been conducted. Many of the review articles and articles including expert comments build on the same basic data from small, non-randomised observational studies, and case studies of which some are industry initiated.

## Description of studies and results

### a) Studies regarding safety and efficacy with recombinant products (Table 3.1.1.1a)

In a multicentre study from 1993, Lusher and co-workers reported on the treatment effects of recombinant factor VIII concentrate (Kogenate<sup>®</sup>) in 95 patients with severe, moderate, and mild hemophilia A [1]. The main purpose was to study the development of antibodies against factor VIII that could be shown in 20 percent (16/81) of the patients. The incidence of inhibitors in patients with severe hemophilia A was 28 percent (14/49) of whom 9 percent had high titres. Efficacy: Response to treatment was excellent and in agreement with previous studies involving the product.

A study by White et al in 1997 included 69 previously treated patients with hemophilia A. Two patients had moderate hemophilia [2]. Forty-six patients were adults and 23 children (3–17 years). The effect of a recombinant FVIII product (Recombinate<sup>®</sup>) on bleeding and in conjunction with surgical procedures (n=24) was assessed in this study. Efficacy: Good or excellent treatment response on bleeding in 91.7 percent of the cases, and in surgery the efficacy was rated as excellent in all 24 procedures.

In an observational study, Aygören-Pürsun and co-workers in 1997 studied 39 hemophilia A patients with FVIII levels <15 percent; 22 severe, 13 with moderate and 4 patients with mild hemophilia A [3]. Of these, 38 were previously treated patients (PTPs). Ages varied between 2 and 62 years, and the median age was 27 years. Patients participated in the study for one year and were treated with prophylaxis, on-demand, or in conjunction with surgery. Efficacy as rated by patient or physician: Hemostasis was achieved by one injection of factor concentrate in 75.5 percent of bleedings and effect was classified as very successful or successful in 89.8 percent of 1 500 registered bleeding episodes. Regarding safety there was no case of inhibitor development reported but 38/39 patients were previously treated.

Courter et al reported results from a clinical multicentre study (phase-III trial) from year 2001 that used B-domain deleted recombinant factor VIII concentrate (ReFacto<sup>®</sup>) in 92 previously untreated children with severe hemophilia A [4]. Only 27 patients were reported

to have had primary or secondary prophylactic treatment. (The definition of *prophylaxis* is vague, and only isolated “prophylaxis patients” received *primary prophylaxis* defined as patients treated with one to three infusions each week for >14 days). The number of bleeding episodes in these 27 patients was reduced from a mean of 14 bleeding episodes during on-demand therapy corresponding to 18 episodes per year to a mean of five bleeding episodes during prophylaxis corresponding to four episodes per year. The patient served as its own control. Efficacy: 65 percent of bleeding episodes responded to one injection of factor concentrate. The response of an infusion of factor concentrate was rated as excellent or good in 93 percent. In 40 surgical procedures treatment was rated as very useful or useful in all procedures. Transfusion was required in 1/40 surgical interventions. Only 54 percent of the patients had completed this study (5 treatment years or  $\geq 50$  treatment days) when the article was written. Thirty-two percent developed inhibitor, whereof 12 percent were high-titre type. Forty-nine centres in 15 countries participated, and included 101 patients. Patients reported here are also reported in the study by Lusher 2003 [5].

Yoshioka et al published in 2003 results from a post-marketing study of 43 previously untreated patients with severe or moderate hemophilia A, aged 3 months to 32 years [6]. The observation time was 11 to 80 months, (mean of 5). Patients were treated with rFVIII concentrate (Kogenate<sup>®</sup>), but dosing is not reported in this study. Exposure time varied between 1 and 48 days. Efficacy: 94.8 percent of 951 reported bleedings responded to a single infusion of factor concentrate and response to treatment was markedly effective or effective in 94.8 percent of bleeding episodes. Inhibitors developed in 34.9 percent of the patients of whom 11.9 percent were high responders.

Lusher et al reported in 2003 on findings from three studies involving B domain-deleted recombinant factor VIII concentrate (BDD-rFVIII, ReFacto<sup>®</sup>). In Table 3.1.1.1a, we only report results from one of these that presents data from a prospective study with 113 previously treated patients with a median of 313 exposure days [5]. Efficacy: 73 percent of 10 594 bleedings responded to one infusion of factor concentrate. Treatment response was rated as excellent or good in 97 to 99 percent of the

infusions. Safety: 1/113 previously treated patients developed an inhibitor but review of the medical records of this patient showed presence of an inhibitor prior to study inclusion. The second study in the same publication (not included in Table 3.1.1.1a) reports results from 101 previously untreated patients. Efficacy: 93 percent of bleeding episodes responded with three or fewer infusions. Response to treatment was as reported by patients excellent or good in 92–95 percent of the bleeding episodes. Regarding safety, 32/101 of previously untreated patients developed inhibitors and 16 of those were high responders. Efficacy with use of BDD-rFVIII is reported in the last study (not included in Table 3.1.1.1a) for 48 surgical procedures in 7 previously untreated and 31 previously treated patients as “excellent” or “good” by the surgeon and the treating physicians in 99.6 percent of infusions administered. The blood loss and transfusion requirement was similar to what is found in non hemophiliacs. Parts of study 2 and results from surgery have previously been reported by Courter et al [4].

Lusher and co-workers report in 2004 results from a study with 102 previously untreated patients that were treated with a recombinant FVIII concentrate (Kogenate®) [7]. Of these patients, 21 had mild, 16 had moderate, and 65 had severe hemophilia A. The mean age was 3.9 years, and only five patients were older than 18 years. Patients with mild hemophilia A were treated for at least 2 years. Patients with moderate and severe hemophilia A were treated for more than 5 years or with at least 100 exposure days, and the mean time in the study for the patients was 4.2 years. Efficacy: 82 percent of bleeding episodes responded to a single dose of factor concentrate, and the mean dose was  $42.2 \pm 23.9$  IU/kg. Twenty-four patients did not complete the study for various reasons, e.g. inhibitor development (n=7), lost to follow-up (n=7), non-compliance (n=5), consent revoked (n=4), and protocol violation (n=1). Four additional patients were enrolled, but were not treated according to the protocol. Inhibitor incidence was 29 percent (19/65) in patients with severe hemophilia A.

**b) Studies regarding safety and efficacy with recombinant or plasma products after modification such as change of stabiliser or addition of a viral inactivation step in production (Table 3.1.1.1b)**

A study by Powell et al published in 2000 presented the experience from two centres with 37 previously treated patients with hemophilia A aged 13 to 66 years [8]. The patients had at least 100 exposure days. They received a plasma-derived FVIII concentrate (KOATE-HP®), administered at least twice per week. It was also assessed in surgery (n=5). The main aim of the study was to evaluate immunogenicity with Koate-DVI® with two viral removal steps (solvent detergent and dry heat 80° for two hours). Efficacy: 82 percent of 306 registered bleedings were managed by one single injection of FVIII. The two centres used partly different definitions on response to treatment of bleedings. Centre 1: Adequate response in 87.1–95.2 percent of bleeds or partial response in 4.8–18.5 percent. Centre 2: Excellent response 18.8–36.7 percent and moderate response in 6.1–14.5 percent of bleeds. This makes evaluation of this rather small study difficult but the fact that 82 percent of bleeds responded to a single factor VIII infusion indicates that efficacy is similar to other products. Safety: The product with two viral inactivation steps did not cause inhibitor developed in any of the previously treated patients.

In an open observational multicenter study, Tarantino and colleagues in 2004 reported results for 111 previously treated hemophilia A patients. The median age was 18 years [9]. Patients were treated with 25 to 40 IU/kg recombinant factor VIII produced with an albumin free method (r-AHF-PFM, Advate®) on at least 75 occasions. Efficacy: Hemostasis was achieved in 93 percent of 510 registered bleedings with one injection of r-AHF-PFM. The effect of treatment was rated as excellent or good in 86 percent of all bleeding episodes. Safety: One patient developed transient low titre inhibitor.

Nemes and co-workers published in 2007 an observational study with 56 previously treated severe hemophilia A patients [10]. The study contained a pharmacokinetic assessment of two different plasma-derived FVIII (Immunate® versus Immunate S/D®), and an assessment of a shorter prophylaxis period of 0.1 to 5.2 months, or on-demand treatment.

Efficacy: 89 percent of bleeding episodes responded to one injection of FVIII. The effect on bleeding was excellent or good in 96 percent of the cases. Safety: No case of inhibitor development. There were no differences regarding efficacy or safety between the products.

Recht et al presented in 2009 the results of a prospective multicentre clinical trial with B-domain deleted recombinant factor VIII (BDD-rFVIII, ReFacto<sup>®</sup>) as two different clinical studies published in the same paper [11]. Study 1 included a total of 94 previously treated patients (12–60 years) with severe or moderate hemophilia A. Pharmacokinetics performed as randomised double blind crossover in 24 patients showed similar pharmacokinetics compared to full length recombinant FVIII. The pharmacokinetic study was followed by an open label prophylaxis study with BDD-rFVIII during six months. All patients were treated with prophylaxis with BDD-rFVIII  $30 \pm 5$  IU/kg three times weekly for 34.4 weeks (range 21.3–42). Efficacy: More than 90 percent of 187 bleeding episodes resolved with fewer than two infusions of BDD-rFVIII. Forty-three percent of the patients had no bleeding episode. Response to the first infusion of BDDr-FVIII was rated as excellent or good in 70.6 percent of bleedings. Safety: A transient low titre inhibitor that disappeared on continued treatment was found in two patients. Study 2 included 110 previously treated patients with severe hemophilia A (7–70 years). One hundred and four patients received BDD-rFVIII as prophylaxis at least twice weekly and six patients were treated on-demand. Efficacy: 86.7 percent of 490 bleedings stopped with  $\leq 2$  infusions. Twenty-four percent of the patients had no bleeding episode and, the response to a first infusion was rated as excellent or good in 86 percent of bleeds. Safety: One low titre inhibitor disappeared after 3 months with ITI (immune tolerance induction). Two patients had recurrence of a previously known inhibitor. The efficacy and risk of inhibitor development was comparable to full length recombinant FVIII [11].

### **c) Studies regarding differences in outcome with prophylaxis and on-demand treatment (Table 3.1.1.1c)**

Bray and co-workers in 1994 studied 79 previously untreated patients aged 2 days to 50 months with severe hemophilia A [12]. The study was designed as an open, observational study. A recombinant FVIII concentrate (Recombinate®) was given either as prophylaxis or on-demand and for invasive procedures. Seventy-one of the 79 patients that were finally evaluated received at least one rFVIII injection, median 11 injections. Efficacy: 92 percent of 810 hemorrhages responded to one or two injections with factor concentrate. Surgery: 10 invasive procedures were performed where the patients were treated with Recombinate®. Hemostasis was rated as excellent in all except one patient who had developed an inhibitor. Safety: 23 percent (17/71) developed inhibitor of whom five were high responders.

Smith and co-workers in 1996 included 93 children in a retrospective observational multicenter study [13]. Patients with hemophilia A with FVIII <2 percent of whom 70 had on-demand and 27 had secondary prophylactic treatment. Both recombinant and immune-affinity purified plasma-derived concentrates were used. The duration of treatment varied from one month to 18 years, with a median of 2 years. Follow-up time in the study varied between 6.5 months and 6 years. Efficacy: Patients with on-demand treatment had significantly more bleeding episodes compared to patients on prophylaxis (31 vs 3) ( $p < 0.005$ ) bleeding episodes/year. Safety: No case of inhibitor development. In the prophylaxis group 10 patients had IVAD (implantable vascular access device) and 6/10 patients had septicaemia requiring in-hospital care. Consumption of factor-concentrate in the group of patients with prophylaxis was approximately three times higher compared to patients treated on-demand. A cost-effectiveness model estimated that every hemorrhage avoided through prophylaxis corresponded to 1 100 US dollars (USD).

Rodriguez–Merchan and co-workers in 1997 reported results from a Spanish single-centre retrospective study on previously treated patients with severe/moderate hemophilia A/B [14]. One group ( $n=43$ ; age 8–30 years) that was treated on-demand with 25–50 IU/kg and followed for 13.6 years (10–15) was compared with a group of patients who was

switched from on-demand to prophylactic treatment with 20–30 IU/kg (FVIII/IX) every third day for 20.4 months (2–38). The study was then stopped due to the emerging HIV-infection among the hemophilia population worldwide. Six patients had inhibitors on inclusion and no regular treatment with factor concentrate. The average change in clinical score and joint score was compared between the two treatment groups. Efficacy: There were no significant differences between groups apart from a significant deterioration in joint score and clinical score in the inhibitor group of patients.

Abshire and colleagues described in 2000 the results from several countries in an observational study [15]. The study included 71 previously treated patients with severe hemophilia A that were treated with a sucrose formulated rFVIII concentrate (Kogenate<sup>®</sup> FS). The dose was 20 IU/kg three times per week for 2 to 4 weeks, followed by the patient's usual prophylaxis, or on-demand treatment for 18 to 24 months. Pharmacokinetics, efficacy, and safety were studied for the sucrose formulated rFVIII concentrate (Kogenate<sup>®</sup> FS) instead of human albumin. Efficacy: 80 percent of 2 585 bleeds responded to one infusion and 75–82.6 percent of the bleeding episodes responded to one infusion of factor concentrate. During the periods of treatment with prophylaxis the patients reported significantly fewer bleeding episodes (0.16 new bleeding episodes per week compared to 0.65 new bleeding episodes per week in the on-demand group). Among the patients in North America, 25/38 reported no bleeding episodes during the prophylaxis period. The effects of the first infusion for each bleeding were reported by the patients to be excellent in 24 to 18.7 percent (North America and Europe) of the cases, and good in 59.4 to 62.5 percent (North America and Europe). Safety: No new inhibitors were detected.

Yee and co-workers reported in 2002 the results from a retrospective single-centre study of the influence of different ages at start of primary prophylaxis and the need for intravenous catheter insertions in these patients [16]. Forty-one patients with severe hemophilia A (n=34) and B (n=7) were reported. Furthermore, a home-treatment programme was evaluated. Thirty-eight of the 41 patients were treated with prophylaxis and 9/38 fulfilled criteria for primary prophylaxis (group 1). Of the 38

patients, 29 started prophylaxis after a median number of 3.5 joint bleeds (group 2). The median age for start of prophylaxis was 3.7 years (range 0.4–12.7). Efficacy: Results from follow-up at median 4.1 years (range 0.3–11.5) showed that patients in group 1 had 0.5 joint bleeds/year before and 0.15 on prophylaxis. The patients in group 2 had 3.5 before and 0.5 joint bleeds per year on prophylaxis. Assessment of a clinical joint score by a physiotherapist showed that 90 percent in group 1 and 70 percent in group 2 had score 0 at follow up. Peripheral venous access was used by 87 percent and thus only eight needed intravenous catheter access. Need for in-hospital care and visits at the outpatient clinic were reduced by 45, 36, and 70 percent, respectively. Safety: Three patients had a low titre (<5 BU, Bethesda units) inhibitor before prophylaxis was started and one patient developed a low titre inhibitor without clinical consequences. All inhibitors disappeared on continued prophylaxis.

Smith MP and co-workers published in 2005 a prospective, postmarketing study with the B-domain deleted recombinant factor VIII concentrate (ReFacto<sup>®</sup>) requested by the European Medicines Agency (EMA) to support a new manufacturing location in the USA [17]. The study included 58 patients (two of whom were previously untreated) with severe or moderate hemophilia A (FVIII <5 percent) that received prophylaxis (n=32) and on-demand treatment (n=28). Efficacy: 92.8 percent of all bleeds were resolved with one or two infusions with Refacto<sup>®</sup> in the prophylaxis group and 95.2 percent in the on-demand group. The median number of spontaneous breakthrough bleeds in the prophylactic group was 6.7. Two patients had inadequate outcome, one was on a lower prophylaxis dose 19.8 IU/kg compared to a mean dose of 29.8 IU/kg for the other patients and one was withdrawn due to inhibitor development. Hemostasis was achieved for seven surgical interventions performed during the study. The type of surgery was not reported. Safety: Two patients developed low-titre antibodies and one of the previously treated patients developed high-titer antibodies against BDD-rFVIII.

Manco-Johnson and co-workers published in 2007 the only randomised trial found to meet the inclusion criteria in the literature search [18]. The study included 65 boys younger than 30 months that were randomised to either prophylactic therapy (n=32) or enhanced episodic therapy (n=33)

with recombinant FVIII (Kogenate<sup>®</sup>). Boys in the prophylactic group received 25 IU FVIII every other day. Breakthrough bleedings, i.e., hemarthrosis, were treated with 40 IU/kg BW extra. The boys in the episodic group were treated on-demand. Joint bleeds in this group were treated with 40 IU/kg on day one and then 20 IU/kg for two more days. The study continued until the boys were six years of age. Outcome as preserved joint structure was evaluated with magnetic resonance imaging (MRI) and conventional radiography by the end of study. Efficacy: 7 percent of the patients in the prophylaxis group (prophylaxis started at 1 to 1.5 years of age) had articular changes at 6 years of age versus 45 percent in the on-demand group. In addition, three boys in the group treated with enhanced episodic therapy had life-threatening bleedings. Safety: Two boys randomised to prophylactic therapy developed inhibitors.

Blanchette et al presented a multicentre study in 2008 including 53 previously treated paediatric patients with severe or moderately severe hemophilia A (FVIII  $\leq$  2 percent) [19]. The number of patients was modest (n=53) although 23 centres participated in the evaluation of a recombinant factor concentrate without human albumin as a stabiliser in any step of the production (Advate<sup>®</sup>). Patients had prophylaxis (rFVIII  $\geq$  46 weeks/ year) modified prophylaxis (any other regimen) or on-demand therapy. The pharmacokinetic part of the study showed that younger children had shorter half-life of injected factor VIII (not product specific) compared to older children. Efficacy: 90 percent of 430 bleeds responded to one to two injections of recombinant FVIII. The treatment response was rated by the care-giver as excellent or good in 93.8 percent of bleeding episodes. The median annual bleeding rate was 4.0 and 4.4 for the prophylactic regimes and 24.4 for on-demand treatment. The treatment effects in surgery and bleeding episodes were similar to other recombinant products. Safety: One patient developed antibodies against factor VIII.

In a study published in 2009 by Collins et al, the bleeding frequency in children and adults with severe hemophilia A in relation to the duration of factor VIII was <1 percent in both groups [20]. The study analysed data from patients that participated in three previous studies with

a recombinant FVIII. Efficacy: Results from the study show an association between bleeding frequency and the calculated time with a FVIII level <1 percent during the week. Thus in the age group 1–6 years, the annual bleeding rate increased by 2.2 percent for each hour spent with FVIII <1 percent. Safety: No safety issues discussed.

**d) Studies with prophylaxis or on-demand treatment reporting orthopaedic or school outcome or resource utilisation (Table 3.1.1d)**

In a retrospective single-centre study in 1996, Liesner and colleagues described the results of prophylaxis during 30 months (range 7–76) in 26 patients with severe hemophilia A and one patient with hemophilia B [21]. The mean dose of factor concentrate was 31.8 IU/kg given three times weekly. Prophylaxis was started at the age of 6.2 years (range 1.3–15.9). Follow-up was on average 30 months (range 7–76). Efficacy: The median number of bleeding episodes per year decreased from 14.7 (range 3.7–35.4) to 1.5 (range 0–12.5). Furthermore, 20/27 patients with arthropathy prior to the start of prophylaxis improved during prophylaxis. Twelve of 27 patients used walking aids/wheelchairs at the start of prophylaxis and 0/27 while on prophylaxis. Quality of life as evaluated by care-giver was improved on prophylaxis. Safety: No new inhibitor developed, 4/9 patients with intravenous port had infections and two of those ports had to be replaced.

Feldman et al presented in 2006 results from a study that included 25 patients with severe hemophilia that received a modified form of prophylaxis [22]. Ten Canadian centres participated. Treatment began with 50 IU FVIII/kg once weekly that could later be increased according to the protocol to 25 IU FVIII/kg every second day if the child had repeated bleeding episodes in one or more joints. Efficacy: At follow-up after median 4.1 years, 36 percent (9/25) had developed a target joint. Safety: One patient developed a transient low titre inhibitor without clinical consequences.

In a study including 131 school children with severe hemophilia A (FVIII <2%), Shapiro et al compared the results in school in relation to bleeding frequency during the year prior to inclusion [23]. Sixty-two percent of

the patients received prophylaxis and 38 percent had on-demand treatment. The median number of bleeding episodes the year before enrollment was 6 in the prophylaxis group versus 25.5 in the on-demand group ( $p < 0.001$ ). The results showed that bleeding frequency and use of prophylaxis correlated with academic performance. Boys with low bleeding frequency performed better in mathematics, and boys that had received prophylaxis >40 percent of their lifetime had significantly better results in mathematics, reading, and in total academic performance. In summary, this study shows that bleeding episodes cause physical disability over time, that school absenteeism affects academic performance and the child's future opportunities, and that prophylactic therapy positively influences academic performance in school.

A single-centre study by Miners et al in 2000 evaluated retrospectively the difference in hospital resource utilisation between patients with severe ( $n = 91$ ) and moderate/mild hemophilia ( $n = 155$ ) [24]. This was accomplished by retrospective data collection regarding hospital in- and out-patient or day-care visits using the hospital patient administration data base. Severe hemophilia was defined as FVIII/IX activity below 0.1 IU/L and mild/moderate as 0.1–0.5 IU/L. It was shown that the severity of hemophilia was an independent predictor of need for in-hospital care ( $p = 0.0001$ ). Furthermore, multivariate analysis showed that the severity of hemophilia, HIV-status, and age were independent risk factors of the rate of day-care visits ( $p = 0.0001$ ). Individuals with severe hemophilia required progressively more day-care visits with increasing age compared to moderate/mild patients whose demand declined with age. Patients with moderate/mild hemophilia were 45 percent (range 31–56), 36 percent (range 30–41), and 70 percent (range 68–73) less likely to need in-, out-patient or day-care visits. They were also 66 percent less likely to have been subjected to orthopaedic surgery than patients with severe hemophilia.

### **e) Studies of treatment with factor concentrate for surgery in hemophilia A (Table 3.1.1.1e)**

In a study published in 1990, Schwartz and co-workers reported results from 107 patients with severe or moderate hemophilia A, of whom 20 patients had been treated previously [25]. The patients were enrolled in a study with three different parts. The first part was a pharmacokinetic comparison between recombinant FVIII Kogenate<sup>®</sup> and a plasma-derived factor VIII concentrate showing similar pharmacokinetics, with the exception that clearance and volume of distribution were slightly lower for recombinant FVIII. The second part of the study was to assess efficacy and safety of recombinant FVIII for home treatment in 76 enrolled patients. The third part of the study was to evaluate the efficacy and safety of recombinant FVIII in surgery. Efficacy with on-demand treatment: 85 percent of the bleeding episodes responded to a single dose of recombinant FVIII. Efficacy in surgery: Hemostasis was excellent in all 32 surgical procedures performed in 26 patients. Safety: Inhibitors developed in 25 percent (5/20) of previously untreated patients and in 2.3 percent (2/86) of previously treated patients.

Scharrer reported in 2000 results from an observational study that was part of a larger multicentre study [26]. The cohort study comprised 15 patients with severe hemophilia A that had undergone 22 surgical procedures (two procedures were performed in one patient and three procedures on three patients). The aim of the study was to investigate if further development of a recombinant factor VIII concentrate (Kogenate<sup>®</sup> FS) influenced the hemostatic effect in conjunction with surgery. There was no control group, but findings were compared against earlier surgical studies using recombinant factor VIII. Twelve of the procedures may be considered as major. The assessment of the effect, i.e. what constitutes excellent and good hemostasis, are not defined. Reported blood loss was within normal ranges for the different surgical procedures used in the study. Safety: One patient had decreased FVIII recovery due to a low titre inhibitor that increased from 0.39 BU to 1.6 BU during treatment after surgery.

In 2008, Negrier and co-workers reported results for surgery in 58 patients with severe hemophilia (FVIII  $\leq 2\%$ ) [27]. They underwent 22 major and 35 minor surgical procedures and eight dental procedures under the protection of recombinant factor VIII concentrate without added albumin in all production steps and in the final product (Advate<sup>®</sup>). The effect of treatment was evaluated by the clinician during the procedure and by other staff postoperatively. The patient's hemophilia physician evaluated the effects after the procedure. Treatment with coagulation factor concentrate was given either as intermittent injections or continuous infusion. Efficacy: Treatment with recombinant FVIII concentrate was deemed to be 100 percent effective in terms of hemostasis in conjunction with, and following, surgery irrespective of method of administration. Safety: No patient developed antibodies against the factor concentrate administered.

### **Information from review articles (Table 3.1.1.2)**

Table 3.1.1.2 summarises information from seven review articles retrieved in the literature search that address similar questions. None of the review articles met the criteria for a systematic literature review.

An expert evaluation and literature review assessed on-demand treatment and primary and secondary prophylaxis by van den Berg and co-workers in 2003 reports, on available evidence addressing different prophylactic regimes, optimum prophylactic regime, dosing, and how long prophylaxis should be pursued [28]. The conclusion was that prophylaxis reduces or prevents articular bleeding and joint damage and should therefore be offered to all children with severe hemophilia, at least until they reach adulthood. The review presents 40 references.

A historical overview including 33 references by Blanchette and co-workers deals with the development of hemophilia treatment and the evidence for primary prophylaxis up to 2004 [29]. The article discusses the time for starting primary prophylaxis, the need for injection ports, how long primary prophylaxis should be given, and compliance (i.e., how well parents follow the recommendations of the hemophilia center).

In one review, Carcao and co-workers summarise the scientific findings on prophylaxis, types, implementation, and effects up to 2003 [30].

In 2007, Hay and co-workers presented a review based on studies available until 2007 regarding primary prophylaxis in children and adolescents, different types of prophylaxis, and costs [31]. They also discuss the basis for prophylaxis in adult hemophilia patients, the consequences of discontinuing prophylaxis in adults, and the costs for prophylaxis in adults. The authors conclude that the earlier prophylaxis is initiated, the greater the benefit in reducing the number of bleeding episodes and joint injuries. As regards prophylaxis in adults, well-performed studies are lacking, and there is no support for starting general prophylaxis in adults with joint damage. Supervision, however, should be individualised. The review includes 17 references.

In 2007, Manco-Johnson and co-workers published a review of important, retrospective, randomised and non-randomised studies comparing prophylaxis with on-demand treatment [32]. They also reported interim results from two randomised trials that were under way when the article was written (ESPRIT Study by Gringeri Italy and the Canadian Tailored Prophylaxis study). The review includes 34 references.

Musso and co-workers reported findings from studies on the safety and effectiveness of all available factor VIII concentrates in 2008 [33]. The authors indicate that no transmission of known viruses or prions has been reported. All reported factor concentrates have good, and similar, effects in the treatment of acute bleeding episodes and for hemostasis in surgery. The risk of inhibitor development in previously treated patients was very low, but 15 to 30 percent in previously untreated patients. Many centres recommend that recombinant factor concentrate should be used as first-line treatment.

A review article by Lee and co-workers compared results in studies with three different recombinant factor VIII concentrates available in 2001. Safety and half-life were similar for three agents, as were dosing requirements and effects in treating bleeding [34].

Three reviews were found in addition to the review articles mentioned above. One is a review with expert comments based on the literature addressing the causes of joint disease in hemophilia, treatment of bleeding, costs for different regimes, quality-of-life studies, and problems with and needs for injection ports [35]. The second article is a review with expert commentary on history, treatment with plasma products and recombinant products, definition and review of prophylaxis regimes presented in the literature, and results presented in the studies. The authors conclude that treatment in countries with access to factor concentrates should have a goal to prevent bleeding episodes and resulting injuries. Prophylaxis must be individualised. This review, does not add anything new to other reviews and is somewhat outside the questions relevant to the SBU assessment [36]. Finally, the same author published a state-of-the-art review with history and biochemistry, including the function of proteins (factors VIII and IX) in coagulation, testing of fetuses, newborns, and carriers, and identification methods for FVIII, IX, and antibodies. Furthermore, it presents an overview of factor concentrates and other drugs used in treatment. It also addresses gene therapy, dosing of different factor concentrates, risks for developing antibodies, and treatment of patients with antibodies. Gene therapy is discussed, as are historical and current perspectives on infection issues. This is an excellent overview, but is considerably outside the objectives assigned to SBU. The article presents 141 references [37].

Generally, the literature addressing the treatment of hemophilia A and B is limited in the sense that the authors of review articles and authors of articles on long-term effects largely base their arguments on the same studies. Hence, the conclusions are similar, i.e., starting prophylaxis at a young age means few or no joint injuries while growing up, fewer bleeding episodes, and lower consumption of health care and surgery.

## Discussion

The tables 3.1.1.1a-e summarises results from 27 studies. Ten studies were found not to meet the established inclusion criteria after closer scrutiny and were excluded. A general, distinguishing feature of the studies compared to other drug studies in other treatment areas is the low number of participants (between 30–131 patients) and that the participants are often divided into groups according to age. This leads to heterogeneity, e.g., as regards the status of the participants' joints on inclusion in the study, which could affect the reported outcomes of treatment.

Pharmaceutical companies initiated most of the studies, which had been preceded by the introduction of a new drug, or change in the formulation of a current drug, the safety and effectiveness of which needed to be verified to comply with the regulations of public agencies. Hence, there are no comparative studies between factor concentrates from different manufacturers, in part because there is no scientific foundation to assume that it would be possible to show any differences in effects in the comparatively small and heterogeneous patient data available to the studies.

Likewise, none of the studies randomise patients or prospectively compare effects in the same patient cohort between plasma-based and recombinant factor concentrates. "Historical data" are used for comparison.

One study [25] includes a pharmacokinetic comparison between a plasma-based and a recombinant factor concentrate from the same manufacturer, but the part of the study addressing treatment effects includes only the recombinant product. Regarding the question of using recombinant versus plasma-derived factor concentrates, only a few comparative studies have been carried out, and they show that the effects (measured as the number of infusions needed to stop articular bleeding) are similar.

The tables include eight studies addressing the effectiveness of factor concentrate in surgical procedures, but in four of these studies the use of factor concentrate in surgery is only a minor component in the clinical trial. Hence, only three studies examine factor concentrate safety and effectiveness in conjunction with surgery as their main purpose, and

where patients had undergone major and minor surgical procedures [25–27]. Effects have been classified as good or excellent, with no difference between different factor concentrates.

Safety in terms of preventing the transmission of possible infections has not been subject to assessment in this literature review, but virus-inactivating and virus-reducing methods used in producing plasma-based factor concentrates have been approved by the Food and Drug Administration (FDA) and EMA, and the products are reported to have a high level of safety.

The definition of severe hemophilia A differs between North America and Europe, where most of the studies have been conducted. In North America, the definition of severe hemophilia A is FVIII below 2 percent, and in Europe it is FVIII below 1 percent. This could have some importance for long-term effects of hemophilia as regards bleeding frequency and joint damage, but does not affect interpretation of the results concerning the effectiveness of individual factor concentrates in treating bleeding episodes or in surgery. Most of the patients included in the studies presented in Table 3.1.1.1a–e have severe hemophilia A, i.e., the largest group of hemophilia patients.

The studies mainly use two parameters to evaluate factor concentrate treatment of an articular hemorrhage. First, the number of infusions needed to stop the bleeding, and second, a subjective rating of effects, where definitions can vary among studies. Most of the more recent studies report patient or parent ratings of effects. This is due to the fact that the majority of patients is on home treatment and do not have to visit the hemophilia centre for treatment or evaluation of treatment. For example, the effect of an injection of factor concentrate on an articular hemorrhage can be rated as: “*excellent, good, moderate, or no response*”. A rating of “*excellent*” usually includes a combined judgement of pain and swelling. Hence, an “*excellent effect*” can be substantially reduced pain and swelling, e.g., within eight hours, and where one infusion is sufficient. A “*good*” response usually means that pain and swelling have not decreased markedly within eight hours, but another infusion of factor concentrate markedly reduces pain and swelling.

The method of rating good treatment effects as a marked reduction in pain and swelling, combined with the number of infusions needed, is generally accepted by clinicians since there is not a generally accepted, objective, *evidence-based* method to identify and report on treatment effects. As regards dosing of factor concentrate to “stop” an articular hemorrhage, in addition to long-term clinical experience there are also results from studies that assess the efficacy of treatment supporting the established routine of administering 30 to 50 IU/kg, depending on the site and estimated extent of the bleeding [18].

The patients in studies reported are categorised as previously untreated patients (PUP) and previously treated patients (PTP). The PUP studies mainly include paediatric patients. In the PUP studies, the focus and endpoints are targeted at safety and inhibitor development, while the PTP studies focus on effects other than safety, e.g., inhibitor development.

Regarding treatment effects expressed as the number of infusions needed to stop the bleeding, or as subjective ratings, e.g., *excellent*, *good*, it is not possible to fully compare PUP and PTP studies since PUP patients seldom have joint damage, which PTP patients do, and the course of a bleeding episode is often more prolonged in a damaged joint.

Results from one study shows an association between bleeding frequency and the time during the week that the factor level is <1 percent [20].

Given the reservations mentioned above, the methods of reporting on treatment effects in most studies make it possible to jointly weigh the results. In summary, we conclude (general conclusion) that treatment with modern factor concentrates, either recombinant or plasma-based, has a very good effect on pain and swelling in joint bleeding at doses of 30 to 50 U/kg adjusted to the patient’s weight and type of bleeding. One or two doses are usually sufficient to stop the bleeding. This applies to studies [3,5,7–10,12,15,25].

## Summary

Treatment with factor VIII concentrate has a documented effect on acute bleeding episodes and to prevent bleeding in surgery. Although the number of patients in each study is limited, the results regarding high efficacy in treatment of bleedings and in surgery are consistent. Even if there are few randomised studies, evidence is accumulating that early start of primary prophylaxis with factor VIII concentrate may prevent the development of hemophilic arthropathy later in life.



**Table 3.1.1.1** Clinical studies in hemophilia A evaluating efficacy of factor VIII concentrates in prophylaxis, surgery and as on-demand treatment.

a. Studies regarding safety and efficacy with recombinant products.

Author Year Reference Country	Study design Sponsors	Population Characteristics Number Gender/Age	Intervention Drug, dose and dosage schedules	Outcome measures	Results	Drop-outs	Study quality and relevance  Comments
Lusher et al 1993 <sup>o</sup> [1]	Multicentre Observational Prospective Part of clinical trial <sup>y</sup>	n=95 Previously untreated children with severe hemophilia A (FVIII <2%) n=59  Moderate hemophilia A (FVIII 2–5%) n=18  Mild hemophilia A (FVIII >5%) n=18	Treated with recombinant FVIII- product on-demand or prophylaxis (Kogenate <sup>®</sup> ). Tested for inhibitors at start and every three months during study period	Study period 1989– 1992  <u>Efficacy</u> Response to treatment  <u>Safety</u> Main issue for the study was to follow development of inhibitors	<u>Efficacy</u> Excellent response to treatment  <u>Safety</u> 16 of 81 (20%) of evaluated patients developed inhibitor to F VIII  14/49 with severe hemophilia after median 9 exposure days 7/16 had high titre antibodies 9/16 had low (<10 BE) titre antibodies  4 patients were started on ITI	125 patients were recruited 98 patients were treated with product 95 patients evaluated	Low
White et al 1997 <sup>o</sup> USA [2]	Prospective Open-label Multicentre Investigation <sup>β</sup>	Previously treated patients (PTP) n=69  Severe hemophilia A n=67  Moderate hemophi- lia n=2  46 adult patients median age 31 years, (range 18–63)  23 children Mean age 12 years, median 13 (range 3–17)	1: Pharmacokinetic eva- luation of recombinant FVIII-Recombinate <sup>®</sup> vs Hemofil M <sup>®</sup>  2: Efficacy evaluation of treatment of bleeding and surgical procedure with Recombinate <sup>®</sup>  Dosing at the discre- tion of investigator and patient  Treatment period 18 months or longer  Median treatment period in the trial 3.7 years (range 1.0–5.7)	Safety and efficacy of treatment with Recombinate <sup>®</sup> in part 2	<u>Efficacy</u> Excellent response for treat- ment of bleeding in 36.2% Good response in 55.5%, fair response in 7.2%, no response in 0.89%, and 0.086% reported worsening  24 surgical procedures in 13 patients: hemostasis excellent in all procedures. Nine surgical procedures were major  <u>Safety</u> Adverse reactions: 13 out of 13 591 infusions (0.096%)  No patient developed an inhibitor	2 patients lost to follow-up	Low

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Table 3.1.1.1a continued

Author Year Reference Country	Study design Sponsors	Population Characteristics Number Gender/Age	Intervention Drug, dose and dosage schedules	Outcome measures	Results	Drop-outs	Study quality and relevance  Comments
Aygören-Pürsün et al 1997 <sup>6</sup> [3] Germany	Observational Open Multicenter study <sup>Y</sup>  Study period 1993–1995	39 patients with hemophilia A with FVIII <15% (0.15 KIE/L) Severe hemophilia A n=22, moderate hemophilia A n=13 mild hemophilia n=4 38/39 PTP (previously treated patients)  Median age 27 years (range 2–62)	Study period one year/patient with recombinant FVIII (Kogenate®)	Main criteria for efficacy  Response to prophylaxis and treatment of bleeding episodes self estimation or by physician graded from 0–4 (4=very successful)	1 500 bleeding episodes  <u>Efficacy</u> Number of infusions of rFVIII required for the treatment of a single episode  75.5% of bleeding episodes were treated with 1 infusion of rFVIII  14.5% of bleeding episodes were treated with 2 infusions of rFVIII  5.6% of bleeding episodes were treated with 3 infusions of rFVIII  1.4% of bleeding episodes were treated with 4 infusions of rFVIII  3.1% of bleeding episodes were treated with 5 infusions or more  Assessment of efficacy Grade 3–4: 89.8% successful or very successful 10.2% little or not successful  <u>Safety</u> No case of confirmed inhibitor	Not reported	Low precision: Sample size too small for statistical power evaluation

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Table 3.1.1.1a continued

Author Year Reference Country	Study design Sponsors	Population Characteristics Number Gender/Age	Intervention Drug, dose and dosage schedules	Outcome measures	Results	Drop-outs	Study quality and relevance  Comments
Courter et al 2001 <sup>δ</sup> [4] USA	Multicentre (49 centres 15 countries)  Observational Phase III study <sup>γ</sup>	n=101 Previously untreated children with hemophilia A FVIII <2%	B-domain deleted R-FVIII ReFacto <sup>®</sup>  Prophylaxis (primary or secondary (n=27) On-demand treatment (n=65)  40 surgical procedures	Study period 1994– 1999  <u>Efficacy</u> Response to infusions, number of bleeds. Blood loss at surgery  <u>Safety</u> Inhibitor development	<u>Efficacy</u> 65% of bleeding episodes responded to one infusion. Hemostatic effect as rated by investigators in on-demand therapy: <i>Excellent</i> or <i>good</i> 93% (90% for hemarthroses 95% for soft tissue /muscular 96% for other tissues)  ( <i>Excellent</i> = abrupt pain relief and clear reduction in joint or bleeding size within 8 hours). Bleeding episodes when on prophylaxis corresponds to 4/year and on-demand 18/ year  Surgical efficacy: Blood loss was as expected for all inter- ventions. Overall assessment: very useful or useful in 100% of procedures  <u>Safety</u> 32 (32%) developed inhibitors 12/32 had peak titre ≥10 BU/ml. No sero conversion for HIV or HCV  Antibodies to Chinese hamster ovary cells were transient in 15/15 patients. Antibodies to mouse IgG were transient in 10/12 patients	9/101 withdrew	Low  Many centres and countries for relatively few patients

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Table 3.1.1.1a continued

Author Year Reference Country	Study design Sponsors	Population Characteristics Number Gender/Age	Intervention Drug, dose and dosage schedules	Outcome measures	Results	Drop-outs	Study quality and relevance  Comments
Yoshioka et al 2003 <sup>δ</sup> [6] Japan	Multicentre Observational study <sup>β</sup>	n=43 Previously untreated patients. Patients with severe (<1%) (n=31), moderate (n=9), and mild hemophilia A (n=3)  Age: 3 months to 32 years, mean age 26 months  Observational period 11–80 months, mean 51 months post marketing study	Recombinant FVIII, Kogenate <sup>®</sup> as episodic therapy  Used doses in the study not reported  Exposure time: 1–48 days, median 12 days	<u>Efficacy</u> Hemostatic efficacy as judged by patient and physician  <u>Safety</u> Inhibitor development and adverse reactions	<u>Efficacy</u> 951 observed bleeding epi- sodes  <i>Markedly effective</i> (subjective evaluation by physician) in 73.8%, <i>effective</i> in 21.0%, <i>slightly effective</i> 3.6% and <i>ineffective</i> in 1.2% and <i>aggravated</i> in 0.4%  Hemostasis was achieved with single dose in 94.8% of the 951 bleeding episodes  <u>Safety</u> Inhibitor development in 34.9%, high responders in 11.6% and low responders <10 BU/ml in 23.3%	4 patients	Low  Dosing not reported in the study
Lusher et al 2003 <sup>δ</sup> [5] USA UK South Africa Sweden	Observational Multicentre study <sup>γ</sup>	Previously treated patients with n=113 (intention to treat)  At least 7 years of age At least 30 previous exposure days  Median age 26 years, range 8–73 years 1994–1997	BDD-rFVIII (ReFacto <sup>®</sup> )	<u>Efficacy</u> On bleeding  <i>Excellent</i> : Abrupt pain relief + clear reduction of bleeding size within 8 hours with one infusion  <i>Good</i> : 2 infusions to attain pain relief and reduction for bleeding size	<u>Efficacy</u> Response to BDD-rFVIII was rated as <i>excellent</i> or <i>good</i> in 97–99% of infusions  84% of bleeding responded to 1 or 2 infusions  Inhibitor development: n=1	Intention to treat 116 of whom 113 were treated	Summary of several studies

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Table 3.1.1.1a continued

Author Year Reference Country	Study design Sponsors	Population Characteristics Number Gender/Age	Intervention Drug, dose and dosage schedules	Outcome measures	Results	Drop-outs	Study quality and relevance  Comments
Lusher et al 2004 <sup>δ</sup> [7] USA, Italy, Germany	Observational Multicentre study <sup>γ</sup>	PUP n=102 of whom 101 were treated with Kogenate <sup>®</sup>  Mild hemophilia A n=21 Moderate hemophilia A n=16 Severe hemophilia A n=65  Mean age 3.9 years, median age 1 years 5 patients were >18 years	Patients with mild hemophilia A were treated for ≥2 years  Patients with moderate or severe hemophilia A were treated for ≥5 years or 100 exposure days  Prophylactic or episodic treatment  1989–1997 Mean time on study 4.2 years (0.4–6.3 years) Mean number of exposure days was 126 (range 1–712)	<u>Efficacy</u> Primary efficacy measure was the number of infusions required for the treatment of bleeding episodes  Secondary efficacy measures were in vivo recovery studies and subjective assessment from patient diaries of efficacy of treatment on bleeding  <u>Safety</u> Incidence of adverse events, inhibitor formation, antibody formation to rFVIII, murine IgG or hamster proteins	<u>Efficacy</u> 82% of bleeding episodes required a single infusion for treatment  Mean dose for treatment of bleeding episodes was 42.2±23.9 IU/kg  <u>Safety</u> Inhibitor incidence in patients with severe hemophilia was 29% (19/65) and overall inci- dence was 20.6%. Low titre <10 BU in 9/21 and transient in eight patients	24 patients stopped prematurely in the study	Low

<sup>α</sup> None of the authors declared any conflict of interest

<sup>β</sup> No reported support from pharmaceutical companies

<sup>γ</sup> Reported support from pharmaceutical companies

<sup>δ</sup> One or more of the authors reported relation to pharmaceutical companies involved in the products

**Table 3.1.1.1** Clinical studies in hemophilia A evaluating efficacy of factor VIII concentrates in prophylaxis, surgery and as on-demand treatment.

**b.** Studies regarding safety and efficacy with recombinant or plasma products after modification such as change of stabiliser or addition of a viral inactivation step in production.

Author Year Reference Country	Study design Sponsors	Population Characteristics Number Gender/Age	Intervention Drug, dose and dosage schedules	Outcome measures	Results	Drop-outs	Study quality and relevance  Comments
Powell et al 2000 <sup>6</sup> [8] USA	Observational Two-centre study <sup>6</sup>	Previously treated patients n=37  Age 13–66 years  Without inhibitors Previously treated, at least 100 expo- sure days  6 months treatment in the study, treat- ment at least twice a week	Pharmacokinetic evaluation: Koate-HP <sup>®</sup> (unheated preparation) vs Koate-DVI <sup>®</sup> (heat- treated preparation)  Koate-HP <sup>®</sup> compared to Koate-DVI <sup>®</sup>  Home treatment and treatment of surgical procedures  Median number of exposure days was more than 50 days (range 23–94)	<u>Efficacy</u> Number of treatments for bleedings and evalua- tion of response to treat- ment of bleedings  <u>Safety</u> Viral and inhibitors	<u>Efficacy</u> 82% of 306 bleeding episodes were treated with one single infusion  <u>Centre 1</u> Adequate response to treatment of bleeding episodes: 87.1–95.2% of bleedings Partial response to treatment of bleeding: 4.8–18.5% Inadequate response to treatment of bleeding: 0–1.6%  <u>Centre 2</u> Excellent response: 18.8–36.7% Good response: 18.8–36.7% Moderate response: 6.1–14.5% No response: 0–1.2% Surgery: 5 surgical procedures in 3 patients  No case of inhibitor development	Not reported	Low

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Table 3.1.1.1b continued

Author Year Reference Country	Study design Sponsors	Population Characteristics Number Gender/Age	Intervention Drug, dose and dosage schedules	Outcome measures	Results	Drop-outs	Study quality and relevance  Comments
Tarantino et al 2004 <sup>δ</sup> [9] USA, UK, Sweden	Part 1+3: Pharmacokinetics double-blind, randomised  Part 2 Open cohort multi- centre study <sup>β</sup>	n= 111 Previously treated patients Median age 18 years	Parts 1+3: Pharmacokinetic part, double-blind cross-over Recombinat rAHF vs plasma- and albumin-free prepared recombinant antihemophilic factor (r-AHF-PM, Advate <sup>®</sup> ) Part 2: Prophylaxis 3 to 4 times per week with 25–40 IU/kg rAHF-PFM <sup>®</sup> for at least 75 exposure days	<u>Efficacy</u> Effect on bleeding  <u>Safety</u> Inhibitor development	<u>Efficacy</u> 93% of 510 bleeding episodes were managed with one or two infu- sions  86% had excellent or good rating on effect on bleeding  12% fair effect 2% unknown 0% none  <u>Safety</u> One case with non persistent low-titre inhibitor 2.0 BU	Not reported	Low
Nemes et al 2007 <sup>δ</sup> [10] Hungary, Poland, Bulgaria, Czech Republic, Germany	Observational Multicentre study <sup>β</sup>	n=56 Previously treated patients with severe hemophilia A  Immunate S/D <sup>®</sup> as prophylaxis or on- demand or as both	1: Pharmaco-kinetic evaluation of Immunate <sup>®</sup> vs Immunate <sup>®</sup> S/D  2: Prophylactic treat- ment for 0.1–5.2 months 17–76 ED, mean 47 ED	Efficacy on treatment of bleeding	<u>Efficacy</u> 89% of 623 bleeding episodes required one infusion for treatment of bleeding. Excellent or good response in 96% of all bleeding episodes 29.6 IU/kg  <u>Safety</u> : No development of inhibitor		Low

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Table 3.1.1.1b continued

Author Year Reference Country	Study design Sponsors	Population Characteristics Number Gender/Age	Intervention Drug, dose and dosage schedules	Outcome measures	Results	Drop-outs	Study quality and relevance  Comments
Recht et al 2009 <sup>6</sup> [11] USA, Hungary, Poland, Italy, New Zealand, UK	Multicentre Prospective Observational study <sup>Y</sup>	<u>Study 1</u> 94 previously treated severe hemophilia A patients  Age: Median 24 years (range 12–60) <16 years n=17 ≥16 years n=77  <u>Study 2</u> 110 previously treated severe hemophilia A patients  Age: Median 19 years (range 7–70) <16 years n=45 ≥16 years n=65	B-domain deleted recombinant (BDD) FVIII (albumin free)  <u>Study 1</u> Double blind pharmaco- kinetic comparison of 50 IU/kg for BDD recombinant FVIII with full length R-FVIII  Routine prophylaxis with BDD recombinant FVIII 30 IU/kg 3 times weekly for median 34.4 weeks (range 21.3–42)  <u>Study 2</u> 104 patients routine prophylaxis, investigator prescribed regimes (at least twice weekly) 6 patients on-demand treatment. Subjects should have ≥50 BDD recombinant FVIII exposure days 9 surgeries in 9 patients	<u>Study 1</u> Pharmacokinetic part: Mean factor VIII activity-versus-time pro- files following infusion of 50 IU/kg AUC (IUxh per mL), In vivo recovery  <u>Efficacy of routine prophylaxis</u> Subjects with bleeds and annual number of bleeds during prophylaxis  <u>Efficacy of treatment of break through bleeds</u> Number of infusions for each bleed and response to treatment evaluated by patient/guardian. Frequency of less-than expected therapeutic response (LETE). Safety Inhibitor development  <u>Study 2</u> Efficacy as in study 1 Efficacy in surgery: Blood loss Need for transfusions Safety as in study 1	<u>Study 1</u> Pharmacokinetics: BDD recombinant FVIII was equivalent to full length recombinant FVIII <u>Efficacy</u> >90% of 187 bleeds were resolved with ≤2 infusions No bleeding episodes: 43/94 No spontaneous bleeds: 14/94 Response to first infu- sion was rated as excel- lent or good for 70.6% of hemorrhages. LETE incidence ≤0.5% <u>Study 2</u> <u>Efficacy</u> 86.7% of 490 bleedings resolved with ≤2 infusions. Response to first infu- sion was rated as excel- lent or good for 86% of 490 hemorrhages. 24% had no hemorrhages 49% had no sponta- neous bleedings during prophylaxis. LETE incidence ≤0.2%	<u>Study 1</u> 4/94  <u>Study 2</u> 7/110	Low

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**Table 3.1.1.1b** continued

Author Year Reference Country	Study design Sponsors	Population Characteristics Number Gender/Age	Intervention Drug, dose and dosage schedules	Outcome measures	Results	Drop-outs	Study quality and relevance  Comments
Continued Recht et al 2009 <sup>δ</sup> [11] USA, Hungary, Poland, Italy, New Zealand, UK	See previous pages	See previous pages	See previous pages	See previous pages	<p><u>Safety</u> &gt;90% of subjects achieved &gt;50 EDs with BDDr-FVIII</p> <p><u>Study 1</u> Transient low titre antibody not influencing treatment was found in 2 patients</p> <p><u>Safety</u> 1 patient had a non- transient low titre inhibitor that resolved during 3 months ITI. Two patients had recur- rence of previously detected inhibitor</p>	See previous pages	See previous pages

<sup>α</sup> None of the authors declared any conflict of interest

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**Table 3.1.1.1** Clinical studies in hemophilia A evaluating efficacy of factor VIII concentrates in prophylaxis, surgery and as on-demand treatment.  
**c.** Studies regarding differences in outcome with prophylaxis and on-demand.

Author Year Reference Country	Study design Sponsors	Population Characteristics Number Gender/Age	Intervention Drug, dose and dosage schedules	Outcome measures	Results	Drop-outs	Study quality and relevance  Comments
Bray et al 1994 <sup>a</sup> [12] USA, Italy, France, Germany, Denmark	Prospective Open-label Observational Multicentre study <sup>y</sup>	Previously untreated patients n=79 with severe hemophilia A (FVIII <2%)  Median age 10 months (range 2 days to 50 months)	Treatment with recombinant FVIII (Recombinate <sup>®</sup> ) either on-demand for bleeding or as prophylaxis  10 invasive procedures	Median number of infusions n=11 A total number of 1 785 infusion in 810 bleedings events	71 evaluated patients received at least one infusion of Recombinate <sup>®</sup>  <u>Efficacy</u> 92% of 810 bleedings responded to one or two infusions  <u>Surgery</u> Of 10 invasive procedures (n=10), hemostasis was rated as excellent in nine. One patient bled due to an inhibitor  <u>Safety</u> Inhibitor development in 17/71 patients (23.9%)	Four patients were never treated with recombinant FVIII	Low

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Table 3.1.1.1c continued

Author Year Reference Country	Study design Sponsors	Population Characteristics Number Gender/Age	Intervention Drug, dose and dosage schedules	Outcome measures	Results	Drop-outs	Study quality and relevance  Comments
Smith et al 1996 <sup>a</sup> [13] USA	Observational Retrospective Multicentre study <sup>b</sup>	Randomly selected patient records from boys with severe hemophilia A (FVIII <2%)  70 boys on-demand treatment and 27 on secondary prophylactic treatment  Prophylaxis group: Age: range 6 months to 15 years, median 7 years  Episodic therapy: 1 month–18 years, median 24 months	<u>Cases</u> n=27 Prophylaxis at least three times per week  <u>Controls</u> n=90 Episodic therapy	Recording of bleeding events, factor consump- tion and modelling of cost-effectiveness  Median observatio- nal period 26 months, ranging from 6.5 to 72 months	<u>Efficacy</u> Bleeding events per year 31 vs 3 (episodic vs prop- hylaxis) p<0.005  Use of factor concentrate 1 015 (episodic therapy) vs 3 323 IU/kg (prophylactic therapy) per year  <u>Safety</u> No difference in inhibitor 6/10 in the prophylactic group with IVAD had septic episodes  <u>Modelling of cost- effectiveness</u> Prophylactic care from 3–20 years cost USD 1 100 for bleeding averted and prophylaxis from 3–50 years costs USD 1 380 for bleeding averted  Prophylaxis from age 3 to 50 costs USD 1 870 per bleeding averted, compared with prophylaxis until age 20 years followed by episodic care	NA	Low

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Table 3.1.1.1c continued

Author Year Reference Country	Study design Sponsors	Population Characteristics Number Gender/Age	Intervention Drug, dose and dosage schedules	Outcome measures	Results	Drop-outs	Study quality and relevance  Comments
Rodriguez-Merchan et al 1997 <sup>a</sup> [14] Spain	Single centre Observational Retrospective study <sup>b</sup>  Study period: 1978–1981	Severe/moderate previously treated hemophilia A and B patients  “Group D” n=43 Age 16.3 years (range 8–30)  “Group D+P” n=66 Age 14.8 years (range 2–38)  Inhibitor group n=6 Age 14.5 years (range 5–22)	Group D On-demand treat- ment FVIII/IX 25–50 IU/kg repeated if needed for 2–3 days Follow up 13.6 years (range 10–15)  Group D+P Prophylaxis with 20–30 IU FVIII/IX every 3 days for 20.4 months (range 2–38)	Clinical and radiological evaluation (Pettersson score) at start and end of study period  Patient Score = sum of scores clinical and radiographic scores as recommended by the Orthopaedic Committee of World Federation of Hemophilia for all six joints studied. Hypothetical range 0–186 points	Average decline in patient joint score: Group D: 25.1 Group D+P: 26.9 Inhibitor group: 121.3  Group D and D+P had significantly lower incre- ment in PS (patient Score) than inhibitor group  No significant difference between Group D and Group D+P  In Group D+P: There was no significant difference between those aged <13 and those aged 14–18 years  Those aged <13 years benefited significantly less compared to those aged >19 years (p=0.012) Patients aged 14–18 years benefited more than those >19 years (p=0.001)	No drop-outs	Low

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Table 3.1.1.1c continued

Author Year Reference Country	Study design Sponsors	Population Characteristics Number Gender/Age	Intervention Drug, dose and dosage schedules	Outcome measures	Results	Drop-outs	Study quality and relevance  Comments
Abshire et al 2000 <sup>6</sup> [15] USA, France, Germany	Multicentre Observational study <sup>y</sup>  Study period 1996–1998	Pharmacokinetics 35 previously treated hemophilia A patients  Safety and efficacy  71 previously treated severe hemophilia A, (FVIII ≤2%) patients with more than 100 previous exposure days (ED). Ages 12–60 years	Pharmacokinetic evaluation comparing sucrose formulated Kogenate <sup>®</sup> FS with Kogenate <sup>®</sup> (albumin stabilised) in 35 patients  Safety and efficacy Recombinant FVIII (Kogenate <sup>®</sup> FS )  Prophylaxis 20 IU/kg three times weekly followed by the patients usual treat- ment on-demand or prophylactic treat- ment; 18–24 months treatment period	<u>Efficacy</u> Efficacy of treatment on bleeding, number of infusions need to stop a bleeding episode  <u>Safety</u> Inhibitor formation, viral safety and adverse events	<u>Efficacy</u> In all 80% of 2 585 bleedings responded to one infusion  Number of infusions per bleeding episode on home therapy 1 infusion: 82.6–75% 2 infusions: 12.3–15.7% 3 infusions: 2.7–2.7% 4 infusions: 1.2–1.8% ≥5 infusions: 0.8–1.0%  Less bleeding during prophylactic therapy  25/38 in North America reported no bleeding epi- sodes, 0.16 new bleeds per week vs while on-demand 0.65 bleeds per week  <u>Subjective patient rating of bleeding episodes North America and Europe</u> Excellent: 24–18.7% Good: 59.4–62.5% Moderate: 15.9–17.9% No response: 0.8–1.0%  <u>Safety</u> No case of viral sero conversion. No new inhibitor	No data	Low

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Table 3.1.1.1c continued

Author Year Reference Country	Study design Sponsors	Population Characteristics Number Gender/Age	Intervention Drug, dose and dosage schedules	Outcome measures	Results	Drop-outs	Study quality and relevance  Comments
Yee et al 2002 <sup>a</sup> [16] UK	Single Centre Observational Retrospective study <sup>b</sup>	41 patients with severe hemophilia  Hemophilia A n=34 Hemophilia B n=7  Age at start of prophylaxis: 3.7 years (range 0.4–12.7)  Age at time of study: Group 1: 5 years (range 2.1–8.2)  Group 2: 9.5 years (range 2.8–16.3)	Group 1: (Primary prophylaxis group) 9/38 started prophylaxis at 1.2 years (range 0.4–18)  Group 2: 29/38 started prophylaxis at 4 years (range 2–12.7)	Physiotherapy assessment (clinical joint score)  Joint bleeds/year  Evaluation of home treat- ment training  Venous access and asso- ciated complications  Type and dosing of clotting factor concentrates  Hospital visits	<u>Efficacy</u> Follow up 4.1 years (range 0.3–11.5)  Physiotherapy assessment joint Score Number with score 0 Group 1: 8/9 90% Group 2: 20/29 70%  Number with score 1–10 Group 1: 1/9 10% (median score 1.0) Group 2: 9/29 30% (median score 1.5)  <u>Joint bleeds/year</u> Pre-prophylaxis Group 1: 1.0 (range 0–1) Group 2: 3.5 (range 2–10)  On prophylaxis Group 1: 0.15 (range 0–0.30) Group 2: 0.5 (range 0–1.76)  Home treatment training Time to competence and independence 6 months (3–18)  Venous access and associated complications 33/38  87% used peripheral venous access after training	Results repor- ted for 38 patients	Low

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**Table 3.1.1.1c** continued

Author Year Reference Country	Study design Sponsors	Population Characteristics Number Gender/Age	Intervention Drug, dose and dosage schedules	Outcome measures	Results	Drop-outs	Study quality and relevance  Comments
Continued Yee et al 2002 <sup>a</sup> [16] UK	See previous pages	See previous pages	See previous pages	See previous pages	<p>8/38 had intravenous catheter access 5/38 continued to use catheter after training 10 infections in 6/11 catheters necessitating removal of 5, infection rate 1.74/1 000 catheter days 3/8 children had &gt;1 infection</p> <p>Clotting factor concentrate. All were treated with plasma-derived concentrate until 1996 (hemophilia A) and 1999 (hemophilia B). Dose for prophylaxis 25–40 IU/kg three times a week for hemophilia A and twice a week for hemophilia B patients</p> <p>Hospital visits <i>In-, out-patient</i> and day case visits were reduced by 45, 36 and 70%</p> <p><u>Safety</u> Three patients had low titre inhibitors (&lt;5 BU) pre-prophylaxis and one developed low titre inhibitor during prophylaxis. All inhibitors disappeared on continued prophylaxis</p> <p>No child had high titre inhibitor</p>	See previous pages	See previous pages

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Table 3.1.1.1c continued

Author Year Reference Country	Study design Sponsors	Population Characteristics Number Gender/Age	Intervention Drug, dose and dosage schedules	Outcome measures	Results	Drop-outs	Study quality and relevance  Comments
Smith et al 2005 <sup>6</sup> [17] New Zealand, UK, Germany	Multicentre Open-label Post marketing surveillance Clinical study <sup>Y</sup> Requested by EMA to support a new manufac- turing location in USA	n=58 previously treated patients (PTP) n=2 previously un- treated patient (PUP) with hemophilia A (FVIII <5%)	B-domain deleted recombinant FVIII ReFacto <sup>®</sup> Prophylaxis: n=32 On-demand: n=28 Surgery: 7  Dosing and regimens at discretion of each investigator	<u>Efficacy</u> For prophylaxis: number of break- through bleeds For on-demand treat- ment of bleeds: <i>Excellent, good, moderate, no response</i>  For surgery by surgeon and investigator: <i>Excellent, good, moderate, no response</i>  <u>Safety</u> Inhibitor development Treatment related, serious and allergic type adverse events was recorded	<u>Efficacy</u> Prophylactic treatment 22% completed study with no breakthrough bleeds. <i>Excellent or effective</i> for 27 patients = 93% 81.7% of break-through bleeds resolved with 1–2 infusions. 2 patients had inadequate outcome: 1 patient had mean dose of 19.8 U/kg 3 times weekly compared with mean 29.9 U/kg 1 patient developed inhib- itor (2.4 BU/ml) and was withdrawn  On-demand treatment: 95.2% of bleeds were resolved with 1–2 infusions. Investigators, global assessment of response: <i>Excellent or good</i> for 98.2% of bleeds. Surgical prophylaxis (7 cases): <i>Excellent or good</i> response 100%  <u>Safety</u> 7 serious adverse events unrelated to study. One PTP (1.7%) developed high titre inhibitor. One minimally treated patient developed high titre inhibitor. One PUP developed a transient low titre inhibitor	3/32 prophylaxis patients withdrew	Low

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Table 3.1.1.1c continued

Author Year Reference Country	Study design Sponsors	Population Characteristics Number Gender/Age	Intervention Drug, dose and dosage schedules	Outcome measures	Results	Drop-outs	Study quality and relevance  Comments
Manco-Johnson et al 2007 <sup>a</sup> [18] USA	Open randomised controlled trial Multicentre study <sup>b</sup>  Study period 1998–2000	Severe hemophilia A n=65 younger than 30 months  Prophylaxis n=32 (27 completed protocol)  Enhanced episodic therapy n=33 (22 completed protocol)	Treatment either with intravenous injections with recombinant FVIII (Kogenate <sup>®</sup> ) 25 IU/kg every other day as prophylaxis or as enhanced episodic therapy with recombinant FVIII (Kogenate <sup>®</sup> ) 40 IU/kg at the time of joint hemorrhage and 20 IU/kg at 24 hours and 72 hours after the first dose	Primary outcome was the incidence after 6 years of bone or cartilage damage as detected in index joints with MRI	<u>Efficacy</u> Bone or cartilage damage At 6 years of age 55% of patients in the episodic therapy had normal joints on MRI vs 93.5% of the patients in the prophylaxis group (significant difference, p=0.02)  <u>Bleedings</u> Joint hemorrhages (number/participant/year) 0.63 ± 1.35 vs 4.89 ± 3.57 (prophylaxis vs enhanced episodic therapy), significant difference p<0.001  Total number of hemorrhages 3.27 ± 6.24 (number/participant/year) vs 17.69 ± 9.25 (prophylaxis vs enhanced episodic therapy), significant difference p<0.001  Three boys in the enhanced episodic therapy group had life-threatening bleed  <u>Safety</u> Two patients in the prophylaxis group developed inhibitors vs no patient in the group with enhanced episodic therapy	Reported n=16	Medium

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Table 3.1.1.1c continued

Author Year Reference Country	Study design Sponsors	Population Characteristics Number Gender/Age	Intervention Drug, dose and dosage schedules	Outcome measures	Results	Drop-outs	Study quality and relevance  Comments
Blanchette et al 2008 <sup>6</sup> [19] USA / Europe	Multicentre (12 North American and 11 European centres) Open-label Prospective <sup>y</sup>	n=53 Previously treated patients 52 boys 1 girl Severe (<2%) or moderate hemophilia A <6 years old. Mean age 3.1 ± 1.5 years	Full length albumin free recombinant F VIII Advate® Pharmacokinetic evaluation, Prophylaxis, modified prophylaxis, on-demand treatment	<u>Pharmacokinetics</u> Half life, in vivo recovery  <u>Efficacy</u> Number of joint bleeds annually. Number of infusions to stop bleeds  Rating by care-giver: <i>Excellent</i> = abrupt pain relief and/or clear improvement within 8 hours after 1 infusion <i>Good</i> = as above but possibly requiring >1 infusions  <u>Safety</u> Inhibitor development to FVIII, Chinese hamster ovary cell proteins, murine IgG	<u>Pharmacokinetics</u> Mean terminal half-life 9.88 ± 1.89 hours (increased by 0.4 hours/ year 1–6 years)  <u>Efficacy</u> Mean annual joint bleeds Prophylaxis 0 (range 0.0–5.8) Modified prophylaxis 0 (range 0–6.1) On-demand 14.2 (range 0.0–34.5) 1–2 infusions stopped 90% of bleeds  Rating <i>excellent or good</i> treatment effect in 93.8% of bleeds  <u>Safety</u> No FVIII inhibitors  No evidence of allergic or hypersensitivity responses	All included completed study	Low

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Table 3.1.1.1c continued

Author Year Reference Country	Study design Sponsors	Population Characteristics Number Gender/Age	Intervention Drug, dose and dosage schedules	Outcome measures	Results	Drop-outs	Study quality and relevance  Comments
Collins et al 2009 <sup>δ</sup> [20] UK, Canada, the Netherlands, Sweden, USA, Austria	Observational study <sup>γ</sup>	Hemophilia A Previously treated FVIII level <1%  n=44 Age: 1–6 years  n=99 Age 10–65 years	rFVIII (Advate <sup>®</sup> ) prophylaxis 25–50 IU/kgx3 weekly  Time spent with FVIII level <1, 2 and 5% in relation to total bleeds and hemarthroses  Adherence to inten- ded frequency of FVIII infusions  Registered bleedings in patient diaries	Pharmacokinetics for FVIII for each patient  Time/week calculated with FVIII level <1, 2 and 5%  Bleeds/year Adherence to regimen	<u>Efficacy</u> Time spent with low FVIII appeared more important than weekly FVIII dose. If time with FVIII level <1% increases 10% there will be 44% more bleeds in 1–6 years old and 26% more bleeds in 10–65 years old  Median number of bleeds/year 3.0 25% of 1–6 years old and 16% of 10–65 years old had no bleeds.  Multivariate analysis on pharmacokinetics: all bleeds increased in 1–6 years old as half life decreased. No associa- tion with bleed rates and pharmacokinetics in 10–65 years old	Uncertain	Low  Precision: Sample size too small

<sup>α</sup> None of the authors declared any conflict of interest

<sup>β</sup> No reported support from pharmaceutical companies

<sup>γ</sup> Reported support from pharmaceutical companies

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**Table 3.1.1.1** Clinical studies in hemophilia A evaluating efficacy of factor VIII concentrates in prophylaxis, surgery, and as on-demand treatment.

**d.** Studies reporting orthopaedic or school outcome or resource utilisation with prophylaxis and on-demand treatment.

Author Year Reference Country	Study design Sponsor	Population Characteristics Number Gender/Age	Intervention Drug, dose and dosage schedules	Outcome measures	Results	Drop-outs	Study quality and relevance  Comments
Liesner et al 1996 <sup>a</sup> [21] UK	One centre Observational Retrospective study <sup>b</sup>	Severe hemophilia A n=26 One patient with severe hemophilia B. All on regular pro- phylaxis for at least 6 months  Mean age at start of prophylaxis 6.2 years (range 1.3–15.9)  Mean age at time of study 8.5 years (range 2.9–17.7)	Retrospective analysis of significant bleeds, hospital admissions, days from school before start of prophylaxis  Prophylaxis three times per week for hemophilia A patients and twice a week for hemophilia B patients for 6 months before study start and during study mean duration 30 months (range 7–76)  The dose and interval was adjusted according to breakthrough bleeds  8/27 needed porta cath 1/27 a Hickman line 2 boys were on ITI before starting prophylaxis	Factor concentrate consumption during prophylaxis  Musculoskeletal outcome (target joints, muscular wasting evaluated by physiotherapist). Use of crutches, wheelchairs  Hospital admissions and school absences  Quality of life patients and parent satisfaction	Factor concentrate consumption during prophylaxis median 4 900 IU/kg/year (range 1 900–8 200 IU)  <u>Efficacy</u> Musculoskeletal outcome (target joints, muscular wasting, contracture)  18/27 (67%) had target joints at start of study  3/27 on study  17/27 (63%) had significant wasting before and 12/27 (44%) on prophylaxis  10/27 (37%) had contracture before and 7/27 (26%) on prophylaxis  Use of crutches, wheelchairs 12/27 on entering study 0/27 on prophylaxis	All included completed study	Low

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Table 3.1.1.1d continued

Author Year Reference Country	Study design Sponsors	Population Characteristics Number Gender/Age	Intervention Drug, dose and dosage schedules	Outcome measures	Results	Drop-outs	Study quality and relevance  Comments
Continued Liesner et al 1996 <sup>a</sup> [21] UK	See previous page	See previous page	See previous page	See previous page	<p>Median average number of bleeds/year before 14.7 (range 3.7–35.4) and 1.5 (range 0–12.5) on prophylaxis. Hospital admissions for bleeds 20 before and 0 on prophylaxis</p> <p><u>School absences not recorded before</u> 22/27 in school age. No one had missed &gt;1 school day due to breakthrough bleeding on prophylaxis</p> <p><u>Quality of life patient /parent satisfaction</u> All state that quality of life improved when on prophylaxis</p> <p><u>Safety</u> No inhibitor development 4/9 with iv port had infection 2/4 were replaced</p>	See previous page	See previous page
Feldman et al 2006 <sup>a</sup> [22] Canada	Observational Prospective Multicentre study <sup>y</sup>	Hemophilia A n=25 FVIII <2% Age 1–2.5 years No target joints at inclusion	rFVIII (Kogenate®) Tailored prophylaxis  Step 1: 50 IU weekly Step 2: 30 IU/kg twice weekly Step 3: 25 IU/kg alternate days	Bleeding frequency Target joint development. Physiotherapy and radiographic outcomes	<p><u>Efficacy</u> At median follow up 4.1 years 9/25 = 36% developed target joint</p> <p>28% had escalated to alternate day prophylaxis at 5 years</p> <p><u>Safety</u> One patient developed a transient low titre inhibitor of 3.4 BU</p>	28 non-eligible patients. One refused of 26 eligible patients	Medium  Precision: Sample size too small

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Table 3.1.1d continued

Author Year Reference Country	Study design Sponsors	Population Characteristics Number Gender/Age	Intervention Drug, dose and dosage schedules	Outcome measures	Results	Drop-outs	Study quality and relevance  Comments
Shapiro et al 2001 <sup>δ</sup> USA [23]	Multicentre cross-sectional Population-based cohort study <sup>γ</sup>	n=131 School age children with severe hemophilia A with basal FVIII level <2% (<0.02 KIE/L). On-demand, prophylaxis, 6–12 years old Mean age 9.6 years 62% of children were on prophylaxis and another 9% had previously been on prophylaxis but currently on-demand	Two groups were defined: Treated ever or never on prophylaxis  Ever treated: Duration: 2.7 months to 7.7 years	Academic achievement related to bleeding frequency 12 months before inclusion	Boys with lower number of bleeding episodes (≤11) had higher total achievement in school (p=0.026) and mathematics score (p=0.030) than children in the higher bleeding episode category (≥12). 90% of boys in low bleeding episode group were treated with prophylaxis  Boys with prophylaxis for more than 40% of their lifetime had significantly higher score in mathematics, reading, and total achievement	Median recruitment per centre 77%  131 were included of 181 eligible patients  5 participants were determined ineligible after inclusion due to IQ<70  126 patients available for analysis	Low
Miners et al 2000 <sup>α</sup> UK [24]	One centre Retrospective Data collection study <sup>γ</sup>	n=246 Severe hemophilia n=91 Median age 34 years (range 18–80) Mild/moderate hemophilia n=155 Median age 40 years (range 18–94) (median clotting level 10%, range 1–50)	Retrospective data were collected for the period 1988–1997 from Patient Admission System (PAS) at Royal Free Hospital in London UK regarding in-patient, out-patient, day-case data and orthopaedic procedures and joint replacements	Difference in resource utilisation for patients with severe hemophilia compared to moderate/mild hemophilia	Total 246 individuals = 2 187 patient years 424 in-patients, 4 091 out-patients, 2 757 day-case appointments and 50 orthopaedic interventions  Patients with moderate/mild hemophilia were less likely to have required in-patient/out-patient or day-case visits (45%/36%/70%)  They were 66% and 23% less likely to have undergone orthopaedic procedures or joint replacements compared to patients with severe hemophilia	Not stated	Low

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<sup>β</sup> No reported support from pharmaceutical companies

<sup>γ</sup> Reported support from pharmaceutical companies

<sup>δ</sup> One or more of the authors reported relation to pharmaceutical companies involved in the products

**Table 3.1.1.1** Clinical studies in hemophilia A evaluating efficacy of factor VIII concentrates in prophylaxis, surgery, and as on-demand treatment.  
e. Studies of treatment with factor concentrate for surgery.

Author Year Reference Country	Study design Sponsors	Population Characteristics Number Gender/Age	Intervention Drug, dose and dosage schedules	Outcome measures	Results	Drop-outs	Study quality and relevance  Comments
Schwartz et al 1990 <sup>6</sup> [25] USA, UK, Germany, Japan, Italy	Observational Multicentre study <sup>y</sup>  Study in 3 stages (n=107) Stage 1 Kinetics Stage 2 Home- treatment Stage 3 Surgery	Patients with hemophilia A 52 patients with severe hemophilia A with FVIII <2% and 4 patients with moderate hemophilia A On-demand treat- ment but without known inhibitors  Both previously treated and untrea- ted patients  Mean age: 24.2 years (range 1–72)	Recombinant factor VIII (Kogenate <sup>®</sup> ) for home treatment (n=76) of bleeding episodes and a subgroup (n=26) for treatment at surgery or for treatment in severe bleeding	Median duration of home treatment 618 days (range 69–807)  Subjective estimation of effect of treatment on bleeding outcome	<u>Efficacy</u> 85% of bleeding episodes responded to single injection  Mean yearly consumption of recombinant factor VIII 78 000 IU comparable with plasma-derived product  <u>Efficacy in surgery</u> 26 subjects received recombinant FVIII on 32 occasions for major surgical procedures (n=22) or for in-hospital treat- ment of serious hemorrhage (n=10). On all 32 occasions hemostasis was con- sidered to be excellent  <u>Safety</u> 25 % (5/20) of previously untreated patients developed inhibitor and 2.3% (2/86) of previously treated patients	26%	Low  Precision Sample size too small for statistical power evaluation

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Table 3.1.1.1e continued

Author Year Reference Country	Study design Sponsors	Population Characteristics Number Gender/Age	Intervention Drug, dose and dosage schedules	Outcome measures	Results	Drop-outs	Study quality and relevance  Comments
Scharrer et al 2000 <sup>o</sup> [26] Germany, France, USA	Multicentre Observational (part of clinical trial) <sup>β</sup>	n=15 Previously treated patients with severe hemophilia A FVIII <2% Age: 12–60 years	Patients treated with single recombinant FVIII product Kogenate-Bayer®  22 surgical procedures: 15 major 1 minor 6 tooth extractions 2 procedures 1 patient 3 procedures 3 patients  Bolus injections	<u>Efficacy</u> Investigator reported volume of blood loss and hemostasis  <u>Safety</u> Not stated: “Safety of product already shown for the product in ongoing clinical trial”	<u>Efficacy</u> Blood loss 0–250 ml (“within normal range for the performed surgeries”) Hemostatic efficacy: excellent in 16 and good in 6 procedures  Historic control: Results comparable with earlier surgical studies with recombinant FVIII  <u>Safety</u> One patient with previous low titre antibody needed higher dose. Maximum titre 1.6 BU decreased to 0.02 BU during treatment. No other inhibitors reported	15 enrolled 15 analysed  Small sample	Low
Negrier et al 2008 <sup>o</sup> [27] France, USA, Sweden, Austria	Prospective International Multicenter Open-label Uncontrolled clinical trial <sup>β</sup>	n=58 Previously treated patients with severe hemophilia A (FVIII <2%) ≥5 years old Patients treated with single recombinant FVIII product for 65 surgical procedures	22 major, 35 minor surgeries 8 dental procedures  Bolus injection or con- tinuous infusion	<u>Efficacy</u> Assessed by surgeon, staff member and hematologist accord- ing to protocol  <u>Safety</u> Inhibitor development and adverse events (AE)	<u>Efficacy</u> Intra and postoperative efficacy: Excellent or good in 100% of procedures regardless of administration method (bolus or continuous infusion)  <u>Safety</u> No FVIII inhibitors reported Seven serious and 149 non- serious adverse events. Only eight non-serious adverse events were possibly or proba- bly related to study product	59 enrolled  58 available for analysis	Low

<sup>a</sup> None of the authors declared any conflict of interest

<sup>β</sup> No reported support from pharmaceutical companies

<sup>γ</sup> Reported support from pharmaceutical companies

<sup>o</sup> One or more of the authors reported relation to pharmaceutical companies involved in the products

**Table 3.1.1.2** Review articles and articles with expert opinions in the treatment of hemophilia A.

Author Year Reference Country	Type of article	Title	Aim	Outcome
Van den Berg et al 2003 <sup>a</sup> [28] The Netherlands	Expert opinion <sup>β</sup>	Prophylaxis for severe hemophilia: Experience from Europe and the United States	Overview and discussion of results of prophylaxis in hemophilia	Prophylaxis reduce or prevent joint bleeds and arthropathy Prophylaxis should be offered to all children with severe hemophilia
Blanchette et al 2004 <sup>a</sup> [29] Canada, Italy, USA, Sweden	Review <sup>β</sup>	Optimising factor Prophylaxis for the hemophilia population Where do we stand	Arguments for primary prophylaxis as optimal care and discussion of unanswered questions	Consensus that a programme of prophylaxis started early in life, before joint damage, should be considered optimal therapy  Prospective studies are needed to determine the cost-benefit ratio between different prophylaxis regimens
Carcao et al 2004 <sup>a</sup> [30] Canada	Expert opinion Review <sup>β</sup>	Prophylactic factor replacement in hemophilia	Discussion of the evolution of prophylaxis – when to start, tailored prophylaxis, duration of prophylaxis, and stopping/tapering prophylaxis, outcome and compliance with prophylaxis, prophylaxis in inhibitor patients	Prophylaxis prevents or slows joint damage, should be started at an early age, question of about how long to treat – lifelong? individualised prophylaxis?
Hay 2007 <sup>a</sup> [31] UK	Review <sup>β</sup>	Prophylaxis in adults with hemophilia	Review of arguments for primary prophylaxis in children vs secondary prophylaxis in adults  Consequences of stopping prophylaxis and financial issues are discussed	Evidence suggests that the earlier prophylaxis is initiated the greater the benefit  Large studies in adults are lacking  No convincing data to support secondary prophylaxis with lifelong on-demand treatment Secondary prophylaxis useful for individual problems (i.e. target joints)  Prospective studies to optimise prophylaxis regimens in adults should be conducted
Manco-Johnson 2007 <sup>a</sup> [32] USA	Review <sup>β</sup>	Comparing prophylaxis with episodic treatment in hemophilia A: Implications for clinical practice	Overview of performed and ongoing studies with different regimens of secondary or primary prophylaxis	Retrospective data support benefit of prophylaxis. Two randomised prospective studies were ongoing

*The table continues on the next page*

**Table 3.1.1.2 continued**

<b>Author Year Reference Country</b>	<b>Type of article</b>	<b>Title</b>	<b>Aim</b>	<b>Outcome</b>
Musso 2008 <sup>δ</sup> [33] Italy	Review of clinical trials and post-marketing studies in hemophilia A <sup>β</sup>	Efficacy and safety of recombinant factor VIII products in patients with hemophilia A	Review of studies of all available (= 4) recombinant FVIII concentrates	No transmission of virus or prions  Recombinant products have low frequency of inhibitors in previously treated patients  Low risk of neo-antigenicity  In previously untreated patients, risk of inhibitor from 15–30%  Recombinant highly efficacious and safe in on-demand, prophylaxis, and in surgical episodes
Lee 2002 <sup>α</sup> [34] UK	Review <sup>β</sup>	The use of recombinant factor VIII products in previously treated patients with hemophilia A: Pharmacokinetics, efficacy, safety, and inhibitor development	Review of studies with recombinant FVIII products in the treatment of previously treated patients	Recombinant products rFVIII and BDD-FVIII (Kogenate <sup>®</sup> , Helixate <sup>®</sup> , Recombinate <sup>®</sup> and ReFacto <sup>®</sup> ) is equally effective as plasma-derived products  25 IU/kg is effective in 70% of bleeds regardless of concentrate

<sup>α</sup> None of the authors declared any conflict of interest

<sup>β</sup> No reported support from pharmaceutical companies

<sup>γ</sup> Reported support from pharmaceutical companies

<sup>δ</sup> One or more of the authors reported relation to pharmaceutical companies involved in the products

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## 3.1.2 Replacement therapy for hemophilia B

### Evidence grading of the results

See section 3.1

### Questions

Same as for hemophilia A (see section 3.1.1).

### Inclusion criteria

Same as for hemophilia A, but at least 10 patients.

### Results of the literature search and selection of studies

Only four studies met the inclusion criteria. Three of the studies involved the recombinant factor IX concentrate (BeneFix<sup>®</sup>). A fourth study used plasma-derived FIX concentrate (Mononine<sup>®</sup>). The studies were clinical, observational studies without controls. Since hemophilia B is a rare disease, studies require the participation of many centres, preferably from several countries. Consequently, few studies address the topic, and the formal evidence grade is low. Table 3.1.2 presents the results from these studies.

### Description of studies and results

In 1996, Shapiro et al reported results from treating 32 hemophilia B patients at different levels of severity that participated in two observational studies; one addressing surgery and the other addressing treatment for acute bleeding episodes [1]. The FIX plasma derivative was administered for acute bleeding, using a mean dose of 58.1 units per kg (range 29.4–103.1) for 1 to 30 days, depending on the severity level of bleeding. For surgery, an average dose of 46.1 units per kg (range 20.9–62.4) was administered. The number of infusions was 12.4 (range 5–17). The effects were judged to be excellent in 100 percent of the cases, and no serious side effects were reported.

Roth et al described the experiences in a prospective multicenter study of recombinant FIX concentrate in 57 severe or moderate hemophilia B patients from 20 centres in Europe and the United States [2]. The study includes on-demand treatment, surgery, and some secondary prophylaxis, and the exposure time is two years. Of acute bleeds, 80.9 percent were controlled with one infusion, and 90.9 percent reported excellent/good response to treatment. The corresponding figure for prophylaxis was 93 percent. Twenty-seven surgical procedures were performed on 20 patients, with 98 percent excellent/good hemostasis. One patient developed a low-titre inhibitor.

Ragni and co-workers described a surgery study from the US and UK in 2002 [3]. Twenty-six previously treated men and two female carriers were treated with recombinant FIX concentrate as coverage for 23 major and 13 minor surgical procedures. In nine procedures the concentrate was given as continuous infusion. Efficacy in terms of surgical hemostasis was rated as excellent or good in 34/35 (97.1%) of the evaluated operative procedures and estimated blood loss was normal according to procedure. Four subjects experienced one or more adverse events, of which none was serious and no inhibitor developed.

In 2005, Shapiro et al reported results from an international, multinational, open-label single-cohort study involving 41 centres and including 63 previously untreated patients, aged one month to 14 years, with severe or moderate hemophilia B. The median exposure time is 37 months (range 4–64). This study was introduced with a pharmacokinetic investigation followed by on-demand or prophylactic treatment for two years or 100 exposure days. Of the acute bleeding episodes, 75 percent were treated effectively with one infusion and 94.1 percent were classified as excellent/good. Thirty-two patients received primary or secondary prophylaxis. Of these, 24 patients received treatment twice or more per week at a mean dose of 72.5 units per kg and a mean duration time of 13.4 months. Regarding patient effects (assessed by patients, care-givers, or attending physicians, depending on the situation) 93.1 percent were classified as excellent, 6.4 percent as effective, and 3/172 as inadequate. Of 30 surgical procedures, 29 reported excellent/good hemostasis. Five allergic reactions were described, and two of the patients developed inhibitors.

## Discussion

Four studies met the inclusion criteria. These are prospective observational studies, one of which includes previously untreated patients. The studies include a relatively high number of patients and, consequently, many centres. The studies address treatment on-demand, surgery, and long-term prophylaxis (in the studies with recombinant FIX concentrate BeneFIX<sup>®</sup>). Outcomes are excellent/good with a few exceptions, and the side effects are those routinely observed in treating hemophilia B, i.e., probably more allergies but fewer inhibitors than found in modern treatment of hemophilia A. Although not reported in the cited studies, one should be aware of the risk of severe anaphylactoid reactions in patients with or without inhibitors and some recommend that the first series of FIX injections are supervised in hospital. The studies yield low-grade scientific evidence, but the effects are substantial and unequivocal compared to evidence on the natural history of hemophilia B. Prophylactic treatment substantially reduces bleeding frequency. Using the search criteria we did not find long-term studies of the medical effects of prophylactic treatment on joint diseases in hemophilia B. However, there is reason to suspect that the situation is similar to that found in hemophilia A.

**Table 3.1.2.1** Substitution therapy in patients with hemophilia B. Acute bleeding, surgery, and long-term prophylaxis.

Author Year Reference Country	Study design	Population Number Age Female/male	Intervention	Outcome measures	Results	Drop-outs	Study quality and relevance
Shapiro et al 1996 <sup>δ</sup> [1] USA	Prospective observational study <sup>β</sup>	32 mild, moderate and severe hemophilia B patients from two studies  On-demand study n=24 Age: 2 days to 9 years, mean 1.5 years  Surgery study n=8 patients with mild hemophilia 13 procedures. Age: 22 days to 53 years, mean age 20.8 years	Plasma-derived FIX (Mononine <sup>®</sup> ) On-demand: 1–30 exposure days mean dose: 58.1 IU/kg (range 29.4–103.1)  Surgery mean dose 46.3 IU/kg, (range 20.9–62.4), number of infusions 12.4 range 5–17	<u>On-demand</u> Safety data  <u>Surgery</u> Hemostasis rated on a 5 grade scale (1, excellent to 5, severe bleeding)	<u>On-demand</u> Excellent safety  <u>Surgery</u> Excellent in all procedures		Low
Roth et al 2001 <sup>δ</sup> [2] International	Prospective observational multicenter international study <sup>β</sup>	Severe or moderate FIX deficiency, previously treated. 57 individuals in 20 sites, Europe and North America  Range 4–56 years, median 23	2 years exposition with FIX concentrate (BeneFIX <sup>®</sup> ). Pharmacokinetics  On demand or prophylaxis, and surgery	Efficacy rating scale on-demand: “ <i>excellent, good, moderate or no response</i> ”  Prophylaxis rating every 3 months: “ <i>excellent, effective or inadequate</i> ”  Surgery: estimated blood loss, 4 point scale	Recovery 33.7%, range 15.3–2.2%. Terminal half-life: mean 19.3 hours (range 11–36)  Stable pharmacokinetic assessment over 2-year study period  <u>On-demand</u> 80.9% of bleeds controlled with one infusion. 90.9% excellent or good response to treatment  <u>Secondary prophylaxis</u> Average dose 40.3 IU/kg (range 13–78 IU/kg) 2–3 times per week. 93% rated as excellent or effective.  <u>Surgery</u> 27 procedures in 20 patients. 98% excellent or good hemostasis  Serious side events: one developed a low titre inhibitor	1 patient withdrew before treatment, 5 withdrew mainly for personal reasons, 50 subjects completed  Rekombinant FIX concentrate BeneFIX <sup>®</sup> 50 IU/kg prior to pharmacokinetic assessment	Medium

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Table 3.1.2.1 continued

Author Year Reference Country	Study design	Population Number Age Female/male	Intervention	Outcome measures	Results	Drop-outs	Study quality and relevance
Ragni et al 2002 <sup>6</sup> [3] USA, UK	Multicentre Prospective (12 treatment sites) Observational study <sup>y</sup>	26 previously treated men with hemophilia B. Age median 36 years (range 3–69) 17/26 Severe 6/26 Moderate 3/26 Mild hemophilia B  2 female carriers for hemophilia B (Factor IX 0.28 kIE/L)	Recombinant FIX 72 hour Pharmacokinetics after 50 IU/kg pre-operatively  Recombinant FIX for replacement in 23 major and 13 minor surgical procedures  Continuous infusion was used in 9/36 surgeries	Graded subjective assessment by subject and physician in consultation with surgeon postopera- tively and 30 days after last dose  <i>Excellent response</i> = response as satis- factory as with the best response with other FIX products  <i>Good response</i> = response as satis- factory as with other FIX products  <i>Moderate response</i> = response less satis- factory than other FIX products  Estimated blood loss during and after surgery, duration of blood loss, transfu- sion requirement, presence of hema- tomas or other bleeding symptoms	<u>Pharmacokinetics</u> Half life 21.32±8.11 hours comparable with plasma- derived concentrate  Recovery %: 33.7±8.99 was 30% less than for plasma-derived concentrate  There were no differences in haemostasis or pharma- cokinetic parameters with pulse or continuous infusion administration of FIX  <u>Efficacy</u> Surgical hemostasis: Excellent or good response in 34/35 procedures as rated by physician/surgeon or patient  Estimated blood loss was considered normal according to procedure: Intraoperative blood loss 0–1 500 mL Postoperative blood loss 0–2 676 mL A liver transplant recipient lost in all 9 887 mL  <u>Safety</u> No inhibitor development One patient had hives No thrombembolic events, coagulation activation, or viral transmission	No drop-outs	Low

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Table 3.1.2.1 continued

Author Year Reference Country	Study design	Population Number Age Female/male	Intervention	Outcome measures	Results	Drop-outs	Study quality and relevance
Shapiro et al 2005 <sup>δ</sup> [4] Multinational	Multicenter (41 centres) International Open-label Single-cohort study <sup>γ</sup>	Severe hemophilia B FIX <1% or moderate 1–3%  Previously untreated patients n=63  Age 1 month to 14 years	Rekombinant FIX concentrate BeneFIX® median treatment duration 37 months (range 4–64 months)  FIX 50 IU/kg in a non-bleeding state for pharmacokinetics sampling for 24 hours  Continued with on- demand or prophylaxis at discretion of the patient for 2 years or 100 exposure days	Bleeding control and prevention assessed with a 4-point scale: “excellent, good, moderate, no response” by patient, guardian, or investigator  Surgery assessment using a similar scale and assessed by surgeon and investigator  Prophylaxis rated by investigator every 3 months on a 3-point scale: “excellent, effective or inadequate”	5 032 infusions 748/997 (75%) bleeding events treated in the on- demand group, resolved by one FIX infusion. 938/997 (94.1%) had excellent or good response 1% had no response  Prophylaxis: 32 patients received primary or secondary prophylaxis. 24 received FIX concentrate two or more times per week, mean infusion dose 72.5±37.1 IU/kg Duration: mean 13.4±8.2 months (range 1–25)  Overall 157/172 (91.3%) of the prophylaxis regimen responses were rated as excellent, 11/172 (6.4%) were rated as effective and 3/172 as inadequate  Surgery: 58 patients, 30 surgeries. 29/30 had excellent/ good hemostasis  22 adverse events deemed related or of unknown relationship, 5 allergic reactions, 2 of with had inhibitors	4 patients not treated and 23 did not complete study	Medium

<sup>α</sup> None of the authors declared any conflict of interest

<sup>β</sup> No reported support from pharmaceutical companies

<sup>γ</sup> Reported support from pharmaceutical companies

<sup>δ</sup> One or more of the authors reported relation to pharmaceutical companies involved in the products

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3. Ragni MV, Pasi KJ, White GC, Giangrande PL, Courter SG, Tubridy KL, et al. Use of recombinant factor IX in subjects with haemophilia B undergoing surgery. *Haemophilia* 2002;8:91-7.
4. Shapiro AD, Di Paola J, Cohen A, Pasi KJ, Heisel MA, Blanchette VS, et al. The safety and efficacy of recombinant human blood coagulation factor IX in previously untreated patients with severe or moderately severe hemophilia B. *Blood* 2005;105:518-25.

### 3.1.3 Long-term effects in treating hemophilia A and B

#### Evidence grading of the results

See section 3.1

#### Introduction

Chapters 3.1.1 and 3.1.2 present the results from studies of replacement therapy in hemophilia A and hemophilia B, respectively. Studies meeting the primary inclusion criteria, listed in tables 3.1.3.1 and 3.1.3.2, all have relatively short follow-up periods. The effects assessed in the studies usually involved a subjective estimate of the effects on bleeding from a short-term perspective and the effects related to surgical procedures and pharmacokinetics. The only randomised controlled trial comparing results of different regimens, a study by Manco-Johnson and co-workers, reports on follow-up in boys with hemophilia A after an average of four years [1]. The study is also reported in section 3.1.1. It shows that prophylactic treatment compared to on-demand treatment significantly reduces the number of bleeding episodes, reduces joint damage as assessed by magnetic resonance imaging (MRI), and reduces the number of cerebral hemorrhages.

Injuries resulting from bleeding in joints develop over a long period. Hence, studies showing the long-term effects of different treatment principles in hemophilia are important.

#### **Hemophilia treatment principles can be classified as follows:**

1. "On-demand" treatment using factor concentrate when bleeding occurs, or in situations that present a risk for bleeding.
2. Primary prophylactic treatment starting early in childhood, either before or after the first joint bleed. Often defined as prophylactic treatment for at least 45 of 52 weeks per year. At least two injections per week.
3. Secondary prophylactic treatment, starting later in life, often after a period of frequent bleeding episodes.

Criteria for the type of prophylaxis are not always stringent throughout the studies, and dosing also varies. Furthermore, treatment principles may differ for patients at different periods during life. Randomised studies that compare long-term effects of different types of prophylactic and on-demand treatment are lacking.

In countries where prophylaxis is initiated at different ages, prophylactic treatment is often individualised to different degrees, or managed based on clinical response or after checking pharmacokinetic data for factor VIII or factor IX in the individual patient.

In studies with long-term follow-up of hemophilia patients, the outcome variables have often included one or more of the following:

1. Clinical joint assessment (Gilbert score)
2. Radiological (x-ray) joint assessment
3. Absenteeism from work or school
4. Orthopaedic surgery in patients with hemophilia

## **Question**

- Are there differences in the long-term effects (6–10 years of follow-up) of different treatment regimens for hemophilia A and B?

## **Inclusion criteria**

### ***Patients***

Patients with hemophilia A and B without inhibitors. All ages.

### ***Intervention***

Prophylactic treatment starting at different ages and with different doses of factor VIII or factor IX concentrate, or on-demand treatment.

### *Effects*

- joint bleeds
- clinical joint score
- radiographic joint score
- orthopaedic operations
- days on sick leave
- school absenteeism
- quality of life

### *Type of study*

Systematic reviews, meta-analyses, RCT and observational studies.

### *Numbers of patients*

Hemophilia A, at least 20 patients

Hemophilia B, at least 10 patients

### *Time frame and language*

Literature published since 1995 until spring 2010 in English, Norwegian, Danish, and Swedish.

### *Search strategy*

Presented in the Appendix.

## **Results of the literature search and selection of studies**

The literature search identified 14 studies that met the established inclusion criteria. Several of these are multicentre studies. After reviewing the articles in full text, five more studies were excluded. Table 3.1.3.1 summarises the results of the studies.

## **Description of studies and results**

Manco-Johnson and co-workers published in 2007 the only randomised trial found to meet the inclusion criteria in the literature search [1]. The study included 65 boys younger than 30 months that were randomised to either prophylactic therapy (n=32) or enhanced episodic therapy (n=33) with recombinant FVIII (Kogenate®). Boys in the prophylactic group

received 25 IU FVIII every other day. Breakthrough bleedings, i.e. hemarthrosis, were treated with an extra dose of 40 IU/kg BW. The boys in the episodic group were treated on-demand. The study continued until the boys were six years of age. Outcome as preserved joint structure was evaluated with magnetic resonance imaging (MRI) and conventional radiography by the end of study. Efficacy: 7 percent of the patients in the prophylaxis group (prophylaxis started at 1 to 1.5 years of age) had articular changes at 6 years of age versus 45 percent in the on-demand group. In addition, three boys in the group treated with enhanced episodic therapy had life-threatening bleedings. Safety: Two boys randomised to prophylactic therapy developed inhibitors.

Aledort et al described a retrospective observational, international, multicentre study including 477 patients with severe hemophilia A without inhibitors [2]. The mean age of patients was  $13.5 \pm 6.6$  years. Radiographic examination of joints was performed in 300 patients. The patients were followed for at least six years. Prophylactic treatment reduced the frequency of joint bleeding and other bleedings. Higher doses of FVIII decreased days lost from school or work. Patients treated with prophylaxis for more than 45 weeks per year had significantly lower joint and x-ray score and a significantly lower number of bleedings. The factor consumption among patients treated with prophylaxis was on average 2 903 IU/kg/year.

Fischer et al published in 2002 a single-centre study including 76 patients with severe hemophilia born between 1965–1985 [3]. Retrospective data regarding treatment, dosing of factor concentrate, and age at first joint bleed were collected. Main outcome was joint score according to Pettersson. Results showed a significant worsening of in a mean 8 percent (95% CI 1 to 16) of the Pettersson score for every year prophylaxis was postponed.

In 2002, Fischer et al published a retrospective study where two centres (Van Creveld Clinic in Utrecht, the Netherlands and Malmö, Sweden) reported on patients born from year 1970 to 1990 with severe hemophilia A and without inhibiting antibodies [4]. The median age in both groups was 22.3 years. The study was based on retrospective data from 42 Swedish

and 86 Dutch patients with severe hemophilia A or B and a median age of 16.8 years. The follow-up period was 17 years (median). The study compared two different prophylactic regimens for hemophilia A and B (Utrecht intermediate prophylaxis and Malmö high-dose prophylaxis). Patients receiving high-dose prophylaxis had fewer bleeding episodes per year compared to Dutch patients receiving an intermediate dose. The percentage of patients with a joint score of 0 was significantly higher with high-dose prophylaxis. The quality of life in the groups did not differ.

Fischer and co-workers also published a similar retrospective observational study that compared treatment results in 49 Dutch patients against results from 118 French patients with severe hemophilia A or B, previously reported [5]. Patients were treated on-demand in France and with an intermediate prophylactic dose in the Netherlands. Follow-up was 22 years. Utilisation of factor concentrate was 1 260 IU/kg/year in France and 1 550 IU/kg/year in the Netherlands. The number of joint bleeds was significantly lower in the group treated with prophylaxis, and the number of patients receiving a clinical joint score of 0 was also significantly higher in the prophylaxis group. The clinical score (Gilbert score) was significantly higher in the prophylaxis group, as was the percentage of patients with a clinical score of 0. The number of orthopaedic operations was significantly higher in patients from France treated with on-demand therapy.

Another retrospective study from 2003 compared three cohorts of patients with severe hemophilia A or B from the Netherlands, France, and Sweden born 1970 to 1980 [6]. To some extent, these patients have been included in earlier publications [3,4] comparing intermediate-dose prophylaxis (the Netherlands), on-demand treatment (France), and high-dose prophylaxis (Sweden). This comparison showed no significant differences in effects between high- and intermediate-dose prophylaxis, but treatment in both prophylaxis groups was significantly more effective than in the on-demand group. Double reporting of patients is present in studies [3–6].

Another study compared two national cohorts (Sweden and Norway) comprised of patients with hemophilia A and B without inhibitors and

born between 1949 and 1989 [7]. Patients in Sweden had received regular prophylactic treatment at least twice per week for hemophilia A and once per week for hemophilia B. On-demand treatment patients from Norway were born between 1939 and 1981. Follow-up time was in average 11 years. Outcome measures in the study were annual utilisation of coagulation factor concentrate, number of days absent from work, employment status in December 1999, number of operations from 1989 to 1999, and number of days in hospital. Patients treated on-demand (Norway) had more days absent from work and more hospitalisation days than did Swedish patients treated with prophylaxis. The Norwegian patients also had more surgical procedures and reported a greater need for specialised equipment, e.g., wheelchairs and disability-adapted vehicles, compared to patients in Sweden.

Ahnstrom et al performed a six-year retrospective follow-up study including 51 patients with hemophilia A of whom two patients had moderate hemophilia A and 13 patients with hemophilia B [8]. The total number of patient-years was 364. The relationship between joint bleeding and coagulation factor level in plasma was weak and there was no relationship between coagulation factor level in plasma and other bleeds. Various dosage regimens were used and the conclusion was that dosing of factor concentrate has to be individualised in patients with hemophilia.

Schobess et al published a German multi-centre study where children with severe hemophilia A aged 0–16 years were followed and two different treatment-regimens were compared [9]. Either the children were treated with primary prophylaxis defined as started before the third joint bleed but most often after the first joint bleed or with secondary prophylaxis. At 12 years of age no difference was observed regarding the Pettersson score, frequency of target joints, or synovitis.

A retrospective observational study involving 10 different centres reported treatment results on 84 patients with hemophilia A or B that had switched from on-demand treatment to prophylactic treatment [10]. The average prophylactic dose was 25.5 IU/kg for factor VIII concentrate and 36 IU/kg for factor IX concentrate. Prophylactic treatment reduced the annual number of bleeds from 35.8 to 4.2 and from 32.4 to 3.3 ( $p=0.01$ ), respec-

tively. The number of days absent from school or work decreased significantly in the prophylaxis groups; 34.6 versus 3.0 days ( $p=0.01$ ).

## Discussion

The studies available regarding long-term outcome in patients with hemophilia are limited. Some studies comprise all available hemophilia patients from one single centre or from a whole country. Overall these studies had been rated as with uncertain external and internal validity.

There is only one randomised controlled trial in children that showed beneficial effect of a prophylactic regimen with FVIII-concentrate compared to on-demand treatment but the follow-up period in that study was four years (see section 3.1) [1].

The study by Ahnstrom et al shows a weak correlation between plasma-factor level and joint score and they conclude that individualised treatment is important. Some patients had bleedings despite trough levels >3 percent and other patients did not bleed on factor levels in plasma below 1 percent.

Aledort showed from their large study that full-time prophylactic therapy, defined as at least 45 weeks per year, results in the best orthopaedic outcome and that it also significantly reduces both joint bleedings and other bleedings. In case of prophylactic therapy, higher doses of factor concentrate did not correlate to a better orthopaedic outcome.

The retrospective study by Fischer et al in 2002 [3] showed that starting prophylaxis early is important and for every year prophylaxis is postponed, the joint score is worsened by 8 percent. However, there is a relatively wide range at which age the first joint bleeding occurs. In the study by Fischer et al in 2002 most children experienced their first joint bleed after two years. However, it is not possible to predict when a single patient will have his first joint bleed.

Comparing different intensities of prophylactic therapy with factor concentrate from Sweden (high-dose) and the Netherlands (intermediate-

dose) showed that the Swedish patients born 1970–1990 with high-dose prophylaxis had fewer joint bleeds and a larger proportion of these patients had a lower Pettersson score. Clinical joint score and quality of life was similar in the two groups.

When comparing patients treated with intermediate-dose prophylaxis with on-demand therapy (Dutch centre versus one French centre) data showed an improved outcome for the Dutch patients. They had fewer joint bleeds and also lower clinical scores and less arthropathy assessed by Pettersson score. The annual clotting factor use was equal per year comparing on-demand versus intermediate-dose prophylaxis.

In a German study by Schobess, 109 children with severe hemophilia A were studied and compared primary and secondary prophylaxis. The definition of primary prophylaxis was different from other studies; i.e., defined as starting before the third joint bleeding. A primary prophylactic regimen resulted in a lower annual bleeding frequency. The number of target joints comparing primary and secondary prophylaxis did not differ significantly and the Pettersson score did not differ significantly comparing joints with a previous joint bleed.

Another approach is to compare results in two cohorts of patients from different countries with different treatment strategies. Sweden introduced prophylaxis early and Norway has used on-demand therapy. This study, covering all patients with severe hemophilia A and B without inhibitors and who were born in Sweden or Norway showed that patients treated on-demand were more disabled and had needed more orthopaedic surgical intervention and more days absent from work or school.

Starting secondary prophylaxis in adolescence or in adulthood reduces both joint bleeding and other bleedings and can in some patients reduce the orthopaedic score. In contrast to the study by Fischer et al [5] secondary prophylaxis increased consumption of factor concentrate compared to the on-demand group.

To conclude from these studies it seems that early prophylaxis is important to protect from later development of joint damage assessed both

by radiology and clinical scores. The optimal dosing and frequency of the dosing intervals is still a question where further studies are needed. It seems that intermediate dosing of factor concentrate is better than on-demand therapy, but both regimens use the same amount of factor concentrate. Higher doses of prophylaxis result in higher factor consumption compared to on-demand therapy [7,10].

The weakness in these studies is that most of the studies are based on retrospective data. Results regarding dosing is probably in many cases based on prescribed dosing where patients' compliance to the prescribed regimen is not known.

The use of different definitions of primary and secondary prophylaxis and also the different clinical score may confuse the reader.

## **Summary**

The number of studies regarding long-term follow up data in hemophilia A and B is limited and no randomised trials have been performed except the study of Manco-Johnson reported in the previous section of this report. However, to conclude from these studies it seems that starting early prophylaxis is important but optimal dosing and frequency of dosing is still an area requiring further studies. For the future, there is a need for prospective long-term follow-up studies evaluating different prophylactic regimens.

**Table 3.1.3.1** Studies on the long-term effects of treatment with factor VIII concentrates in hemophilia A and B.

Author Year Reference Country	Study design	Population Characteristics Number (start/end) Gender/Age	Intervention Drug, dose and dosage schedules	Outcome measures	Results	Drop-outs	Study quality and relevance  Comments
Manco-Johnson et al 2007 <sup>δ</sup> [1] USA (also reported in section 3.1.1)	Open randomi- sed controlled trial Multicentre study <sup>β</sup>  Study period 1998–2000	Severe hemophilia A n=65 Younger than 30 months  Prophylaxis n=32 (27 completed protocol)  Enhanced episodic therapy n=33 (22 completed protocol)	Treatment either with intravenous injections with recombinant FVIII (Kogenate <sup>®</sup> ) 25 IU/kg every other day as prophylaxis or as enhanced episodic therapy with recombi- nant FVIII (Kogenate <sup>®</sup> ) 40 IU/kg at the time of joint hemorrhage and 20 IU/kg at 24 hours and 72 hours after the first dose	Primary outcome was the incidence after six years of bone or cartilage damage as detected in index joints with MRI	<u>Efficacy</u> Bone or cartilage damage at 6 years of age 55% of patients in the episodic therapy had normal joints on MRI vs 93.5% of the patients in the prophylaxis group (significant diffe- rence, p=0.02)  <u>Bleedings</u> Joint hemorrhages (number/participant/year): 0.63±1.35 vs 4.89±3.57 (prophylaxis vs enhanced episodic therapy), signifi- cant difference p<0.001  <u>Total number of hemorrhages</u> 3.27±6.24 (number/ participant/year) vs 17.69±9.25 (prophylaxis vs enhanced episodic therapy), significant difference p<0.001  Three boys in the enhan- ced episodic therapy group had life-threatening bleedings  <u>Safety</u> Two patients in the pro- phylaxis group developed inhibitors vs no patient in the group with enhanced episodic therapy	n=6	Medium

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**Table 3.1.3.1 continued**

Author Year Reference Country	Study design	Population Characteristics Number (start/end) Gender/Age	Intervention Drug, dose and dosage schedules	Outcome measures	Results	Drop-outs	Study quality and relevance  Comments
Aledort et al 1994 <sup>a</sup> [2] USA, Japan, UK, Germany, Greece, Hungary, The Netherlands, Sweden, Italy	Multicentre Observational uncontrolled study <sup>y</sup> Retrospective regarding treat- ment data	Severe hemophilia A <25 years  Without inhibitor FVIII <1% n=601 Mean age: 13.5±6.6 years  300 patients with evaluable x-rays	6-year follow-up a minimum  Retrospective analysis of treatment data, weeks per year on prophylaxis, annual factor consumption  Four groups 0–499 IU/kg/year 500–999 IU/kg/year 1 000–1 999 IU/kg/year >2 000 IU/kg/year	Median follow-up 6 years  Evaluation of factor consumption per year and joint outcome (physical and orthopaedic joint score)	Prophylaxis reduced joint and other bleeding frequency  Of 477 patients 55% dete- riorated, 31% stayed the same, and 13.5% improved in score  Higher doses of FVIII decreased days lost from school or work and days spent in hospital. 10% of patients had joint score 0  Patients with prophylaxis more than 45 weeks resulted in better ortho- paedic outcome, they had significantly lower start and final joint and x-ray score and significantly lower number of bleeding both all bleeds and joint bleedings  Average dose in patients with prophylactic treat- ment was 2 903 IU/kg/ year	477 evaluable of 601 included	Low

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**Table 3.1.3.1** continued

Author Year Reference Country	Study design	Population Characteristics Number (start/end) Gender/Age	Intervention Drug, dose and dosage schedules	Outcome measures	Results	Drop-outs	Study quality and relevance  Comments
Fischer et al 2002 <sup>a</sup> [3] The Netherlands	Single-centre Observational retrospective study <sup>y</sup>	n=76 Born 1965–1985 Severe hemophilia A or B	Prophylactic treatment was offered to all patients and adjusted according to bleeding pattern. Median annual clotting factor use on prophylaxis was 1 750 IU/kg/year. Prophylaxis was given three times a week  Median age at start of prophylaxis was 6 years. Median age at first joint bleed was 2.2 years. Bleedings were treated with one or more infusions or factor concentrate in a dosage of 15–30 IU/kg	Effect of age at start of prophylaxis, delay after the first joint bleed and the number of joint bleeds on radiographic joint score (Pettersson score) were assessed	After 20 years the Pettersson score (joint score) was 8% higher (95% CI 1 to 16) for every year prophylaxis was postponed after the first joint bleed	31 patients were excluded because of a history of antibodies (n=14), significant other disease (n=1) other (n=13)	Low

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Table 3.1.3.1 continued

Author Year Reference Country	Study design	Population Characteristics Number (start/end) Gender/Age	Intervention Drug, dose and dosage schedules	Outcome measures	Results	Drop-outs	Study quality and relevance  Comments
Fischer 2002 <sup>a</sup> [4] Sweden, The Netherlands	Two-centre Observational, retrospective study <sup>y</sup>	128 patients with severe hemophilia A or B  Born 1970–1990  42 Swedish and 86 Dutch patients  Median age of all patients 16.8 years	Comparison of two prophylactic regimens (high-dose vs inter- mediate dose)  Netherlands inter- mediate-dose: 15–25 IU/kg 2–3 times/week for hemophilia A 30–50 IU/kg 1–2 times/week for hemophilia B  Malmö: Before 1980; prophylaxis started between the age of 2–4 years and around the age of 1 after 1980  25–40 IU/kg three times/week for hemophilia A and 25–40 IU/kg twice weekly for hemophilia B  Median follow-up 17 years	Outcome: Annual clot- ting factor consumption (retrospective analysis) Radiological score (Petterson score) in elbows, knees and ankles  Age at start of once- weekly prophylaxis, age at start of minimum twice-weekly  Clinical joint score	Patient with high dose prophylaxis had fewer joint bleeds per year  <u>Intermediate dose vs high dose</u> Boys born year 1970–79 n=44 vs n=24 2.5 (range 1–5.7) vs 0.5 (range 0.2–1.8) p=0.05  Boys born year 1980–89 n=42 vs n=18 3.7 (range 1.7–5) vs 0.2 (range 0–0.3) p<0.001  <u>Patients without joint bleeds</u> Boys born year 1970–79 5% vs 25% p=0.042 Boys born 1980–89 10% vs 50% p=0.001  <u>Clinical score (max 90)</u> Boys born year 1970–79 2 (range 0–5) vs 0 (range 0–4) p=0.449 Boys born year 1980–89 0 (range 0–2) vs 0 p<0.001	11/53 patients excluded in Malmö due to inhibitor  In Utrecht 29/115 patients excluded	Low

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**Table 3.1.3.1 continued**

Author Year Reference Country	Study design	Population Characteristics Number (start/end) Gender/Age	Intervention Drug, dose and dosage schedules	Outcome measures	Results	Drop-outs	Study quality and relevance  Comments
Continued Fischer et al 2002 <sup>a</sup> [4] Sweden, The Netherlands	See previous pages	See previous pages	See previous pages	See previous pages	<p><u>Pettersson score (max 78)</u> Boys born year 1970–79 10 (range 3.5–17.5) vs 4 (range 0–15) Boys born year 1980–89 0 (0–5) vs 0 p&lt;0.001</p> <p><u>Pettersson score=0</u> Boys born year 1970–79 11% vs 46% p=0.560 Boys born year 1980–89 54% vs 100% p=0.797</p> <p><u>Quality of life</u> No significant difference between groups</p> <p>In the high-dose prop- hylaxis group there was a higher proportion of patients without arthro- pathy</p> <p>Age-adjusted score median 0 vs 4 point not significant. Clinical scores equal Quality of life equal in the two groups</p>	See previous pages	See previous pages

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Table 3.1.3.1 continued

Author Year Reference Country	Study design	Population Characteristics Number (start/end) Gender/Age	Intervention Drug, dose and dosage schedules	Outcome measures	Results	Drop-outs	Study quality and relevance  Comments
Fischer et al 2002 [5] The Netherlands, France	Multicentre study Retrospective Observational study <sup>Y</sup>	Severe hemophilia A or B n=167  49 Dutch patients Hemophilia A n=43 Hemophilia B n=6 Median age 22.3 years (range 18.5–24.5)  118 French patients (data from previous study) Hemophilia A n=88 Hemophilia B n=18 Median age 22.3 (range 18.9–25.4)	Prophylaxis 15–25 IU/kg two or three times weekly in hemophilia A and 30–50 IU/kg once or twice weekly in hemophilia B  Dutch patients vs on- demand French patients  22 years of follow-up	<u>Outcome</u> Annual clotting factor consumption. Number of joint bleeds, Clinical score (Gilbert score) (min–max: 0–90) Orthopaedic score (Petterson score). Quality of life (SF-36)	Annual clotting factor consumption on-demand (France): median 1 260 IU/kg/year  Prophylaxis (The Netherlands): 1 550 IU/kg/year  Short term outcome: On-demand vs prophylaxis  Joint bleeds per year: 11.5 (range 3.8–24.0) vs 2.8 (range 0–7.8) p-value <0.001  Patients without joint bleeds: 9 vs 29% p=0.002  Clinical score 8.0 (range 3.3–14.0) vs 2.0 (range 0.3–5.0) p<0.001  Patients with clinical joint score = 0: 11 vs 25% p=0.038  Long-term outcome, history of orthopaedic surgery: (on-demand vs prophylaxis) 55 vs 20% p<0.001  Petterson score: 16 (range 8–28) vs 7 (range 3–15) p<0.001  Patients without arthro- pathy: 2 vs 14% p=0.010	12 French patients exclu- ded (inhibitors or moderate hemophilia)  17 Dutch patients were excluded because of a history of inhibitors or insufficient data to follow-up	Low

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Table 3.1.3.1 continued

Author Year Reference Country	Study design	Population Characteristics Number (start/end) Gender/Age	Intervention Drug, dose and dosage schedules	Outcome measures	Results	Drop-outs	Study quality and relevance  Comments
Fischer et al [6] 2003 <sup>a</sup> The Netherlands	Multicentre study <sup>b</sup> Three different cohorts compared	Patients with severe hemophilia A born between year 1970– 1980 with no history of inhibitor  Three different treat- ment groups 1) On-demand treat- ment, n=105, age at evaluation 22.3 years (range 18.9–25.4)  2) Prophylactic treat- ment with intermediate dose, n=49 Age at evaluation: 22.3 years (range 18.9–24.5)  3) Prophylactic treat- ment with high-dose n=24 Age at evaluation: 17.2 (range 15.2–20.4)	Comparisons of treatment with factor concentrate either 1) On-demand 2) Intermediate dose 3) High dose	Short-term outcome: Annual number of joint bleeds  Long-term outcome: Clinical joint score (Gilbert score)  Radiological score (Petttersson score)	1) On-demand 2) Prophylaxis inter- mediate dose 3) Prophylaxis high-dose  <u>Joint bleeds per year</u> 1) 11.5 (range 3.8–24.0) 2) 2.8 (range 0–7.8) 3) 0.5 (range 0.2–1.8)  <u>Clinical score</u> 1) 8.0 (range 3.3–14.0) 2) 2.0 (range 0.3–5.0) 3) 0 (range 0–1.0)  <u>Petttersson score</u> 1) 16 (range 8–28) 2) 7 (range 3–15) 3) 4 (range 0–15)  <u>Petttersson score=0 (%)</u> 1) 2% 2) 14% 3) 46 %	Not shown	Low

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Table 3.1.3.1 continued

Author Year Reference Country	Study design	Population Characteristics Number (start/end) Gender/Age	Intervention Drug, dose and dosage schedules	Outcome measures	Results	Drop-outs	Study quality and relevance  Comments
Steen Carlsson et al 2003 <sup>a</sup> [7] Norway, Sweden	Observational, Retrospective study <sup>y</sup> Two centers	Patients with severe hemophilia A or B without inhibitor n=156  <u>Prophylaxis patients</u> Born between 1949 and 1989. Regular prophylactic treatment 1989–1999 (twice weekly for hemophilia A and once weekly for hemophilia B). Exclusion: ad mortem after 31 Dec 1988  <u>On-demand patients</u> Born between 1939–1981. Treated on-demand Exclusion criteria: ad mortem after 31 Dec–1988	Prophylactic treatment (Sweden) vs on-demand (Norway)  11 years of follow-up	Outcome  Annual consumption of factor concentrate  Number of days lost work during study period  Employment status per 31 December 1999  Number of invasive procedures 1989–1999  Total number of days of hospitalisation	Patients on-demand the- rapy had more receiving days lost from work and higher number of total hospital days  On-demand patients had more special equipment as cars, wheelchairs, adjustable furniture  Patient treated on- demand underwent more surgical procedures 1989–1999; 121 vs 48  Number of procedures divided by group size: 1.98 vs 0.51	14 patients in Norway excluded due to inhibitor, not on-demand therapy for the whole period or migration  58 patients in Sweden were excluded due to inhibitor, not on-demand therapy for the whole period or migration	
Ahnström et al 2004 <sup>a</sup> [8] Sweden	Single centre Retrospective Survey of medical records <sup>b</sup>	Hemophilia A n=51 49 with severe form and 2 with moderate  Hemophilia B n=13 All severe  A total of 364 patient years	Retrospective survey 6 years 1997–2002  <u>FVIII-dosing</u> In between 11.9 IU/kg once a day to 67.7 IU/kg  <u>FIX dosing</u> Every other day to once a week 34.5 IU/kg–35.1 IU/kg  No controls	<u>Primary aim</u> Investigate possible relationship between coagulation factor level and bleeding frequency during prophylactic treat- ment of hemophilia after stratification of patients according to joint score  <u>Secondary aim</u> Obtain systematic overview of the doses of coagulation factors prescribed for prophylaxis at the Malmö hemophilia centre	A weak but significant relationship between time below 1% FVIII level and incidence of joint bleeding	82 patients were invited 64 participated 16 patients either did not want to partici- pate or did not answer. 2 patients developed an inhibitor	Low

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Table 3.1.3.1 continued

Author Year Reference Country	Study design	Population Characteristics Number (start/end) Gender/Age	Intervention Drug, dose and dosage schedules	Outcome measures	Results	Drop-outs	Study quality and relevance  Comments
Schobess et al 2008 [9] Germany	Multicentre Comparative Data-base study	Previously untreated Caucasian patients with severe hemophilia A aged 0–16 years admit- ted at the first sympto- matic and spontaneous onset of disease n=109  Primary prophylaxis: n=42  On-demand: n=67	Comparison of primary prophylaxis (starting before the third joint bleed but usually starting before the third joint bleed) vs therapy with on-demand treatment or early started second- ary prophylaxis (matched controls)	<u>Primary aim</u> The occurrence rate and severity of imaging- proven hemophilic joint damage  <u>Secondary aim</u> Development of target joint and the maximum annual bleeding frequency	No significant difference between the group with primary prophylaxis vs early started secondary prophylaxis regarding frequency of children with target joints, the Petters- son score at a median age of 12.5 years and the occurrence of synovitis  The primary prophylactic regimen showed a lower annual bleeding frequency, multivariate analysis OR 0.89 (95% CI 0.81 to 0.99)	Of 147 initial patients 109 patients were included in the final cohort	Low
Tagliaferri et al 2008 <sup>a</sup> [10] Italy	Multicentre Retrospective Observational Cohort study <sup>b</sup> Each patient his own control	Adolescents (≥10 years): n=30 Adults (>18 years) n=54 switched from on-demand to prophyl- actic treatment  Hemophilia A n=76 Hemophilia B n=8	Average prophylactic dos 25.5 IU/kg (range 16–33) for factor VIII concentrate and 36 IU/kg (range 34–39) for factor IX concentrate  11 patients two times and 63 patients three times a week, 2 patients every other day	<u>Efficacy</u> Annual number of total and joint bleeds.  Orthopaedic score  Days of hospitalisation  Orthopaedic consultations  Medical visits to hemophilia centres  <u>Safety</u> No safety issues discussed	<u>Efficacy</u> Prophylaxis reduced mean annual number of total and joint bleeds: 35.8 vs 4.2 and 32.4 vs 3.3 p=0.001 and number of days off work/school: 34.6 vs 3.0 p=0.01  Secondary prophylaxis as used in this study reduced mean orthopaedic score 18.1 vs 13.8 but difference not statistically significant p=0.13 in the whole cohort but in adolescents (7.3 vs 3.5 p=0.01)  Prophylaxis reduced hemophilia related phy- sical restrictions (VAS- score)	10 centres provided data for 84 patients	Low

<sup>a</sup> None of the authors declared any conflict of interest

<sup>β</sup> No reported support from pharmaceutical companies

<sup>γ</sup> Reported support from pharmaceutical companies

<sup>δ</sup> One or more of the authors reported relation to pharmaceutical companies involved in the products

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## 3.2 Treatment for patients with inhibitors

Treatment with recombinant factor VIIa and activated prothrombin complex concentrate, so-called bypass therapy, can arrest bleeding and allows surgical procedures on patients with hemophilia A and B and inhibitors.

### Evidence grading of the results

- The scientific evidence is insufficient to evaluate and to compare the effects of recombinant factor VIIa (rFVIIa) with activated prothrombin complex concentrate (aPCC), so-called bypass therapy, in the treatment of acute bleedings in patients with inhibitors. Results from observational studies indicate that both available bypassing agents can prevent and control bleeding episodes, including surgical settings. Treatment failure occurs. Clinical data suggest that the response may vary between individuals.
- The scientific evidence is insufficient to assess the effect of prophylactic treatment with recombinant factor VIIa and activated prothrombin complex concentrates on the potential to reduce the number of bleeding episodes and to prevent bleedings in patients with inhibitors. More studies are required to appreciate this treatment modality and to elucidate the optimal dosing.
- The scientific evidence is insufficient to evaluate the effect of immune tolerance treatment with factor concentrates for a certain period of time to induce tolerance and to eliminate antibody formation in hemophilia patients with inhibitors. Results from observational studies show that immune tolerance treatment with factor concentrates may be successful in approximately 80 percent of patients with hemophilia A, and in most cases, the result is permanent. Clinical experience suggests that treatment should begin at a young age. Scientific data of immune tolerance therapy for inhibitors to factor IX are scarce and suggest a lower efficacy rate.

## Introduction

Inhibitor development in patients with hemophilia is one of the most serious complications of the factor replacement therapy and challenges hemostatic management. The antibody attaches to the factor VIII or IX and neutralises or inhibits the hemostatic effects. The incidence of inhibitor development in patients with severe or moderate hemophilia A is between 20 and 30 percent. Among persons with hemophilia B, inhibitors are less frequent. The presence of an inhibitor is usually confirmed using a specific blood test called the “Bethesda inhibitor assay”. When an antibody is detected, it is usually classified as either “high” or “low responding” depending on how a person’s immune system is stimulated upon repeated exposure to factor VIII or IX. The antibodies usually appear within the first 50 treatment doses (exposure days).

Eradication of the inhibitors through immune tolerance induction (ITI) is the most favourable option for these patients. In this therapy, regular infusions of factor concentrates (factor VIII or IX) are administered (usually daily and at high doses) for weeks to years, with or without immune-modulating drugs.

In the majority of inhibitor patients, bleedings are treated with “bypassing agents” that activate the coagulation cascade and stop bleedings despite factor VIII or IX inactivating antibodies. There are two products available in Sweden (year 2010), one plasma-derived activated prothrombin complex concentrate (aPCC) and one recombinant factor VIIa, (rFVIIa). They may not be as effective as regular replacement therapy using factors VIII and IX, and therefore it is essential to achieve immune tolerance if possible.

Bypassing agents are also used on patients with inhibitors for achieving hemostatic effects in surgery.

Prophylactic treatment using bypassing agents could be another therapeutic option for patients with persistent inhibitors.

The questions regarding ITI and the hemostatic efficacy of bypassing agents in treating bleeding episodes and in performing surgical procedures as well as in secondary prophylaxis are listed below.

## Questions

- Can recombinant factor VIIa or activated prothrombin complex concentrate, so-called bypass products, stop acute bleedings in patients with hemophilia A and B with inhibitors and are any differences shown between the two products?
- Can recombinant factor VIIa or activated prothrombin complex concentrate reduce bleedings during surgery in patients with hemophilia A and B with inhibitors?
- Can recombinant factor VIIa or activated prothrombin complex concentrate prevent bleedings and reduce the number of bleeding episodes?
- Can treatment with factor concentrates (VIII or IX) for a given time period, so-called immune tolerance treatment, eradicate the antibody formation against factors VIII and IX?

## Inclusion criteria

### *Patients*

Patients with hemophilia A and B with inhibitors. All ages.

### *Interventions*

Treatment of acute bleeding episodes and surgical interventions.

1. Activated recombinant factor VIIa (rFVIIa) or activated prothrombin complex concentrate (aPCC).
2. Recombinant or plasma-derived FVIII and FIX concentrates, combination therapy with other agents (aPCC) and immunosuppressive drugs.

### *Effects*

Hemostatic effects on acute bleedings.

Hemostatic effects in surgery.

Reduced number of bleeding episodes (prophylaxis).

Tolerance development is defined as no detectable inhibitors and in some cases normal half-life and recovery.

### *Study types*

Systematic reviews, meta-analyses, randomised controlled studies, observational studies, and narrative reviews.

### *Number of patients*

At least five.

### *Time frame and languages*

Literature published from 1985 to spring 2010 in English, Norwegian, Danish, and Swedish.

## **3.2.1 Studies on the use of bypass products for acute bleeding, surgery, and as prophylaxis**

### **Results of the literature search and selection of studies**

We identified 28 studies that address the effects of bypass products, i.e., recombinant factor VIIa (rFVIIa) or activated prothrombin complex concentrate (aPCC) (Table 3.2.1a). Seven of the studies are randomised, but without control groups. The others are retrospective observational studies and presentations of case series. In addition, 16 review articles, systematic reviews, and consensus reports on the topic are listed in Table 3.2.1b. Most of the articles address the effects of rFVIIa, probably because this product is newer than aPCC and was launched in the 1990s. Several studies, including randomised studies, on aPCC were published prior to 1985 and are therefore not included in this literature review.

## Descriptions of studies and results

(Table 3.2.1a)

Scharf and colleagues [1] described 10 years experience with aPCC alongside human and porcine FVIII. A total of 29 surgical interventions was conducted on 27 patients. Six of the patients received aPCC. The effect of aPCC was difficult to predict and sometimes inadequate.

Negrier et al [2] reported their experience with aPCC-treatment at doses of 65 to 100 IU/kg with an interval of 6–12 hours. Effective treatment was usually defined as a need for a maximum of three doses. A total of 433 bleeding episodes and surgical procedures was treated in 60 patients with hemophilia A or B. The treatment was effective in 81.3 percent of cases and failed in 1.8 percent. Adverse events such as myocardial infarction and disseminated intravascular coagulation were reported in five cases.

Santagostino et al [3] conducted a prospective follow-up of 10 patients, one with acquired hemophilia, in which treatment with rFVIIa was administered at home in case of bleeding at a dose of 90 µg/kg every 3±1 hour (maximum 4 doses). A total of 42 (79%) of the bleedings was treated effectively while treatment failed in five cases (10%). In other cases, there was a partial effect. The bleedings that were treated effectively were characterized by early treatment and fewer doses.

Lusher [4] used data from three different studies to assess the importance of early treatment with rFVIIa for muscle bleeds in inhibitor patients. The time interval from the onset of bleeding symptoms to the start of treatment with rFVIIa averaged five days in the “compassionate use” data, and the number of doses administered averaged 13.6. This should be compared to 9 hours and 3.5 doses with 72 percent efficacy in the dose-finding studies and an average fewer than 8 hours and 2.3 doses with 92 percent efficacy in the home treatment studies. The results indicate that early treatment is more effective and requires fewer doses.

In a prospective blinded study, Shapiro et al [5] compared the effects of 35 and 90 µg/kg rFVIIa every second hour for the first two days, followed by every two to six hours for another three days for surgical

procedures in 29 patients with inhibitors. All high-dose patients had effective hemostasis during the first 48 hours compared to 12 of 15 in the low-dose group. Efficacy in the high-dose group was significantly better during both minor and major surgical interventions. According to the authors, first-line dosing should be 90 µg/kg even though 35 µg/kg yielded good treatment effects in many cases.

Arkin et al [6] described an uncontrolled observational study of 11 inhibitor patients with intracranial bleeding treated with rFVIIa at a dose of 90 µg/kg every second hour. Treatment was effective in 85 percent of the cases, with an average total consumption of 8.1 mg/kg.

Scharrer [7] summarised efficacy data for rFVIIa within the framework of compassionate use in 45 acute bleeding episodes and 22 surgical procedures on inhibitor patients. The initial dose was 90 µg/kg every second hour with the possibility to adjust the dose to 120 µg/kg if no improvement was achieved. The average number of doses was 42.2 for severe bleeding, with an efficacy of 85 percent. Treatment was not effective in three cases. The number of doses given averaged 89 for major surgery and 34.1 for minor procedures; only two cases reported greater than normal bleeding.

Shirahata et al [8] reported treatment results of 157 bleeding episodes in inhibitor patients with rFVIIa. The dose averaged 97 µg/kg with a distribution between 86 and 129 µg/kg. Between 1 and 85 doses were administered, and in only 3.2 percent of the cases did the product show no effects. The efficacy level was higher (90%) when the product was given at three-hour intervals versus longer intervals (31%).

Ingerslev [9] described the efficacy of rFVIIa in an initial dosing of 90 to 110 µg/kg every second hour along with tranexamic acid in 21 surgical procedures conducted on patients with inhibitors at one hemophilia centre. In all 21 interventions, hemostatic effects were very good, and no side effects of treatment were reported.

Smith and colleagues [10] described retrospectively the results of treatment with rFVIIa in continuous infusion during surgery in six patients

aged 33 to 76 years with congenital or acquired hemophilia. The infusion rate was 16.5 µg/kg/hr with a target level of 10 IU FVII:C per mL. Effective hemostasis was obtained in only one patient while additional doses of rFVIIa were required in the other cases.

Later Smith reported in two separate papers [11,12] the outcome of treatment with rFVIIa in six very serious bleeds and 20 surgical procedures in the same retrospective cohort consisting of 13 inhibitor patients, one with hemophilia B. The rFVIIa dose was 90 µg/kg every 2 to 4 hours. Good efficacy of rFVIIa was reported for all except for one case with oral surgery in whom local treatments with other hemostatics were needed.

Gringeri et al [13] assessed costs and quality of life in an observational study including 52 inhibitor patients aged 15 to 64 years. The utilisation of rFVIIa averaged 13 mg/patient and month in 71 percent of the cases. Corresponding figures for aPCC were 3 000 IU/patient and month in 46.7 percent of the cases. Pure FVIII agents had been used in 30.8 percent of the cases with a utilisation of 2 140 to 6 300 IU/patient and month. The agents represented 99 percent of the cost, and averaged 17 935 euros per patient. However, the cost for 60 percent of the patients was below 10 000 euros, i.e. some individual patients drove up the costs. Quality of life was at the level of hemophilia patients without inhibitors, physical activity at the level of diabetes and dialysis patients, and mental health was comparable to the normal population.

Bohn et al [14] assessed the costs for factor concentrates, bleeding frequency, and need for health services in a group of 12 patients with inhibiting antibodies. The results were compared with a matched control group of 28 individuals without inhibitors, of whom six received prophylactic treatment. The median cost for inhibitor patients was 55 853 US dollars (USD) per year, and the corresponding cost in the control group was USD 58 300. The frequency of bleeding and the consumption of health services did not differ significantly between the groups. Total costs were impacted by the high cost of individual patients with inhibitors.

Rodriguez-Merchan et al [15] reported 97 percent effectiveness with rFVIIa and aPCC in 108 surgical procedures on 51 different patients with inhibitors, aged 5 to 40 years. Dosing for radiosynoviorthesis was either four rFVIIa doses of 150 µg/kg every second hours, or aPCC 100 IU/kg before and after 6 hours followed by a dose every 12 hours. Dosing for the 20 major surgical procedures was not specified in detail. Postoperative bleeding that required further intervention was observed in only three (15%) of the major interventions.

Quintana-Molina et al [16] described experiences with aPCC and rFVIIa in surgery over a 20-year period. In total, 64 surgical procedures were conducted in 48 patients, of which 10 were major and 54 were minor interventions. Insufficient hemostasis occurred in only 1 of 32 cases with aPCC treatment and in 4 of 18 cases with rFVIIa. The pre-operative dose of aPCC was 100 IU/kg, followed by another 50 IU/kg after 6 hours and thereafter every 12 hours. Doses of rFVIIa between 90 and 210 µg/kg were given pre-operatively, followed by a dose between 90 and 100 µg/kg every 2 hours together with antifibrinolytics.

Tjønnefjord [17] summarised results from Oslo consisting of 6 major and 15 minor surgical procedures under the protection of aPCC. Dosing was 100 IU/kg preoperatively followed by 200 IU/kg/day divided into three doses during the following two days. The dose was then gradually reduced to between 100 and 150 IU/kg/day. No bleeding complications were reported.

Parameswaran and co-workers [18] described in an analysis of registry data, the efficacy of treatment with rFVIIa for 555 bleeding episodes in 38 patients aged 1 to 55 years. Home treatment was administered in 88 percent of cases and the doses of rFVIIa ranged from less than 100 to more than 200 µg/kg. Effective treatment was defined as complete hemostatic control in 72 hours. The treatment was effective in 87 percent of cases with a variation between the dosage groups from 83.8 to 96.6 percent. The number of doses required ranged from 1 to 29 with a median of 2 to 4 in the groups. Nine adverse events were reported in five patients.

Santagostino et al [19] conducted a prospective randomised study including 18 patients. Patients with articular bleeding were treated with either three rFVIIa doses of 90 µg/kg at three-hour intervals, or a single dose of 270 µg/kg. A verbal scale and a VAS scale were used to measure the efficacy. Treatment was effective in 31 and 25 percent of the cases, respectively, after nine hours (primary endpoint) and in 66 and 64 percent of the cases, respectively, after 48 hours. The authors conclude that efficacy of the single higher dose is comparable to that of the repeated lower dose, but the single dose is preferred since it is more convenient for the patient.

Kavakli et al [20] reported on a randomised, blinded, crossover study that compared the efficacy of two different doses of rFVIIa. In total, 24 patients were included, with 22 patients receiving at least one of the treatment regimens comprised of either a single dose rFVIIa at 270 µg/kg followed by two placebo injections, or three doses at 90 µg/kg at three-hour intervals. Efficacy was assessed in terms of pain and joint mobility in addition to hemostasis. The hemostatic efficacy in the treatment arms was 90.5 and 85.7 percent, respectively, with no preference between the dose regimens.

Konkle et al [21] conducted a randomised study aimed at assessing prophylactic treatment with rFVIIa. Thirty-seven patients were included, but only 22 completed the study. The dose was either 90 or 270 µg/kg/day for three months followed by three months of follow-up. The frequency of bleeding decreased by 45 and 59 percent, respectively, during prophylactic treatment, and the authors concluded that prophylactic treatment with rFVIIa at both doses was effective in preventing bleedings in inhibitor patients.

Pruthi et al [22] reported treatment results with rFVIIa in 36 surgical procedures in patients with inhibitors, where treatments with aPCC and/or conventional FVIII/IX agents were found to yield insufficient effects. Dosing was either bolus 90 µg/kg rFVIIa every second hour for five days followed by every fourth hour for another five days, or as continuous infusion of 50 µg/kg/hour during days 1 to 5 followed by 25 µg/kg/hour for another six days. The results were compared with those of a control group consisting of 12 patients without inhibitors.

Efficacy of the treatment regimens was 73 and 75 percent, respectively. Treatment was not effective in six of the cases.

Astermark et al [23] conducted a randomised study (FENOC study) that compared the efficacy of rFVIIa and aPCC for joint bleeds in 48 patients with inhibitors. The study used a crossover design and was not blinded. The number of drop-outs was relatively high (18/66). Treatment up to the primary endpoint after six hours consisted of either two doses of rFVIIa 90 to 120 µg/kg at two-hour intervals, or a single dose of aPCC at 75 to 100 IU/kg. After six hours, continued treatment with the respective agents was recommended, but the attending physician made this decision. Treatment should be started within four hours, and the effects were followed for 48 hours. After six hours, 80.9 percent of the bleeding episodes were effectively treated with aPCC and 78.7 percent with rFVIIa. The patients reported that bleeding had stopped completely after six hours in 97.6 and 85.4 percent of the cases, respectively. Criteria for bioequivalence were not fully met, and high discordance was observed at six hours in that one product showed better efficacy in one and the same patient compared to the other. However, no preference between the products was expressed. The authors concluded that both products have good effects on joint bleeds, but the efficacy varies among patients. Hence, the choice of agent might be of importance in achieving optimal efficacy.

Steen Carlsson et al [24] also presented an economic assessment of the study by Astermark et al [23]. The patients in the study were aged 8 to 55 years. Two of the 48 patients that completed the treatment study dropped out and were not included in the economic analysis. The cost analysis showed that aPCC was the most cost-effective treatment. A correlation could be identified between cost, body weight, and age.

Young et al [25] described the second randomised study that aimed at comparing the efficacy of rFVIIa and aPCC on joint bleeds in patients with inhibitors. In total, 42 patients were included, but only 21 completed the study. Three different treatment arms were included; rFVIIa 90 µg/kg every third hour, one dose of rFVIIa 270 µg/kg, or one dose of aPCC 75 IU/kg. The study used a crossover design and was blinded for rFVIIa. The need for rescue medication was greater following treat-

ment with aPCC (36.4%) than after rFVIIa (8.3 and 9.1 percent, respectively). No significant difference in the global assessment score was observed between the treatments.

Jimenez-Yuste et al [26] reported results in a retrospective case series of prophylactic treatment with aPCC and rFVIIa in ten patients with severe hemophilia A and inhibitors compared to earlier on-demand treatment. The aPCC dose was 50 IU/kg every second to every third day or rFVIIa 90 to 100 µg/kg daily. The bleeding frequency decreased from a median value of 14 (range 8–19) to 5 (range 1–22) in the group treated with aPCC and from 4 (range 3–10) to 1 (range 0–5) in the group treated with rFVIIa. The study also included an economic analysis.

Pan-Petesich and co-workers [27] described in a retrospective study the efficacy of treatment with rFVIIa at a dose of 270 µg/kg in 8 patients, adults and children, with mild to moderate bleedings. All bleedings were successfully treated, but in three of the cases one or two further doses were needed.

Valentino [28] summarised the results of prophylactic treatment with aPCC in six patients with hemophilia A and B. The median age at start of prophylaxis was 8.4 years. The oldest patient was 24 years. All patients received – during any period – an aPCC dose of 100 IU/kg/d. The treatment lasted between 41 and 1 552 days. The number of bleedings was reduced by an average of 84 percent (range 43–100 percent) from 9.27 to 4.2 bleeds per year.

Table 3.2.1b presents literature reviews and expert reports [29–44].

## **Discussion**

Most of the studies of rFVIIa and aPCC are retrospective and observational with low scientific value if one applies strict scientific criteria. The few randomised studies that were found were without controls. Patients with inhibitors however comprise a small, but exclusive group of patients that do require treatment to avoid life-threatening situations even when bleeds and/or interventions are initially minor. Both agents have shown to

be effective in the majority of cases. Hence, randomisation with placebo must be considered unethical. Treatment must be administered, so the question becomes to identify the optimum product, dose, and dose interval in each patient from clinical and economic standpoints.

Treatments with rFVIIa and aPCC are expensive and should be optimised to the extent possible. This is enabled by randomised studies between the different agents. Two studies of this type have been conducted to date and are found to be of medium study quality and relevance. Astermark et al 2008 (FENOC study) described the first study, where a crossover design was used to assess the effects of rFVIIa and aPCC. The number of patients is relatively low, and the drop-outs high, but the results support earlier case series and cohort studies showing high hemostatic efficacy with both products (approximately 80 percent at the primary endpoint). However, a difference in efficacy was observed with the respective products in one and the same patient, suggesting that predictive markers for the treatment response need to be identified. The FENOC study was also assessed from a health economics standpoint [13], and aPCC was found to be the most cost-effective treatment option. Nevertheless, in this case the study's design can be of importance, and in other assessment models of treatment with both agents rFVIIa is found to be the most cost-effective option [20]. The different results emphasise the need for more accurate treatment data upon which to base analyses and models.

The randomised study by Young et al [25] compared not only rFVIIa with aPCC, but also two treatment doses of rFVIIa in a blinded design. The study is smaller than the FENOC study, and the drop-out rate is higher, which further limits its scientific value. Similar to other cohort studies and case series of rFVIIa, the results suggest that rFVIIa can be administered at a dose of 270 µg/kg on a single occasion, instead of three doses of 90 µg/kg, without reducing the efficacy or exposing the patient to risk. In the study, the efficacy of the products was lower than expected at the primary endpoint (range 27–54 percent), but no significant difference was found.

Two randomised treatment studies of articular bleeding with rFVIIa have been published, comparing the efficacy of 90 µg/kg on three occa-

sions versus 270 µg/kg on a single occasion [19,20]. Both studies support the findings from the study by Young et al [25] and show the same effects at both dosages. In total, 85–90 percent of the bleeding episodes in the study by Kavakli et al [20] were controlled while the figures were lower in the study by Santagostino and co-workers [19], i.e., approximately 65 percent.

Randomised studies concerning the hemostatic efficacy of bypassing agents in surgery in inhibitor patients are lacking, but Pruthi et al [22] used a randomised approach to assess the efficacy of bolus treatment and continuous infusion, finding that the treatment regimens yielded effective hemostasis in 73 to 75 percent of the cases. The results were compared with a group of patients treated with FVIII and IX. Smith et al [12] reported good efficacy of rFVIIa in surgery at a dose of 90 µg/kg every 2 to 4 hours. In only one case of oral bleeding was local treatment required. However, the effect was insufficient with continuous infusion with a target value of 10 IU/mL FVII:C.

Rodriguez-Merchan et al [15] summarised experiences of using rFVIIa and aPCC in 108 surgical procedures and reported 90 percent efficacy. In only 3 of the 20 cases of major surgery was there a need for extra surgical intervention due to bleedings. The reported effect of rFVIIa in surgery is also supported by experiences from Ingerslev et al [2], where all 21 reported procedures were performed without complications. Negrier et al [2] reported good effect of aPCC to cover 30 surgical procedures and Quintana-Molina et al [16] described 20 years of experience with both aPCC and rFVIIa for minor and major surgical interventions. The hemostatic efficacy was insufficient in only 1 of 32 cases with aPCC and in 4 of 18 cases with rFVIIa. Finally, Tjønnefjord [17] reported that aPCC was used in 21 surgical interventions in 10 patients without bleeding complications. However, myocardial infarction occurred in one patient on the third postoperative day, and here the influence of factor concentrate therapy is unclear.

Prophylactic treatment with bypass agents is being increasingly discussed, and the study by Konkle et al [21] is the first randomised study to assess this type of treatment. The results suggest that prophylactic treatment

with rFVIIa significantly reduces the number of bleeds. No corresponding study with aPCC has yet been published. Valentino [28] summarised the experience with prophylactic aPCC-treatment in six patients and described a significant reduction in the frequency of bleeding events by 43–100 percent, but otherwise the efficacy of this agent has only been highlighted and supported in various case reports not included in this literature review.

The study by Gringeri et al [13], which assesses costs and quality of life, is important since it shows that treatment of an inhibitor patient costs, on average, 18 000 euros per month, with the medication costs basically comprising the entire sum. A small number of patients, however, influences these costs, and most patients can be treated at a substantially lower cost. Further, it is asserted that the mental health of patients with inhibitors receiving treatment is at the same level as that in the normal population, and the physical activity measures are at the level of other patient groups and patients without inhibitors.

### **3.2.2 Studies of immune tolerance treatment**

#### **Results of the literature search and selection of studies**

In total, 24 studies evaluating the efficacy of different treatment regimens to induce immune tolerance (ITI treatment) were identified (Table 3.2.2a). None of the studies is randomised, but comprises retrospective case series and register data. In addition, eight review articles and consensus reports are listed in Table 3.2.2b.

#### **Description of studies and results**

(Table 3.2.2a)

Scheibel and colleagues [45] described retrospectively the results of ITI with a factor dose of 90–200 IU/kg/d with or without immunosuppression in 11 patients. The inclusion criteria for treatment and the proportion of successful treatments were not defined, but the antibody titre decreased in all cases.

Nilsson and colleagues [46] evaluated the efficacy of ITI according to a model with high-dose FVIII, steroids, intravenous immunoglobulin and cyclophosphamide in 11 patients (aged 3 to 56 years) with high-titre antibodies. The antibodies disappeared in nine of the patients after 2–3 weeks. The half-life was normalised in all but one case.

Mauser-Bunschoten et al [47] conducted a study in which 24 of 33 hemophilia A patients, aged 1 to 43 years, with inhibitors underwent low-dose immune tolerance treatment (25 IU/kg every second day or 2–3 times per week). Eleven patients with low titer initially received a higher dose of FVIII before surgical procedures, or for life-threatening bleeds, followed by 25 IU/kg twice daily for 1 to 2 weeks. Tolerance, defined as an inhibitor titer <2 BU, at least 50 percent recovery, and normal half-life, appeared in 21 of the patients (87%). High inhibitor titre and age at inhibitor development prolonged the required treatment time.

Kucharski et al [48] compared retrospectively the outcome of ITI with a plasma-derived product in low FVIII dose (25 IU/kg twice per week) with the combined use of immunosuppression and higher FVIII dose among a total of 26 patients (aged 17–57 years) with high-responding antibodies. Very good efficacy – defined as the permanent eradication of the antibody response and a half-life >5 hours – was obtained in three of 11 patients after 5–20 months with low dose and in five of 15 patients after 17–36 days of immunosuppression and a higher dose.

Oldenburg et al [49] retrospectively described 60 patients (36 high- and 24 low responders) with immune tolerance treatment based on the Bonn Protocol, i.e., an initial FVIII dose of 200 IU/kg combined with aPCC 100 IU/kg per day, followed by 150 IU/kg FVIII twice daily in patients with measurable recovery and inhibitor titre <1 BU. Fifty-two patients (86.7%) achieved tolerance. Predictors of prolonged treatment time were interrupted treatment, high inhibitor titre at onset and during treatment, and catheter-related infections.

Battle et al [50] described a retrospective case series of 11 patients, aged 11 months to 47 years, where immune tolerance treatment involved recombinant FVIII in doses of 50 IU/kg every second day to 220 IU/kg

daily. Tolerance, defined as no detectable inhibitor titer, was obtained in nine of the patients (81.8%).

In a retrospective observational study, Damiano et al [51] described experiences from 17 US hemophilia centres. In total, 104 patients (including six with hemophilia B) aged one month to 44 years were treated. The daily doses of factor concentrates varied from 25 to 200 IU/kg. Tolerance was defined as an inhibitor titre <1 BU and was obtained in 57 of 81 patients (78%). Twenty-three patients were currently undergoing treatment. Normal recovery was reported in only 24 patients (41%). Inhibitor titres <10 BU at the start of ITI were associated with higher probability of successful treatment. Treatment results were worse in children under two years of age.

Unuvar et al [52] reported a retrospective case series including 14 patients aged two months to 17 years where ITI consisted of either rFVIII (10 patients) or plasma-derived FVIII (four patients) in doses from 50 to 220 IU/kg per day. Tolerance, defined as no detectable inhibitor titre and normal half-life and recovery, was obtained in 11 of the patients (79%). The unsuccessful cases were treated with doses from 100 to 200 IU/kg per day. A high inhibitor titre (>200 BU) indicated a greater risk for unsuccessful treatment.

In a retrospective follow-up, Alfy et al [53] described the outcome of ITI using cryoprecipitate in 10 patients with an average age of 6.6 years. Tolerance was defined as no detectable inhibitor titre and normal half-life and recovery. Dosage varied from 25 to 50 IU/kg every second day. Tolerance was achieved in eight of the patients (80%).

Lenk et al [54] summarised the data available in the national German registry of ITI. The register consisted of 130 hemophilia patients with different levels of severity. Average age was 6.6 years, and most patients received high-dose treatment with no further details. Tolerance was defined as no detectable inhibitor titre and normal half-life and recovery. Complete tolerance was achieved in 99 of the patients with hemophilia A (78.6%) and in one of four cases (25%) with hemophilia B. Partial response was observed in another 11 individuals.

Berntorp et al [55] reported the outcomes of 26 patients treated according to the Malmö model in an attempt to induce tolerance, i.e. immunosuppressive treatment in addition to FVIII or FIX. Tolerance was defined as no detectable inhibitor titre and normal half-life and recovery. Complete tolerance was achieved in 10 of 17 (59%) patients with hemophilia A and in 6 of 9 (67%) patients with hemophilia B. The conclusion was that immunosuppressive ITI is effective in many cases, and may be considered as one of the first-line options in patients with hemophilia B to reduce the risk of severe adverse events. The time to tolerance is generally shorter compared with other treatment regimens.

Aledort et al [56] presented a model study in health economics based on retrospective data from the International Immune Tolerance Registry. The cost of treatment was calculated for patients with favourable prognostic factors (i.e. inhibitor titre prior to ITI <10 BU, a factor dose used >100 kg/day and a time interval between inhibitor detection and ITI start <5 years) and compared to that of patients with poor prognostic factors i.e. the opposite features. The assumptions included a body weight of 25 kg for a child and 75 kg for an adult, a factor consumption of 200 IU/kg per day, and a medication cost corresponding to 0.5 USD/IU for plasma-derived (pd) products and 1.0 USD/IU for recombinant (r) products. The time to 50 percent success was 9.5 months for the good prognosis (Gp) group and 19 months for those with poor prognosis (Pp). The corresponding costs were 712 500 (pd) and 1 425 000 (r) in the Gp group, and 4 275 500 (pd) and 8 550 000 (r) in the Pp group, respectively. The conclusion was that the cost-effectiveness of ITI treatment may be optimised by identifying patients with favourable and poor predictors of success.

Haya et al [57] summarised current data in a national Spanish registry of ITI. In total, 42 patients (including one with hemophilia B) at different severity levels of hemophilia were treated at ages between 0 and 57 years. Several different treatment regimens were used, from 25 IU/kg every second day to 500 IU/kg daily. Immunosuppression was also used in one case. Tolerance development defined as no detectable inhibitor titre and a half-life  $\geq 8$  hours had been achieved in 26 of 38 cases (68%). Low titre at the onset of treatment and during the course of treatment, as well as doses  $\leq 100$  IU/kg, were associated with better outcome.

Rocino et al [58] described the experiences from ITI based on pharmacokinetic data. Twelve patients with severe hemophilia A and inhibitor titre >10 BU were treated at ages 2 to 25 years. A daily dose of 100 IU/kg was given up to two months until the inhibitor was undetectable, followed by a successive dose reduction to regular prophylaxis with 25 IU/kg three times weekly. Tolerance, defined as the absence of inhibitors in at least two negative tests with a one-month interval, normal recovery, and half-life >6 hours, was achieved in 10 patients (83.3%) including one patient with partial tolerance. Very high inhibitor titres (4 000–16 000 BU) during treatment were associated with less favourable outcome.

Mariani et al [59] reported on current data from an international registry study. In total, 314 patients with severe hemophilia A and inhibitors were treated, but treatment data were available for only 275 of the patients. The dose for immune tolerance treatment varied from <50 to >200 IU/kg per day. Tolerance was defined as undetectable inhibitor titre, normal recovery (>80%) and half-life (>6 hours). Negative titres were obtained in 140 (50.9%) of the cases, but only 128 demonstrated normal pharmacokinetic parameters. Higher treatment doses were associated with better outcome. Other factors of importance for outcome included maximum inhibitor titre, age, inhibitor titre at treatment start, and the time interval between inhibitor diagnosis and the start of treatment.

DiMichele and Kroner [60] summarised available data in a North American registry study, identifying 188 patients (including 17 with hemophilia B). Daily treatment doses from <50 to  $\geq$ 200 IU/kg FVIII and 25 to 200 IU/kg FIX were used. Adjuvant immunomodulating treatment was used in 40 percent of the patients with hemophilia A and 47 percent with hemophilia B. The individual attending physicians determined tolerance without strict criteria. Tolerance was obtained in 115 of 164 (70%) of hemophilia A patients and 5 of 16 (31%) hemophilia B patients. High inhibitor titre before and during ITI treatment was associated with less favourable outcome. In contrast to earlier studies, higher treatment doses were associated with less favourable outcome.

Mathias et al [61] reported their experiences with ITI in 15 patients (including one patient with hemophilia B) at ages of 15 to 205 months. Different types of products were used, and doses varied between 50 IU/kg three times per week to 200 IU/kg per day. Exact criteria for success were not reported, but the authors reported tolerance in 12 of the patients (80%). Short intervals from inhibitor diagnosis to the start of treatment and low titre during treatment were associated with better outcome.

Orsini et al [62] assessed the efficacy of ITI with factor VIII concentrate containing von Willebrand factor in a retrospective observational study. All eight patients were high-responders (titre >5 BU) aged between 11 months and 24 years. Both low- and high-dose regimens were used. Tolerance was defined as no detectable inhibitors and normal recovery and half-life. Seven patients (87.5%) achieved tolerance.

Barnes et al [63] reported data from a multicentre, retrospective study including 32 hemophilia A patients. Different treatment doses were used, where 72.4 percent of the patients received doses between 50 and 200 IU/kg per day while the remainder of the group was treated with FVIII 50 IU/kg every second day, or three times per week. Criteria for tolerance varied from undetectable inhibitor titre alone to normal recovery and half-life. Twenty-three patients (79.3%) developed tolerance.

Rocino et al [64] reported current data from an Italian prospective, observational study of ITI with recombinant FVIII. In total, 26 patients aged between 0.9 and 25 years were treated. Dosing varied between 50 IU/kg every second day to 200 IU/kg per day. Tolerance was defined as no detectable inhibitor titre and normal recovery and half-life. Treatment succeeded in 19 of the patients (73%) and partial success was observed in another two patients, i.e., the treatment results were in agreement with previously published data.

Gringeri et al [65] described the retrospective follow-up of 17 patients with hemophilia A that underwent ITI with FVIII concentrates containing high concentrations of von Willebrand factor. The patients were characterised by at least one unfavourable factor for tolerance to be indu-

ced, i.e., >6 years of age, treatment start >1 year after inhibitor diagnosis, peak titre > 200 BU, >10 BU at start of treatment, and/or previously failed attempt to develop tolerance. Dosing varied between 50 IU/kg three times per week to 200 IU/kg per day. Tolerance was defined as no detectable inhibitor titre and normal recovery and half-life. Nine of the patients (53%) were successfully treated while seven had a partial treatment response. The study concluded that agents containing von Willebrand factor are effective in many cases despite unfavourable prognostic factors.

Unuvar et al [66] reported a retrospective case series including 21 patients with hemophilia A aged 1.5 to 20 years where ITI was conducted with low-dose plasma-derived FVIII, i.e., 20 to 50 IU/kg 2 to 3 times per week, along with immunosuppression in one case. Tolerance was defined as no detectable inhibitor titre and/or normal half-life and/or normal recovery. Two patients dropped out during follow-up. Tolerance development was obtained in five of the remaining 19 patients (26.3%), and a partial response was achieved in seven patients. Inhibitors re-appeared in one patient. The authors concluded that low-dose protocols were not sufficiently effective.

Platokouki et al [67] retrospectively described six patients treated with ITI at a dose of 100 IU/kg every second day. A plasma-derived FVIII concentrate containing von Willebrand factor was used in all cases. Tolerance defined as no detectable inhibitor titer or normal half-life and recovery developed in five patients (83.3%).

Valentino et al [68] reported a case series including 12 patients aged 7 months to 6 years. FVIII concentrate was used at doses ranging from 100 to 200 IU/kg per day. Tolerance was defined as no detectable inhibitor, normal recovery ( $\geq 66\%$ ), and normal half-life ( $\geq 6$  hours). The treatment was successful in nine patients (75%), and it failed in one patient.

Table 3.2.2b presents the results of the literature review and expert reports [69–76].

## Discussion

ITI treatment with the intent to induce tolerance is costly, but the risks of bleedings are substantially increased in hemophilia patients with inhibitors, and, therefore, in agreement with consensus reports and recommendations, the ultimate goal should be to induce tolerance. This also has a long-term potential to save costs, since patients that develop tolerance can return to replacement therapy with the relatively less-expensive FVIII and FIX concentrates. Registries are an important source of data, and the different registers available in Europe [59], Germany [54], Spain [57], and North America [60] reveal prognostic markers that indicate the probability of a favourable outcome, i.e. whether tolerance can be induced. Treatment with immunosuppressive agents, combined with factor concentrates, is a less attractive option for children due to the risk of adverse effects, but can provide an effective and adequate option in adults and young therapy resistant patients [55].

The studies are difficult to compare since the agents, doses, dose intervals, and definitions of tolerance vary. However, most of the retrospective analyses show tolerance to be induced in 70–80 percent of the cases regardless of the type of agent and dose [50,52,53,61,64]. This coincides relatively well with registry data presented above. The study by Unuvar et al [66] indicates, however, that treatment at low doses, i.e. up to 50 IU/kg two to three times per week yields less favourable results than treatment at higher doses, at least in high responders. In addition, data in the International Immune Tolerance Registry suggest that high daily doses yield relatively better treatment results. A higher efficacy rate of FVIII concentrates containing von Willebrand factor to induce tolerance compared with more highly purified products has been suggested in patients with unfavourable prognosis. However, additional studies and data are needed to confirm these findings.

## Summary

There have been few randomised trials performed comparing the efficacy of bypassing agents, and the studies have been found to be of low to intermediate scientific value mainly due to the small number of patients.

Both available bypassing agents, rFVIIa and aPCC, can be effectively used in patients with hemophilia A or B with inhibitors to prevent and control bleeding episodes, including the surgical settings. As individual patients might respond better to one bypassing agent than the other, both products are needed as treatment options.

Bleeding risks are substantially increased in hemophilia patients with inhibitors, and therefore the ultimate goal of treatment should be to induce tolerance. The various ITI studies are difficult to compare since the agents, doses, dose intervals and definitions of tolerance achievement vary. However, a success rate of 70–80 percent is reported in most studies.

Scientific evidence supporting the prophylactic use of bypassing agents to prevent arthropathy is still limited.



**Table 3.2.1a** Studies of the effects of bypassing agents in acute bleeding, surgery and as prophylaxis in patients with hemophilia and inhibitors.

Author Year Reference Country	Study design	Population Number Age	Intervention	Results	Drop-outs	Study quality and relevance
Scharf et al 1996 <sup>a</sup> [1] Poland	Retrospective case series <sup>b</sup>	29 minor and major surgical procedures in 27 patients with hemophilia A (23 high responders)	Human and/or porcine FVIII was given to 23 of the patients and aPCC to 6 patients  In some patients plasmapheresis and extracorporeal antibody adsorption were also given	It is usually possible to achieve a hemostatic level of FVIII:C (>30 IU/dl) with human and/or porcine FVIII for 5–7 days in patients with an inhibitor titer <10 BU/mL. Bypassing agents are required, but the effect is unpredictable and in some cases ineffective  In high responders surgery should, if possible, be avoided and bleeds treated with bypassing agents	–	Low
Negrier et al 1997 <sup>a</sup> [2] France	Retrospective case series <sup>y</sup>	58 patients with hemophilia A (including 6 acquired) and 2 with hemophilia B and high-titer inhibitors	aPCC was given for 433 bleeding episodes including 168 home treatments and 30 surgical procedures  aPCC was given in intermittent doses of 65 to 100 IU/kg/d with an interval of 6–12 hours  Effective treatment of hemarthrosis was in the majority of cases defined as less than 3 infusions required	Treatment was considered effective in 81.3% of the cases. No control of the bleed was reported in 1.8%.  aPCC was given as first-line treatment in 23 cases and second-line treatment after human and porcine FVIII in 7 procedures. Two of the second-line treatments failed and both of these were in patients with acquired hemophilia. In all 23 first-line episodes, the outcome was favorable although excessive bleeding was reported in one patient  Adverse events were reported in 5 cases (1.2%) including one myocardial infarction and 3 DIC	–	Low
Santagostino et al 1999 <sup>a</sup> [3] Italy	Prospective case series <sup>b</sup>	9 patients with congenital hemophilia and inhibitors and 1 post-partum acquired hemophilia (historical titre 2–712 BU)  Median age 2.5 years (range 1 to 16)	Home treatment with self-administered doses of 90 µg/kg rFVIIa every 3±1 hours was used (up to 4 doses) to treat 45 hemarthrosis and 8 hematomas	Hemorrhage stopped or decreased substantially in 42 episodes (79%) and failed in 5 (10%). The other treatments were partially effective  The bleeds were treated within a median time of 1 hr (range 0.3 to 11.9) with a median of 2 doses per event (range 1–4)  Effective treatments were characterised by earlier treatment (p=0.02) and fewer infusions (p=0.007)	–	Low

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Table 3.2.1a continued

Author Year Reference Country	Study design	Population Number Age	Intervention	Results	Drop-outs	Study quality and relevance
Lusher 1998 <sup>a</sup> [4] USA	Retrospective evaluation of three different databases <sup>β</sup>	193 intra-muscular bleeding episodes treated with rFVIIa according to com- passionate use or study protocol	A comparison between early vs late treatment  Compartment syndromes included  Dosing varied between 35 to 120 µg/kg	The mean number of doses given was:  <u>Compassionate use study</u> 13.6 (64.8 for tense muscle and compartment syndromes with a 62% efficacy). Average time between onset of bleed and treatment with rFVIIa was 5 days. Other agents given  <u>Dose-finding study</u> 3.5 (72% efficacy for 70 µg/kg). Average delay 9 hours  <u>Home treatment study</u> 2.3 (92% efficacy). Average time <8 hours  Data indicate a greater success rate and fewer doses when rFVIIa was given early	–	Low
Shapiro et al 1998 <sup>a</sup> [5] USA	Prospective, double-blind multicentre study <sup>β</sup>	26 inhibitor patients with hemophilia A, 3 patients with hemophilia B undergoing surgery 11 major and 18 minor procedures  Age distribution (range 0–40 years)	Comparison of two doses of rFVIIa (35 µg/kg and 90 µg/kg) every 2 hours for the first 48 hours and thereafter with an interval of 2–6 hours for another 3 days  After day 5, open label product (90 µg/kg) was available to maintain hemostasis	<u>Overall efficacy</u> 23 patients successfully completed the study with satisfactory hemostasis. 9 patients completed the study with satisfactory results within the 5-day double-blind period. Treatment failure in 5 patients  A dose of 90 µg/kg was effective for patients under- going both major and minor surgery  A statistically significant difference in efficacy from day 3 to day 5 in favour of the high-dose group:  Satisfactory hemostasis in minor surgery: 70% low-dose vs 100% high-dose p=0.03 Major surgery: 40% low-dose vs 83% high-dose p=0.03	2	Medium
Arkin et al 1998 <sup>a</sup> [6] USA	Open-label uncontrolled emergency-use study <sup>β</sup>	11 patients with severe hemophilia A or B and 1 patient with FVII- deficiency  Intracranial hemorrhage Age 1–38 years	rFVIIa at an initial dosage of 90 µg/kg every 2 hours.  Primary efficacy para- meter: attainment of hemostasis at the end of the treatment period by physician's assessment	Effective hemostatic control in 10 of 12 (85%) patients  The mean total administration of rFVIIa was 153.3 mg (range 43.2–331.2 mg), corresponding to 8.1 mg/kg  rFVIIa effectively controlled CNS hemorrhage in hemophiliacs with inhibitors	–	Low

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**Table 3.2.1a** continued

Author Year Reference Country	Study design	Population Number Age	Intervention	Results	Drop-outs	Study quality and relevance
Scharrer 1999 <sup>a</sup> [7] Germany	Compassionate use multicentre <sup>β</sup> Prospective	28 patients (19 severe hemophilia A or B with inhibitors; 4 acquired hemophilia and 5 FVII deficient)  Age between 1 and 70 years (all)	Acute bleeds rFVIIa 90 µg/kg every 2 hours (120 µg/kg if no improvement)  <u>Surgical procedures</u> rFVIIa 90 µg/kg every 2 hours	<u>Mean number of injections in hemophilia A and B patients</u>  <u>Serious bleeds</u> (n=45 in 23 patients): 42.2 with an efficacy rate of 85% – bleeding stopped <8 hours in 9 cases (20%) – ineffective treatment in 3 cases  <u>Major surgery</u> (n=5): 89.0 <u>Minor surgery</u> (n=17): 34.1  Minimal bleeding was observed in 88% of cases and in only 2 procedures bleeding was rated as more than normal	–	Low
Shirahata et al 2001 <sup>a</sup> [8] Japan	Multicentre open-labeled observational study <sup>γ</sup>	10 patients (hemophilia A n=9 and hemophilia B n=1) Age 13–51 years	rFVIIa mean dose 97 µg/kg (86–120) 1 to 85 times in patients with high-responding inhibitors (>10 BU)	Total 157 bleeding episodes 91/157 (58%) were treated effectively or excellent, whereas 5 (3.2%) were ineffective  Higher efficacy rate when repeated treatment within 3 hours (36/40, 90%) compared with longer intervals (31%)	–	Low
Ingerslev 2000 <sup>a</sup> [9] Denmark	Retrospective case series <sup>β</sup>	21 surgical procedures in 7 hemophilia A and 1 hemophilia B patients  Age range 4–52 years	rFVIIa 90–110 µg/kg every 2 hours  Tranexamic acid orally 25 mg/kg every 6 hours  The duration of rFVIIa treatment was subjecti- vely assessed based on the procedure	In all 21 surgical procedures the clinical and result of surgery was excellent  No serious adverse events or side effects occurred	–	Low

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**Table 3.2.1a** continued

Author Year Reference Country	Study design	Population Number Age	Intervention	Results	Drop-outs	Study quality and relevance
Smith et al 2001 <sup>δ</sup> [10] United Kingdom	Retrospective case series <sup>β</sup>	6 patients with congenital hemophilia A and inhibitors and 2 acquired hemophilia with high-responding inhibitors  Age range 33 to 76 years	6 elective major surgical procedures and 2 minor surgical procedures were covered by rFVIIa in continuous infusion at a fixed rate of 16.5 µg/kg/hour to achieve a target FVII:C level of 10 IU/mL	Effective hemostasis was observed in only 1 of the major and 1 of the minor procedures, and in the others additional doses of 60 µg/kg rFVIIa at 2–3 hours interval were required  Superficial thrombophlebitis was seen in 2 patients, but no other thrombotic events  The data suggest that a FVII:C level of 10 IU/mL does not provide reliable hemostasis	–	Low
Smith 2002 <sup>α</sup> [12]  and O’Connell et al 2002 <sup>α</sup> [11]  Ireland (same cohort)	Retrospective case series <sup>β</sup>	12 patients with hemophilia A 1 patient with hemophilia B and inhibitors (historical titer 2–712 BU)  Median age 2.5 years (range 1 to 16)	Doses of 90 µg/kg rFVIIa every 2–4 hours were used  20 minor surgical procedures in 12 patients were covered by a median total dose of 43.2 mg (range 19.2–124.8) for a median time of 48 hours (range 12–72)  6 life- or limb-threatening bleeds in 3 patients were covered by a median total dose of 43.2 mg (range 2.4–46.8) for a median time of 20 hours (range 4–96)	All surgical procedures and all bleeds were successfully covered by rFVIIa except for one case involving a frenulum tear, which was brought under control by application of tropical fibrin glue	–	Low

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**Table 3.2.1a** continued

Author Year Reference Country	Study design	Population Number Age	Intervention	Results	Drop-outs	Study quality and relevance
Gringeri et al 2003 <sup>a</sup> [13] Italy	Retro- and pro- spective Multi- centre observa- tional study <sup>b</sup>	52 Median age: 34.8 years (range 15–64)	Cost of care and quality of life evaluated in 52 hemophilia A patients with high-responding inhi- bitors (>5 BU) – retro- spective data 6 months prior to enrollment and prospectively for 12 months	0.6 bleeding episodes per month and patient were recorded (81% at least one bleeding event) 11 surgical procedures (6 major surgeries)  <u>Factor usage</u> rFVIIa 13 mg/patient/month in 71% of patients; aPCC 3 000 IU/patient/month in 46.7%; pdFVIII 6 300 IU/patient/month in 25%; rFVIII 2 140 IU/patient/month in 5.8% to treat bleeding episodes or ITI  <u>Cost/patient/month</u> 17 935 Euros (99% CFC); 60% of patients <10 000 Euro QoL: Similar to hemophilia patients without inhibitors; physical quality similar to patients with diabetes and on dialysis; mental health comparable to general population  Treatment regimen affects outcome. Good QoL possible to achieve to a reasonable cost in most patients. Single patients treated at a very high cost	–	Low-medium
Bohn et al 2004 <sup>a</sup> [14] USA	Retrospective observational study <sup>y</sup>	12 patients with inhi- bitors to FVIII or FIX and 28 controls inclu- ding 6 on prophylaxis  Age ≤14 years in 8 of 12 cases and 22 of 28 controls	Cost of products used, bleeding frequency and the number of hospita- lisations and duration of hospitalisation during each year was defined	No significant difference between groups in annual number of bleeding episodes and hospitalisation  The median cost of factor/year among inhibitor patients was USD 55 853 compared with USD 58 300 for controls, p=0.80. Two outliers with an annual cost of factor USD >400 000	–	Low

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**Table 3.2.1a** continued

Author Year Reference Country	Study design	Population Number Age	Intervention	Results	Drop-outs	Study quality and relevance
Rodriguez-Merchan et al 2004 <sup>a</sup> [15] Spain	Retrospective multicenter observational study <sup>b</sup>	51 patients Mean 22.5 years (range 5–40)	108 surgical procedures (88 radiosynoviorthesis and 20 major surgeries)  Dosing for radio-synoviorthesis: rFVIIa 150 µg/kg times four at 2 hours interval  aPCC 100 IU/kg before and after 6 hours followed by 50 IU/kg every 12 hours  Dosing for major surgery not stated	The effect was good or fair in 97 (90%) of all 108 procedures  Postoperative bleeding complications requiring further surgical intervention were seen in 3 (15%) of the major procedures – all treated with rFVIIa	–	Low-medium
Quintana-Molina et al 2004 <sup>a</sup> [16] Spain	Retrospective observational study <sup>b</sup>	64 surgical procedures in 48 patients with inhibitors (10 major and 54 minor surgeries)  Age ranged from 2 to 53 years	40 of the surgical procedures performed with aPCC (n=32) and rFVIIa (n=18)  Dosing of aPCC: 100 IU/kg followed by 50 IU/kg after 6 hours and then 50 IU/kg every 12 hours  Dosing of rFVIIa: Initial dose of 90–210 µg/kg followed by 90–150 µg/kg every 2 hours together with antifibrinolytics	One hemorrhagic complication in a minor procedure with aPCC. All others without complication  Hemorrhagic complication in 1 major and 3 minor procedures with rFVIIa  Both bypassing agents are effective in most cases to achieve hemostasis during surgery, but biological tests to evaluate the hemostatic capacity are warranted	–	Low

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**Table 3.2.1a** continued

Author Year Reference Country	Study design	Population Number Age	Intervention	Results	Drop-outs	Study quality and relevance
Tjønnefjord 2004 <sup>a</sup> [17] Norway	Retrospective observational study <sup>b</sup>	21 surgical procedures in 8 patients with con- genital hemophilia and inhibitors and 2 with acquired hemophilia (6 major and 15 minor surgeries)  Age from 22 to 79 years	Dosing of aPCC: 100 IU/kg pre-operatively followed by 200 IU/kg divided by 3 doses for 2 days  Thereafter, dose was tapered to 100–150 IU/kg daily	The hemostatic effect was excellent or good in all performed surgical procedures  One patient suffered a myocardial infarction the third postoperative day after a major procedure	–	Low
Parameswaran et al 2005 <sup>a</sup> [18] USA	Retrospective registry study <sup>y</sup>	38 patients with hemophilia A or B and low- or high-respon- ding inhibitors  Median age 14 years (range 1–55)	rFVIIa was used for treatment in 555 bleeding episodes  Dose of rFVIIa given was between <100 to >200 µg/kg  Home treatment was used in 88% of the cases  Effective treatment was defined as a complete hemostatic control at 72 hours indicating that the bleed had ceased	Treatment was considered effective in 87% of all bleeds. In the subgroups <100, 100–150, 150–200 and >200 µg/kg, the corresponding figures were 84.9%, 84.4%, 83.8% and 96.6%, respectively  The median number of doses required was between 2 and 4 in the different subgroups with the lowest number of 2 infusions given in the highest subgroup. The range for all groups together was between 1 and 29 doses  Nine adverse events were reported in 5 patients  rFVIIa treatment appears to have a wide safety margin but optimal dosing remains to be determined	–	Low
Santagostino et al 2006 <sup>b</sup> [19] Italy	Prospective rando- mised multicenter study <sup>y</sup>	18 patients Joint bleeds	Randomised between 90 µg/kgx3 and 270 µg/kgx1 rFVIIa	Efficacy measured according to verbal scale and VAS after 9 hours: 31% (90 µg/kgx3) vs 25% (270 µg/kgx1) success After 48 hours: 66% vs 64%  Similar efficacy and consumption of factor concentrate but easier for the patient to self-treat with one high dose than with three lower doses	2 of 20	Low-medium

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**Table 3.2.1a** continued

Author Year Reference Country	Study design	Population Number Age	Intervention	Results	Drop-outs	Study quality and relevance
Kavakli et al 2006 <sup>δ</sup> [20] Turkey	Multicentre, randomised, cross-over, double-blind trial <sup>Y</sup>	24 patients were included  22 patients received at least one treatment  Mean age 27.5 years (range 6–60)	To compare efficacy and safety of treating hemarthrosis with two rFVIIa regimens in a home treatment setting  Randomisation in a cross- over design between 90 µg/kg rFVIIa times 3 every 3 hour and 270 µg/kg followed by 2 placebo injections at 3 hours interval  Pain and mobility were assessed by patients (using a novel global treatment response rating tool) at 1, 3, 6 and 9 hours (primary endpoint) after the 1st injection	<u>Efficacy</u> A single 270 µg/kg dose of rFVIIa was as effective at achieving hemostasis, increasing joint mobility, and controlling pain as the 90 µg/kg x 3 dose regimen (65% of patients vs 70%)  A total of 37/42 (88.1%) bleeding episodes was successfully controlled per protocol: 19/21 (90.5%) with the 270 µg/kg dose and 18/21 (85.7%) with the 90 µg/kg x 3 regimen  <u>Safety</u> No withdrawals due to adverse events, deaths, or thromboembolic adverse events	2 of 24	Medium
Konkle et al 2007 <sup>δ</sup> [21] USA	Prospective randomised study <sup>Y</sup>	37 patients of whom 22 were randomised	Randomised between daily 90 or 270 µg/kg rFVIIa for 3 months with 3 months additional follow-up	Bleeding frequency decreased from 5.6 to 3.0 per month (45%) in the low-dose group and from 5.3 to 2.2 bleeds per month (59%) in the high-dose group. A significant reduction in the bleeding frequency was also seen after the 3-month prophylaxis period (4.1 and 2.7, respectively). No difference was seen between the two regimens  rFVIIa is effective as secondary prophylaxis to reduce the number of bleeds in inhibitor patients	15 of 37	Low

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**Table 3.2.1a** continued

Author Year Reference Country	Study design	Population Number Age	Intervention	Results	Drop-outs	Study quality and relevance
Pruthi et al 2007 <sup>δ</sup> [22] USA	Randomized, open-label, multicenter <sup>γ</sup>	36 Hemophilia A and B with inhibitors (≥5 BU) or inadequate response to 250 IU/kg of FVIII/IX or to conventional doses of aPCC (n=24 patients) and a control group without inhibitors (n=12 patients)  Age range 10–76 years	rFVIIa in bolus injection (90 µg/kg every 2 hours for day 1–5 and every 4 hours day 6–10) (n=11)  Continuous infusion (50 µg/kg/hour for day 1–5 followed by 25 µg/kg/hour for days 6–10) (n=12) for major surgery after a bolus to all of 90 µg/kg  Control group treated with FVIII and FIX pro- ducts	Hemostatic efficacy similar for bolus injection (73%) and continuous infusion (75%)  In the remaining patients treatment was regarded as ineffective  In 7 patients (20%) treatment was discontinued due to ineffective hemostasis (including 1 patient in the control group)	1 of 36	Medium
Astermark et al 2007 <sup>δ</sup> [23] Sweden	Prospective randomised, open-label, cross-over, equivalency multicenter <sup>γ</sup>	48 patients with an inhibitor and the need of bypassing agents  Mean age 27.5 years (range 8–55)	Two joint bleeds in each patient treated in a randomised way with two doses of rFVIIa 90–120 µg/kg (interval 2 hours) or one dose of aPCC 75–100 IU/kg  Primary outcome after 6 hours: treatment after 6 hours at discretion of the local physician. Every bleed followed for 48 hours	Equivalency was not meet at the primary end- point, but a clear trend was seen (p=0.059)  The effect at 6 hours, rated as effective or par- tially effective, was 80.9% for aPCC and 78.7% for rFVIIa. At 48 hours the rating was 97.6% and 85.4%, respectively  The corresponding figures for bleeding stopped were at 6 hours: 76.1% (aPCC) and 65.2% (rFVIIa)  High frequency of discordant bleeds (31% at 6 hours) indicated a different effect of the products on several patients	18 of 66	Low-medium

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Table 3.2.1a continued

Author Year Reference Country	Study design	Population Number Age	Intervention	Results	Drop-outs	Study quality and relevance
Steen Carlsson et al 2008 <sup>δ</sup> [24] Sweden	Randomised, multicentre, open-label study <sup>Y</sup> Patients included in the study performed by Astermark et al 2008 [23]	46 of the 48 patients included in the original study [23]  Age: 8–55 years (mean 27.5)	Cost and cost-effectiveness analysis was performed as part of the FENOC study designed as a equivalence study with a randomisation between two doses rFVIIa 90–120 µg/kg and one dose aPCC 75–100 IU/kg as treatment for 2 joint bleeds in each patient	The cost of aPCC was on average lower than rFVIIa with a median cost in USD of 6 230 (range 5 450–6 761) for aPCC and 9 000 (range 10 800–13 500) for rFVIIa. A difference in price between countries did not reverse the results  A relationship identified between cost per episode and body weight as well as age	20 av 66	Low-medium
Young et al 2008 <sup>δ</sup> [25] USA	Randomised, multicenter, cross-over, double-blind <sup>Y</sup>	21 Age 1–54 years (median 19.5)	Randomised between 90 µg/kgx3, 270 µg/kgx1 rFVIIa and 75 IU/kgx1 APCC for joint bleeds	Outcome measure according to the need for rescue medication (RM) and global assessment score (GAS)  Significant higher need for RM for aPCC (36.4%) vs rFVIIa 270 µg/kgx3 (8.3%), but not for rFVIIa 90 µg/kgx3 (9.1%)  No significant difference for GAS (27.3% vs 37.5% vs 54.5%)	20 of 42	Low-medium
Jimenez-Yuste et al 2009 <sup>δ</sup> [26] Spain	Retrospective case series <sup>β</sup>	10 patients with severe hemophilia A and inhibitors and prophylactic treatment with aPCC or rFVIIa for >4 months  Median age 4 years (range 1 to 31)	<u>Prophylaxis regimen</u> aPCC: 50 IU/kg/48 hours or 3 times per week rFVIIa 90–100 µg/kg once daily  Previous treatment in aPCC group: On-demand with or without ITI  Previous treatment in rFVIIa group: On-demand FVIII or ITI + on-demand	aPCC (n=5): The median number of bleeds/patient prior to prophylaxis was 14 (range 8–19) and during prophylaxis 5 (range 1–22). The median cost per patient per month was 59 398 euros (range 31 495–110 687) prior to prophylaxis and 27 144 euros (range 11 928–44 456) during prophylaxis  rFVIIa (n=5): The median number of bleeds/patient prior to prophylaxis was 4 (range 3–10) and during prophylaxis 1 (range 0–5). The median cost per patient per month prior to prophylaxis was 6 588 euros (range 2 094–62 062) and 23 544 euros (range 19 794–29 588) during prophylaxis	–	Low

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**Table 3.2.1a** continued

Author Year Reference Country	Study design	Population Number Age	Intervention	Results	Drop-outs	Study quality and relevance
Pan-Petesch et al 2009 <sup>δ</sup> [27] France	Retrospective case series <sup>γ</sup>	8 patients with hemophilia A and inhibitors  Age 19 months to 40 years	Treatment of mild to moderate bleeds with rFVIIa 270 µg/kg	All patients were successfully treated One dose was used in 5 patients, whereas a second and a third dose were after 6 hours or daily in the remaining 3 patients  No safety issues were raised	–	Low
Valentino 2009 <sup>α</sup> [28] USA	Retrospective case series <sup>β</sup>	6 patients with hemophilia A and B and high-titre inhibitors  Median age at start of prophylaxis was 8.4 years (range 3.7 to 24.1)	All 6 patients received prophylactic treatment with aPCC in a dose of 100 IU/kg/d for at least part of the observation time – in one patient 50–75 IU/kg every third day was also given. Median duration of treat- ment was 818 days (range 41 to 1 552)  Breakthrough bleeds were initially treated with aPCC 100 IU/kg every 12 hours. In resistant cases therapy with rFVIIa was also given	The number of bleeding episodes was reduced by a mean of 84% (range 43–100) from 27.88 per year (range 8–113) on-demand and 4.21 (range 0–16.47) on prophylaxis	–	Low

<sup>α</sup> None of the authors declared any conflict of interest

<sup>β</sup> No reported support from pharmaceutical companies

<sup>γ</sup> Reported support from pharmaceutical companies

<sup>δ</sup> One or more of the authors reported relation to pharmaceutical  
companies involved in the products

**Table 3.2.1b** Systematic reviews and consensus reports describing the effects of bypassing agents in acute bleeding, and surgery and as prophylaxis in patients with hemophilia and inhibitors.

Author Year Reference Country	Type of article	Title	Aim	Outcome	Study quality and relevance
Shapiro 2000 <sup>a</sup> [29] USA	Review of the literature and abstraction of data available at the company <sup>y</sup>	Recombinant factor VIIa in the treatment of bleeding in hemophilic children with inhibitors	To evaluate the use of rFVIIa in the paediatric population regarding pharmacokinetics and hemostatic effects	Available data suggest children to have a shorter half-life and more rapid clearance of rFVIIa than adults. rFVIIa seems to be effective and safe for the control of bleeds and surgical procedures. The optimal dosing regimens for both intermittent and bolus dosing remain to be defined	Low
Kulkarni et al 2001 <sup>a</sup> [30] USA	Consensus report <sup>b</sup>	Therapeutic choices for patients with hemophilia and high-titre inhibitors	A workshop on the treatment of bleeds in patients with high-titre inhibitors	Recommendation of porcine FVIII or rFVIIa for CNS bleeds and acute bleeds in plasma naïve patients – in other patients aPCC was considered a safe first-line treatment	Low
Wilde 2002 <sup>a</sup> [31] UK	Review of the literature <sup>b</sup>	Evidence for the use of activated prothrombin complex concentrates (aPCCs) in the treatment of patients with hemophilia and inhibitors	To present published experience on the use of aPCC to control or prevent bleeds in patients with inhibitors to factor VIII and IX	aPCC appears to be effective and safe in the management of bleeding episodes and surgery	Low
Lloyd Jones et al 2003 <sup>a</sup> [32] UK	Systematic review <sup>b</sup>	Control of bleeding in patients with hemophilia A with inhibitors: a systematic review	A systematic review of the best available evidence of clinical effectiveness in the treatment of acute bleedings in hemophilia A patients with inhibitors	aPCC appear to be more effective than PCC to control bleeds and there is no good evidence for the use of PCCs in surgery  aPPC controlled bleeding in 90% and rFVIIa in 60–100% of surgical episodes  aPCC was effective in >85% and rFVIIa in 70–100% of bleeds when the usage was not restricted by a protocol. Dosing varies and side-effects usually mild to infrequent	Medium

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**Table 3.2.1b** continued

Author Year Reference Country	Type of article	Title	Aim	Outcome	Study quality and relevance
Hind et al 2004 <sup>a</sup> [33] UK	Cochrane Database Systemic review <sup>β</sup>	Recombinant factor VIIa concentrate versus plasma-derived concentrates for the treatment of acute bleeding episodes in people with hemophilia A and inhibitors	To determine the clinical effectiveness of rFVIIa concentrate in comparison to plasma-derived concentrates for the treatment of acute bleeding episodes in people with hemophilia A and inhibitors	A total of five studies was identified by the searches, however, none were eligible for inclusion in this review  No RCTs on the relative effectiveness of rFVIIa concentrate compared to human plasma-derived concentrates were identified for inclusion in this review. The research evidence on which to base clinical decisions is therefore limited to case reports and other less robust evidence	Medium
Abshire et al 2004 <sup>a</sup> [34] USA	Review of the literature <sup>γ</sup>	Recombinant factor VIIa: review, dosing regimens and safety in patients with congenital and acquired factor VIII or IX inhibitors	To review the clinical experience with rFVIIa dosing in acquired and congenital hemophilia with inhibitors including all reported thrombotic adverse events	Mega-doses of 300 µg/kg should only be considered for the treatment of bleeds in young patients. For adults standard dosing of 90 µg/kg every 2–3 hours should be used. Optimal dosing for continuous infusion is not yet known  16 thrombotic events have been described with >700 000 standard infusions of rFVIIa – the majority with predisposing factors	Low
Negrier et al 2006 <sup>a</sup> [35] France	Review of the literature <sup>β</sup>	The history of FEIBA: a lifetime of success in the treatment of hemophilia complicated by an inhibitor	A summary of FEIBA regarding composition, mechanism of action, and efficacy during more than 30 years usage	FEIBA has been used to effectively and safely treat patients with inhibitors, but laboratory tests for in vivo monitoring are still missing	Low
Stephens et al 2007 <sup>δ</sup> [36] USA	A systematic review of the literature <sup>γ</sup>	Health economic review of recombinant activated factor VII for treatment of bleeding episodes in hemophilia patients with inhibitors	Review of 13 economical analysis performed with rFVIIa and compared with plasma-derived agents. 6 cost impact/general burden studies for rFVIIa (3 prospective and 3 retrospective) and 7 comparative analysis for on-demand treatment	Data suggest that total cost of treating a bleed with rFVIIa may be lower than with plasma-derived agents due to faster resolution, higher efficacy rate, and avoidance of second and third line treatment	Low

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**Table 3.2.1b** continued

Author Year Reference Country	Type of article	Title	Aim	Outcome	Study quality and relevance
Astermark et al 2007 <sup>a</sup> [37] Sweden	Survey, literature review and consensus recommendations <sup>y</sup>	Current use of bypassing agents in Europe in the management of acute bleeds in patients with hemophilia and inhibitors	Survey of the current use of bypassing agents in inhibitor patients  Consensus recommendations from the EHTSB Network	The use of bypassing agents varied among the 22 comprehensive hemophilia care centres from 14 European countries  Well-designed comparative studies are warranted	Low
Tjønnefjord et al 2007 <sup>b</sup> [38] Norway	Review of the literature <sup>y</sup>	Factor eight inhibitor bypass activity aPCC (FEIBA <sup>®</sup> ) in the management of bleeds in hemophilia patients with high-titre inhibitors	Review of available literature with focus on the treatment of bleeds and the prevention of chronic joint disease	aPCCs and rFVIIa have shown an efficacy of 80–90% in the manage- ment of bleeds in inhibitor patients  The combined use of aPCC (FEIBA <sup>®</sup> ) and rFVIIa has been put forward as an approach for bleeds that are refractory to either agent alone  Prophylaxis with bypassing agents is not supported by solid clinical evidence  rFVIIa seems to be a suitable treatment of choice in patients with hemophilia B and a history of anaphylaxis to FIX-containing concentrates	Low
Kenet et al 2008 <sup>b</sup> [39] Israel	Review of the literature <sup>b</sup>	Single-dose recombinant activated factor VII therapy in hemophilia patients with inhibitors	Review of 3 randomised con- trolled trials (Kavakli 2006, Santagostino 2006, Young 2008) comparing single-dose rFVIIa (270 µg/kg) with the standard regimen (90 µg/kgx3 or other repeated doses regimen)	Comparable efficacy between the two regimens with no safety issues identified, suggesting that single-dose rFVIIa represents a safe and effective alternative to standard multiple-dose regimens	Low
Shapiro 2008 <sup>b</sup> [40] USA	Review of the literature <sup>y</sup>	Single-dose recombinant activated factor VII for the treatment of joint bleeds in hemophilia patients with inhibitors	A review of clinical trials evalua- ting the usage of a single-dose of 270 µg/kg rFVIIa for the treat- ment of joint bleeds as well as additional published cases and case series using this dose	The data suggest a single dose of 270 µg/kg rFVIIa to be as safe and effective as repeated standard dosing of 90 µg/kg	Low

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**Table 3.2.1b** continued

Author Year Reference Country	Type of article	Title	Aim	Outcome	Study quality and relevance
Goldstein et al 2008 <sup>6</sup> [41] USA	Review of the literature and registry data <sup>y</sup>	Evidence-based use of recombinant FVIIa (NovoSeven <sup>®</sup> , Niastase <sup>®</sup> ) for the treatment of hemophilia with inhibitors in children and adolescents	To review PMS and HTRS registry data and published literature on the usage of rFVIIa for treatment and prevention of bleeds in children and adults with hemophilia A and B and inhibitors	rFVIIa is safe and effective for use in controlling bleeding	Low
Obergfell et al 2008 <sup>6</sup> [42] Switzerland	Review of the literature <sup>y</sup>	Recombinant activated factor VII for hemophilia patients with inhibitors undergoing orthopaedic surgery: a review of the literature	To review published data on elective orthopaedic procedures covered by rFVIIa in patients with inhibitors from January 2002 to November 2006	Data of 80 procedures suggest rFVIIa to be safe and effective for providing adequate hemostatic cover. In patients with bleeding complications, an inadequate amount of rFVIIa was considered to be the cause. The optimal treatment regimen has yet to be identified and further controlled studies are needed	Low
Knight et al 2009 <sup>6</sup> [44] UK	A systematic review of the literature <sup>y</sup>	Systematic review of efficacy of rFVIIa and aPCC treatment for hemophilia patients with inhibitors	To perform an overall review of the efficacy of rFVII and aPCC, establish robust estimates of the efficacy, speed of bleed resolution, and adverse event profile of both agents  11 open-label cohort studies, 6 randomised trials including 2 head-head studies and one meta-analysis identified	The wide variations in definitions of efficacy and study methods make comparison of results across studies difficult. Further head-to-head studies should include a standardised measurement for defining efficacy	Low

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**Table 3.2.1b** continued

Author Year Reference Country	Type of article	Title	Aim	Outcome	Study quality and relevance
Knight et al 2009 <sup>6</sup> [43] UK	A systematic review of the literature <sup>y</sup>	A systematic review of cost-effectiveness of rFVIIa and aPCC in the treatment of minor/moderate bleeding episodes for hemophilia patients with inhibitors	<p>Review of economical analysis performed with rFVIIa and compared with plasma-derived agents including model type, design, assumptions, and results</p> <p>12 studies identified that met the inclusion criteria of comparative analysis including 4 abstracts</p> <p>One cost-utility analysis, one lifetime analysis and 10 decision models evaluating cost to resolve a bleed with aPCC or rFVIIa</p>	<p>Data suggest that rFVIIa may be the cost-effective alternative to treatment with aPCC (7 of 9 studies)</p> <p>The efficacy of aPCC derived from retrospective studies was lower than reported in the literature</p>	Low

**Table 3.2.2a** Studies on immune tolerance induction (ITI) in patients with hemophilia A and B and inhibitors.

Author Year, Reference Country	Study design	Population Number Age	Intervention	Results	Drop-outs	Study quality and relevance
Scheibel et al 1987 <sup>a</sup> [45] Denmark	Retrospective case series <sup>β</sup>	11 patients with hemophilia A and high-responding inhibi- tors (>5 BU)  Age from 6 to 42 years	Evaluation of the out- come using high dose i.e. 90 to 200 IU/kg/d for ITI. 3 patients also received immunosup- pression (prednisone and cyclophosphamide)  Success not defined	In all 11 cases the inhibitor was suppressed, but the rate of tolerance not possible to evaluate	–	Low
Nilsson et al 1988 <sup>a</sup> [46] Sweden	Retrospective case series <sup>β</sup>	11 patients with hemophilia A, 9 of whom were high responders (10 BU)  Age from 3 to 56 years	Evaluation of the ITI out- come using the Malmö protocol i.e. high-dose FVIII and immunosup- pression (prednisone, IVIg, cyclophosphamide) with or without extra- corporeal adsorption to protein A	The inhibitor disappeared in 9 of 11 cases after 2–3 weeks. In 8 of the 9 patients also the half-life was normalised  The data suggest ITI according to the Malmö protocol to be effective, but also that all components of the protocol are required for success	–	Low
Mauser- Bunschoten et al 1995 <sup>a</sup> [47] The Netherlands	Prospective observational study <sup>β</sup>	33 patients eligible of whom 24 patients with severe hemophi- lia A and inhibitors were treated with ITI  Median age: 12 years (range 1 to 43)	ITI regimens used: Initial high doses of FVIII to neutralise the antibo- dies prior to surgery or because of life-threate- ning bleeding followed by twice daily 25 IU/kg (n=11) or 25 IU/kg two times per week up to every other day (n=13)  Response defined as inhi- bitor titre <2 BU, FVIII recovery ≥50% of and half-life ≥6 hours	Low-dose ITI regimen was successful in 21 of 24 patients (87%)  The success was obtained within 0.5 to 28 months (median 1 year)  The highest inhibitor level and age at inhibitor development were indepen- dent predictors of the response  The type of factor VIII used to obtain IT did not affect the results  In 1 patient recurrence of inhibitory activity was seen after 48 months	9 of 33	Low

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**Table 3.2.2a** continued

Author Year, Reference Country	Study design	Population Number Age	Intervention	Results	Drop-outs	Study quality and relevance
Kucharski et al 1996 <sup>a</sup> [48] Poland	Retrospective case series <sup>Y</sup>	26 patients with hemophilia A and high-responding inhibitors (>5 BU)  Age from 17 to 57 years	A comparison of the outcome of ITI with plasma-derived factor VIII concentrates using a low dose (25 IU/kg twice weekly) or immunosup- pression with high-dose factor VIII (modified Malmö protocol)  Very good results defi- ned as permanent elimi- nation of the inhibitor and half-life >5 hours	Very good results were observed in 3 of the 11 patients using low dose after 5 to 20 months and in 5 of the 15 patients using the modified Malmö protocol after 17 to 36 days  Good results (permanent suppression to low-titre) were described in 2 and 5 patients, respec- tively	–	Low
Oldenburg et al 1999 <sup>a</sup> [49] Germany	Retrospective case series <sup>B</sup>	60 hemophilia A patients: 36 high and 24 low responders	ITI according to the Bonn protocol i.e. 100 IU/kg and 50 IU/kg aPCC, twice a day until the inhibitor decreased to less than 1 BU and the 30 min FVIII reco- very became measurable  Therapy was continued with 150 IU FVIII/kg twice a day until disap- pearance of inhibitors and normal half-life	Successful ITI in 52 patients (86.7%) while the therapy failed in 8 patients (13.3%). No inhibitor relapse  Median time to success was 14.1 months (range 1.8–103.2)  Interruptions of treatment during the ITI led to prolongation of ITI duration  Predictors of failure were high initial inhibitor titre or high titre during ITI	12 of 72	Low
Batlle et al 1999 <sup>a</sup> [50] Spain	Retrospective case series <sup>Y</sup>	11 patients with severe hemophilia A (9 high responders 2 low responders)  Age from 11 months to 47 years	ITI with recombinant FVIII  Dosing varied between 50 IU/kg every 2 days to 220 IU/kg daily  Success defined as a titre ≤0.6 BU	Success in 9/11 cases (81.8%)  Continued treatment with rFVIIIa on-demand or prophylactic	–	Low

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**Table 3.2.2a** continued

Author Year, Reference Country	Study design	Population Number Age	Intervention	Results	Drop-outs	Study quality and relevance
Damiano et al 2000 <sup>a</sup> [51] USA	Retrospective observational study <sup>b</sup>	139 individuals with hemophilia A or B and inhibitors of whom 104 were treated with ITI  Age ranged from 1 month to 44 years	Variable ITI regimens among centres and for individual patients  Initial doses of clotting factor ranged from 25 to 200 IU/kg/day with a median dose of 50 IU/kg/day  Successful ITI defined as inhibitor titre <1.0 BU	A success rate of 78% (57 of 81 patients) was achieved  19 patients failed ITI and 23 patients were currently undergoing ITI  The probability of achieving a successful response to ITI treatment was significantly greater if the inhibitor titre at initiation of ITI was <10 BU	–	Low
Unuvar et al 2000 <sup>a</sup> [52] USA	Retrospective case series	14 patients with severe hemophilia A (13 high responders, 1 low responders)  Age from 2 months to 17 years	ITI with recombinant (n=10) and plasma- derived (n=4) FVIII  Dosing varied between 50 to 200 IU/kg daily  Success defined as a no inhibitor titer, and normal recovery and half-life	Success in 11/14 cases (79%). The 3 failures were treated with 100–200 IU/kg rFVIIIa  A historical and/or maximum titer during ITI >200 BU indicated a higher risk of failure or prolongation of treatment  Recombinant and plasma-derived FVIII is effective in eradicating the inhibitor	–	Low
El Alfy et al 2000 <sup>a</sup> [53] Egypt	Retrospective case series <sup>b</sup>	10 patients with severe hemophilia A (all high responders)  Mean age 6.6 years	ITI with cryoprecipitate  Dosing varied between 25 IU/kg every other day (<40 BU) to 50 IU/kg every other day (>40 BU)  Success defined as an inhibitor titre <2 BU, and 60% recovery	Success in 8/10 cases (80%)  Cryoprecipitate and low dose effective as ITI regimen	–	Low

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**Table 3.2.2a** continued

Author Year, Reference Country	Study design	Population Number Age	Intervention	Results	Drop-outs	Study quality and relevance
Lenk et al 2000 <sup>a</sup> [54] Germany	Prospective German Registry study <sup>b</sup>	126 patients with hemophilia A and 4 with hemophilia B (all severities) (104 high responders 22 low responders)  Mean age 6.6 years	Type of concentrate not stated  High-dose regimen  Success defined as a no-inhibitor titre, and normal recovery and half-life	Complete success in 99/126 (78.6%) cases with hemophilia A and 1/4 (25%) hemophilia B Partial response in 11/126 (8.7%) Failure in 16/126 (12.7%)	–	Low
Berntorp et al 2000 <sup>a</sup> [55] Sweden	Retrospective case series <sup>b</sup>	17 patients with hemophilia A and 9 with hemophilia B (severes and moderates). All high responders  Age 2 to 46 years	ITI with recombinant and plasma-derived factor VIII/IX  Malmö protocol (Prot A adsorption, hydrocorti- sone, cyclophosphamide, IVIg, factor VIII/IX)  Success defined as a no-inhibitor titre, and normal recovery and half-life	Complete success in 10/17 (59%) cases with hemophilia A and 6/9 (67%) hemophilia B  Time to tolerance is shorter in successful cases which might be beneficial in hemophilia B in order to reduce the risk of complications	–	Low

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Table 3.2.2a continued

Author Year, Reference Country	Study design	Population Number Age	Intervention	Results	Drop-outs	Study quality and relevance
Aledort et al 2000 <sup>a</sup> [56] USA	Retrospective cost-modeling data extracted from the International Immune Tolerance Registry <sup>b</sup>	Total number of patients included in the analysis not stated	Cost-modeling data for ITI - treatment using the following assumptions: children 25 kg; adult 75 kg; factor VIII dose of 200 IU/kg/day; a factor VIII plasma- derived (pd) cost of 0.50 USD/IU; a factor VIII recombinant (r) cost of 1.00 USD/IU	85% of the patients with successful treatment became tolerant within 2 years and 60% within 1 year  The patients were divided into two groups: a) Favourable prognosis (group 1): patients with titre <10 BU prior to ITI, treated with a factor VIII dose >100 IU/kg/day and <5 years between inhibitor detection and start of ITI b) Poor prognosis (group 2): patients with the opposite features  Patients in group 1 had a 65% chance of becoming tolerant within 1 year, in contrast to those with poor indicators, who had a 35% chance  Time to 50% success rate was 9.5 months in group 1 and the corresponding costs in USD 712 500 (pd) and USD 1 425 000 (r), respectively. The time to 50% success rate in group 2 was 19 months and the costs USD 4 275 000 (pd) and USD 8 550 000 (r), respectively  It may be cost effective to identify patients with indicators of a good and poor ITI out- come before start of treatment	–	Low
Haya et al 2001 <sup>a</sup> [57] Spain	Retrospective Spanish Registry study <sup>b</sup>	41 patients with hemophilia A and 1 hemophilia B (all severities) 39 high responders 3 low responders  Age from 0 to 57 years	The types of product used were recombinant products in 9 cases and plasma-derived in 6 cases  Various ITI regimens was used with a factor dosage of 25 IU/kg every other day to 500 IU/kg daily. In one case immuno-suppression was used  Success defined as no inhibitor titre or half-life of ≥8 hours	Success in 26/38 cases (68%)  Low inhibitor titre at start of ITI, a dose ≤100 IU/kg/d and low maximum titre during ITI were associated with a higher probability of success	–	Low

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**Table 3.2.2a** continued

Author Year, Reference Country	Study design	Population Number Age	Intervention	Results	Drop-outs	Study quality and relevance
Rocino et al 2001 <sup>a</sup> [58] Italy	Retrospective Case series <sup>b</sup>	12 patients with severe hemophilia A and high-responding inhibitors  Median age at inhibi- tor development: 3 years (range 1.1–7.8)	FVIII dosage of 100 IU/ kg/day until the inhibi- tor was undetectable and then after another 2 months gradually reduced to regular prophylaxis 25 IU/kg 3 times weekly  Criteria for complete success of ITI were no detectable inhibitor, normal vivo recovery, and normal half-life (>6 hours)	Overall success rate: 10 patients (83.3%) including 1 patient with partial success  Time to undetectable inhibitor ranged from 1 to 6 months (median 3.5)  Pharmacokinetic data showed that complete tolerance will not be reached until a normal half-life of infused FVIII is achieved	None	Low
Mariani et al 2001 <sup>a</sup> [59] Italy	Retrospective International Registry study <sup>b</sup>	314 patients with severe hemophilia A and inhibitors  94.8% high responders  Median age at inhibi- tor development 4 years (range <1–64)	The dose for ITI ranged from <50 IU/kg/day to >200 IU/kg/day  Definition of success not uniformly defined	Success as defined by undetectable inhibitor (<0.6 BU) was reported in 140 patients (50.9%) including 128 with normal recovery (>80%) and half- life (>6 hours). Treatment failed in 66 patients (24%). 48 patients (17.5%) had ongoing ITI  Treatment dose was associated with outcome: suc- cess was 48% <50 IU/kg/day compared with 86% with ≥200 IU/kg/day)  Predictors of success was early start of ITI, low inhibitor titer and high dose	37	Low
DiMichele et al 2002 <sup>a</sup> [60] USA	Retrospective Registry study <sup>b</sup>	171 patients with hemophilia A and 17 with hemophilia B  Mean age 5.6 years (range 0.1–64)	Dosing ranged from <50 IU/kg/day to ≥200 IU/kg/day  Immune modulation was used in 40% of hemophi- lia A patients and in 47% of hemophilia B  Definition of success varied between different centres and according to the physician	Successful ITI in 115/164 subjects (70%) with hemophilia A  The peak titer during ITI, low dose and pre- induction titer were significant predictors of success  Only 5 (31%) of the 16 completed ITI courses in patients with hemophilia B were successful	8	Low

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**Table 3.2.2a** continued

Author Year, Reference Country	Study design	Population Number Age	Intervention	Results	Drop-outs	Study quality and relevance
Mathias et al 2005 <sup>a</sup> [61] United Kingdom	Retrospective case series <sup>β</sup>	14 patients with severe hemophilia A and 1 severe hemophilia B 39 high responders 3 low responders  Age from 15 to 205 months	Various types of product  Dosing varied between 50 IU/kg 3 times weekly to 100 IU/kg 2 times daily	Success in 12/15 cases (80%)  Low maximum inhibitor titre during ITI and short interval between diagnosis and start of ITI associated with a higher probability of success	–	Low
Orsini et al 2005 <sup>a</sup> [62]	Retrospective observational study <sup>β</sup>	8 patients with severe hemophilia A and high-responding inhibitors  Age 11 months to 24 years	Various doses including both low- and high-dose regimens (FVII and VWF)  Success defined as a titre <0.6 BU and FVIII recovery ≥0.66 IU/dL per IU/kg and/or a half- life ≥6 hours	Success was reported in 7 patients (87.5%)	–	Low
Barnes et al 2006 <sup>δ</sup> [63] Canada	Retrospective observational study <sup>γ</sup>	32 patients with inhibitors to FVIII  Median age at inhi- bitor detection time was 2.1 years (range 4.8 months to 50)	Dosing ranged from 50 IU/kg thrice weekly to 200 IU/kg/d  8 patients received adjuvant therapy  Various definitions of success	ITI was successful in 23 cases (79.3%) and failed in 6 cases (20.7%)  The peak inhibitor titre during ITI was significantly lower in the patients with successful ITI compared with patients that failed in ITI	–	Low

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**Table 3.2.2a** continued

Author Year, Reference Country	Study design	Population Number Age	Intervention	Results	Drop-outs	Study quality and relevance
Rocino et al 2006 <sup>a</sup> [64] Italy	Prospective observational study <sup>b</sup>	26 hemophilia A patients with high responding inhibitors (>5 BU)  Median age 4.2 years (range 0.9–25)	The ITI regimens ranged from 50 IU/kg every other day to 200 IU/kg once daily using recom- binant FVIII  Definition of success was no detectable in- hibitory activity, in vivo recovery >66%, and a half-life >6 hours  The start of ITI was deferred until inhibitor <10 BU	Successful ITI in 19 of 26 patients (73%), partially successful in 2 patients  Failure of ITI in 5 patients (stopped after 9–21 months)  FVIII genotyping: 12 of 17 patients with intron 22 gene inversion had successful ITI treatment  The success rate and duration of treatment were comparable to those reported by inter- national registries	–	Low
Gringeri et al 2007 <sup>b</sup> [65] Italy	Retrospective case series <sup>y</sup>	17 patients with hemophilia A (all severe except one moderate)  All high responders and ≥1 risk factor for poor response  Age from 4 to 54 years	Plasma-derived VWF- containing FVIII  Risk factors for a poor response were age >6 years, interval of >1 year from inhibitor diag- nosis, >10 BU at start of ITI, peak titre >200 BU and previously ITI failure  Dosing from 50 IU/kg three times weekly to 200 IU/kg/day Success defined as negative inhibitor titre or normal recovery and half-life	Success in 9/17 cases (53%) Partial response in 7 patients (41%)  Success and failure not associated with a particular dosing regimen  von Willebrand factor-containing FVIII products are effective as ITI therapeutics in many patients at high risk of poor response	–	Low

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**Table 3.2.2a** continued

Author Year, Reference Country	Study design	Population Number Age	Intervention	Results	Drop-outs	Study quality and relevance
Unuvar et al 2008 <sup>a</sup> [66] Turkey	Retrospective case series <sup>β</sup>	21 patients with hemophilia A (all but 1 severe) All high responders  Age from 1.5 to 20 years	Plasma-derived FVIII  Dosing 20–50 IU/kg 2 or 3 times weekly (including immunosup- pression in 1 patient)  Success defined as nega- tive inhibitor titre and/or normal recovery and/or normal half-life	Success in 5/19 cases (26.3%) Partial response in 7 patients (36.8%)  Relapse in one immune-tolerised patient  The outcome of low-dose protocol was not satisfactory	2	Low
Platokouki et al 2009 <sup>a</sup> [67]	Retrospective case series <sup>β</sup>	6 patients with severe hemophilia A  All high responders	Plasma-derived VWF-containing FVIII  Dosing 100 IU/kg every other day  Success defined as negative inhibitor titer or normal recovery and half-life	Success in 5/6 cases (83.3%)  The role of von Willebrand factor-containing FVIII products and optimal dosing requires further studies	–	Low
Valentino et al 2009 <sup>δ</sup> [68] USA	Retrospective case series <sup>β</sup>	12 patients with severe hemophilia A and inhibitors  Mean age at diagnosis of inhibitor was 19.8 months	Dosing ranged from 100 IU/kg/day to 200 IU/kg/day  In 1 patient a low-dose ITI regimen using 115 IU/kg 3 times weekly was used	Overall tolerance was achieved in 9 of 12 (75%)  Ongoing ITI in 2 patients, failure in 1 patient	–	Low

<sup>a</sup> None of the authors declared any conflict of interest

<sup>β</sup> No reported support from pharmaceutical companies

<sup>γ</sup> Reported support from pharmaceutical companies

<sup>δ</sup> One or more of the authors reported relation to pharmaceutical  
companies involved in the products

**Table 3.2.2b** Systematic reviews and consensus report on immune tolerance induction (ITI) in patients with hemophilia A and B and inhibitors.

Author Year, Reference Country	Type of article	Title	Aim	Outcome	Study quality and relevance
Wight et al 2003 <sup>a</sup> [69] UK	Systematic review of the literature <sup>b</sup>	Immune tolerance induction in patients with hemophilia A with inhibitors: a systematic review	Review available evidence for the clinical effectiveness of ITI treatment	High-dose protocol seems to be more effective than low- dose protocols and immuno- suppression	Medium
Mariani et al 2003 <sup>a</sup> [70]	Literature review <sup>b</sup>	Immune tolerance induction in hemophilia A: a review	Review according to the litera- ture of the outcome using differ- ent ITI protocols in patients with hemophilia A  Comparison of data, definitions and predictors of outcome in three different ITI registries	Comparison between studies and registries difficult due to heterogeneity of data and defi- nitions  Consistent predictors include age at start, maximum inhibitor titre, or titre at start of ITI. High dose associated with higher success. von Willebrand factor- containing products might be beneficial in some patients but additional studies needed	Low
Paisley et al 2003 <sup>a</sup> [71] UK	Systematic review <sup>b</sup>	The management of inhibitors in hemophilia A: introduction and systematic review of current practice	A systematic review of current international practice for the clinical management of hemo- philia A patients with inhibitors concentrating on literature published from 1995 onwards including guidelines and registries	Of a total of 4 100 references, 27 relevant papers were iden- tified  There appears to be a consensus about the need of early identi- fication of patients with inhibi- tors by regularly screening for inhibitors and that ITI should be performed  However, the choices of ITI regimen vary between diffe- rent countries and centres, and various approaches are used to control bleedings	Medium

*The table continues on the next page*

**Table 3.2.2b** continued

Author Year, Reference Country	Type of article	Title	Aim	Outcome	Study quality and relevance
Makris M 2004 <sup>a</sup> [72] UK	Literature review <sup>β</sup>	Systematic review of the management of patients with hemophilia A and inhibitors	Review of the literature on epidemiology of inhibitors and treatment of acute bleeds in inhibitor patients  Economic modeling of different treatment strategies including ITI and on-demand treatment with bypassing agents	High-dose ITI protocol more efficient than low dose and immunosuppression  aPCC, rFVIIa and porcine FVIII were all efficacious in the treatment of bleeds	Low
Teitel 2006 <sup>a</sup> [73] Canada	Literature review <sup>β</sup>	Inhibitor economics	Review to discuss the cost of managing inhibitor patients regarding bypass therapy and ITI as well as the distribution of cost between patients	Inhibitor treatment is costly, but there is a wide-spread cost between patients with some extremely expensive outliers	Low
Astermark et al 2006 <sup>a</sup> [77] Sweden	Survey of current practice, literature review and consensus recommendations <sup>γ</sup>	Current European practice in immune tolerance induction therapy in patients with hemophilia and inhibitors	Survey of the current management of inhibitor patients and the use of ITI  Consensus recommendations from the EHTSB network	Dosing, time to start, duration, type of product, and definition of success varied among the 21 comprehensive hemophilia care centres from 14 European countries  Well-designed studies and consensus recommendations for the future are warranted	Low
DiMichele 2007 <sup>a</sup> [75] USA	Review of the literature <sup>β</sup>	Immune tolerance therapy for factor VIII inhibitors: moving from empiricism to an evidence-based approach	To explore the current and future role of ITI treatment and discuss current knowledge of host and treatment factors, as well as supportive care initiatives, known or suspected to influence ITI outcome	Prognostic factors for success: low pre-ITI titer and historical peak titer. Comparison between studies regarding factor VIII dose/regimen and product type and purity difficult due to heterogeneity of data  Uncertain role of immune modulation therapy. Few data on recommendations for inhibitor eradication in moderate/mild hemophilia	Low

*The table continues on the next page*

**Table 3.2.2b** continued

Author Year, Reference Country	Type of article	Title	Aim	Outcome	Study quality and relevance
Kreutz W 2008 <sup>a</sup> [76] Germany	Review of the literature <sup>b</sup>	The role of von Willebrand factor for the success of immune tolerance induction	Comparison of success of ITI between plasma-derived FVIII concentrates with a high content of VWF and high-purity FVIII concentrates	<p>Single-centre experiences suggest that the efficacy of ITI is significantly lower with high-purity FVIII compared with VWF-FVIII (success rate 29% vs 90–100%)</p> <p>Similar experience has been reported from 2 other centres (overall success rate 54% with rFVIII vs 82% with pdVIII)</p> <p>Some case studies suggest that switching from high-purity to plasma-derived VWF containing FVIII concentrates may be successful</p>	Low

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### **3.3 Replacement therapy with factor concentrates in von Willebrand Disease**

Treatment with factor concentrates containing von Willebrand factor (VWF) and FVIII is efficacious in acute hemorrhage in patients with von Willebrand disease (VWD) type 1 and type 2 with insufficient response to desmopressin and in von Willebrand disease type 3.

Even if the scientific evidence is based mainly on retrospective clinical studies without controls, published efficacy results are pronounced and clinically relevant.

#### **Evidence grading of the results**

- The scientific evidence for the prophylactic treatment with factor VIII/VWF concentrates in patients with von Willebrand disease is insufficient and limited to observational studies. It can be anticipated that prophylaxis, especially in von Willebrand disease type 3, is efficacious and ongoing large prospective studies address this issue. Comparative clinical efficacy studies between concentrate brands are lacking. Clinical experience from long-term treatment with regular prophylaxis also indicates reduced occurrence of joint disease and improved quality of life but the scientific evidence is limited and further studies are needed.
- Clinical experience and observational studies suggest that treatment with coagulation factor concentrates containing von Willebrand factor and FVIII as prophylaxis during surgery is efficacious in patients with von Willebrand disease insufficiently responsive to desmopressin.
- The scientific evidence is insufficient to assess if the different factor concentrates differ in their effect on bleeding.
- The scientific evidence is insufficient to permit comparison of the effect of bleeding with different dosage regimens.

## Introduction

Von Willebrand disease (VWD) is the most common congenital bleeding disorder. It occurs in several subtypes. The most common, type 1, is characterised by a decreased level of von Willebrand factor (VWF) with normal molecular structure. Most of these patients respond well to desmopressin and only few patients in this category need treatment with VWF containing concentrate. Type 2 VWD is characterised by an altered structure of VWF, or decreased binding of factor VIII, and can be divided into several subtypes. Some type 2 patients respond to treatment with desmopressin but a majority is dependent on treatment with concentrates. Type 3 VWD virtually lacks VWF; hence, they also display low levels of FVIII since VWF is the carrier for FVIII. These patients may consequently present with hemophilia-like bleedings due to their FVIII deficiency and in acute situations replacement with FVIII containing VWF concentrates is a prerequisite for achieving hemostasis. As increased levels of VWF gradually enhance and more or less restore the factor VIII level, purified VWF concentrates may be feasible to use if given well ahead of e.g. elective surgery. Type 3 VWD is extremely rare and in Sweden the prevalence is estimated at three to four patients per million inhabitants. There are several types of VWF-FVIII containing concentrates licenced in Sweden. In the following review, treatment effects and adverse events with such concentrates are discussed without any comparison between brands of concentrate.

## Questions

- Does factor concentrate containing von Willebrand Factor (VWF) and factor VIII (FVIII) have an effect on bleeding in patients with VWD?
- Does long-term prophylactic treatment with VWF containing factor VIII concentrate result in fewer bleeding episodes compared to on-demand treatment?
- Does treatment with factor concentrates containing von Willebrand factor and factor VIII as prophylaxis during surgery have demon-

strated effects on bleeding in patients with VWD that are not responsive to desmopressin?

- Do the factor concentrates differ in their effect on bleeding?
- Can dosing be optimized?

## **Inclusion criteria**

### ***Patients***

Patients with VWD that do not respond satisfactorily to desmopressin, mainly type 3 VWD, most patients with type 2 VWD, and individual patients with more severe forms of type 1 VWD. All ages.

### ***Interventions***

von Willebrand factor (VWF) and factor VIII (FVIII) concentrate.

### ***Outcome***

Treatment effects are presented as:

- Hemostatic effects on minor or major bleeds
- Impact of prophylactic treatment on bleeding frequency, long-term sequels, and quality of life
- Hemostatic effects in connection with surgical procedures

### ***Study types***

Systematic reviews, meta-analysis, randomised and controlled studies and observational studies. Pharmacokinetic studies have not been included.

### ***Number of patients:***

At least 20.

### ***Timeframe and languages***

Literature published from 1985 to spring 2010 and in English, Norwegian, Danish, and Swedish.

## Results of the literature search and selection of studies

The systematic literature search resulted in 18 articles that met the inclusion criteria, including four articles that presented overviews. Table 3.3.1 presents 14 studies, of which six are prospective and eight are retrospective. The study populations include 21 to 100 patients and are relatively large given the low prevalence of VWD requiring treatment with factor concentrate. By nature, the data are heterogeneous as regards subtypes of VWD. The most severe form, type 3, is relatively well represented, and gender distribution is good. Few children are included in the studies.

These outcome studies do not compare products and lack of studies prevent this question being addressed. Some studies include tranexamic acid, mainly for mucocutaneous bleeds, and the studies are not designed to distinguish the effects from the treatment effects of concentrate.

Most of the studies present results in terms of spontaneous or traumatic bleeds and/or surgical bleeds. One study presents long-term prophylactic treatment in Sweden, and three other studies include smaller cohorts of patients that have undergone prophylactic treatment.

The evaluation of hemostatic effects is often subjective, i.e. rated by the patient or physician without any objective measurement, but surgical studies introduce an objective component with the surgeon's comparative judgement of the situation in patients that do not have any bleeding disorders. Since treatment with concentrate in VWD is often home-based and early delivery is important, treatment effects are often judged by the patients themselves, or by their guardians. Few patients have been excluded when this information is available. Few side effects are reported, and these are mild.

All studies present low-grade evidence based on current criteria since it is difficult to conduct prospective, controlled studies in this area. The severe and painful symptoms caused by acute bleeds in VWD (at times life-threatening), and the good clinical effects observed from treatment, render placebo-controlled studies unethical.

Table 3.3.2 presents three guidelines, one from the UK, one from the USA, and one from Italy. Also presented is a systematic review of human-plasma-derived von Willebrand factor (VWF) and human coagulation factor VIII (FVIII/VWF) (Haemate P<sup>®</sup>), i.e., the product for which there is most experience in treating VWD.

## Description of studies and results

(Table 3.3.1)

Goudemand et al [1] reported a retrospective study of 75 patients comprising a spectrum of different types of VWD, including seven patients with acquired VWD and four having type 3 VWD. The majority of patients (n=42) had type 1 VWD. Fourteen bleeding episodes and 54 surgical procedures (31 minor and 23 major) were treated with a very high-purity VWF-containing concentrate, with a low content of FVIII (LFB Les Ulis France). Initial doses were around 50 U per kg VWF:RCo (von Willebrand factor: Ristocetin cofactor). Epistaxis and gingival bleedings were generally stopped after one infusion. If subsequent infusions were needed they were usually given for several days. No bleeding complications were seen during surgery.

Nitu-Whalley et al [2] reported a retrospective study of 65 patients that had undergone 103 surgical procedures, whereof 38 patients (68 surgical procedures) were treated with concentrate, namely BPL 8Y<sup>®</sup> or FVIII/VWF concentrate (Haemate<sup>®</sup>). The initial dose was approximately 50 IU per kg. Hemostatic effects were reported to be excellent in 82 percent of the procedures, while the remainder were equally distributed between moderate and poor effects.

Federici et al [3] conducted a retrospective review of 22 patients treated with virus-inactivated FVIII/VWF concentrate (Fandhi<sup>®</sup>) for surgery or acute bleeding. Hemostatic effects were excellent to good in 92 percent of the treatment cases. The median dose of FVIII was 51 IU per kg within the initial days of major surgery.

Mannucci et al [4] studied the VWF/FVIII concentrate Alphanate<sup>®</sup> in an industry-sponsored prospective multicentre study. Of the 81 patients,

32 had type 3 VWD. Dosing was 40–50 VWF:RCo IU per kg for bleeding and 60–75 IU per kg for surgery. Less bleeding than expected was observed during surgery and median number of infusions for stopping bleeding events was one for type 1 and 2A, and three for type 3 VWD. Two adverse events were recorded.

Cox Gill et al [5] reported a prospective study of 41 patients, whereof 12 are type 3 VWD. Fifty-three acute bleeding episodes were treated with FVIII/VWF concentrate (Haemate®) at an initial dose of 67 IU VWF:RCo per kg and usually for three days. In 98 percent of the cases the effects were found to be excellent/good. Being prospective, the study has relatively high clinical relevance.

Franchini et al [6] presented a retrospective study comprising 26 patients treated with FVIII/VWF concentrate (Haemate®) for 43 procedures, whereof 14 were major surgery. Initial doses in major surgery averaged 61.2 IU VWF:RCo per kg with a range of 47.5– 81.1 IU. The mean dose administered per day was 39.3 units (range 25–52.5), and the number of treatment days was 9.7 (range 5–23). In all cases, the effects were judged to be excellent/good. No side effects were observed.

Thompson et al [7] reported, similar to the preceding study, a prospective multicentre study from the U.S. including treatment of 39 surgical patients with FVIII/VWF concentrate (Haemate®). Initial dose is 60 to 80 IU VWF:RCo per kg with a somewhat lower dose in subsequent days. Treatment time is up to seven days. In all cases, the hemostatic effect is reported to be excellent/good. The prospective nature gives it relatively high clinical relevance. Seven adverse events possibly related to the drug were reported. In one event, study medication was withdrawn because of pseudo-thrombocytopenia in a subject with type 2B VWD.

Berntorp and Petrini [8] presented experiences of prophylactic treatment for VWD in a retrospective study including 35 patients, of which 28 patients have type 3 VWD (i.e. basically all cases in Sweden). In children, the indications for prophylaxis were bleeding in the nose or mouth and, in older children, also joint bleeds. Bleeding in joints dominates among adults, but gastrointestinal bleeds and profuse menstruation are also

common indications. Before the mid-1980s, AHF-Kab<sup>®</sup>i (human fraction 1-0, no longer available) and thereafter FVIII/VWF concentrate Haemate P<sup>®</sup>/Humate-P<sup>®</sup> were used. The dose has been 24 IU FVIII per kg bodyweight (range 12–50 units) given one to three times per week. Of the adult patients, 63 percent received prophylaxis for at least 10 years, and 89 percent of the 18 children for at least 5 years. The results show that the number of bleeds decreased substantially and significantly during prophylaxis, and in many patients bleeding ceased. It is noteworthy that children starting prophylaxis early did not develop joint bleeds or joint damage later in life. This study contains the longest observed and largest cohort of patients given prophylactic treatment. Three patients developed inhibitors during treatment without further details given.

Borel-Derlon et al [9] presented a prospective, multi-European study of 50 patients, including 18 with type 3 VWD. This study used factor concentrate VWF (Wilfactin<sup>®</sup>), which is the only concentrate enriched in VWF and containing little FVIII. The study includes patients with acute bleeds, surgical procedures, and long-term prophylaxis. For spontaneous bleeds, 41.8 IU VWF:RCo per kg were delivered as a median dose per infusion, and the mean number of infusions was three. In some cases (severe bleeds) FVIII was given initially to achieve a more rapid effect. Effects were reported to be excellent/good in 88 and 89 percent at 6 and 24 hours post-treatment, respectively. In elective surgery, only VWF concentrate (Wilfactin<sup>®</sup>) was administered, starting 12 to 24 hours prior to the procedure, but in emergent surgery FVIII was also given for a rapid effect. The median dose of VWF concentrate (Wilfactin<sup>®</sup>) was 45.5 units (range 11.1–100), treatment was three days (range 1–57), and the median number of infusions was 3.0 (range 1–65). At discharge, the effects were reported as excellent/good in 100 percent of cases. Ten patients underwent prophylactic treatment, but only four were classified as long-term prophylaxis (range 3–25 months). The median dose for these patients was 40 IU VWF:RCo per kg two to three times per week, administered for 66.5 cumulative months. Neither thromboembolic complications nor the development of any antibodies were observed.

Lethagen et al [10] reported results from a prospective study of 29 patients, whereof 27 underwent elective surgery under the protection of

FVIII/VWF concentrate (Haemate®). Eight of these patients had type 3 VWD. Sixteen procedures were classified as major surgery. The pre-operative median dose was 62.4 IU per kg, and the maintenance dose was lower with a median of 19.4 IU per kg. This was given up to six days or more. On the first postoperative day, 92.6 percent had excellent effects and 7.4 percent had good effects. All received a final rating of excellent. One patient, reportedly having multiple risk factors, was affected by pulmonary embolism. Given its prospective design and surgical setting, this study is of high clinical relevance.

Federici et al [11] reported a retrospective study from 10 centres. The study includes 100 patients, whereof 37 have type 3 VWD. Fifty-nine patients were treated, due to 280 apparently spontaneous bleeds, with 1 003 infusions at a daily median dose of 72 IU (range 27–135) VWF:RC<sub>0</sub> per kg. In 95 percent of the cases, the effects were excellent/good. Fifty-six patients underwent different procedures, whereof 17 were major. The daily median dose for all types of procedures was 80 IU per kg (range 27–146). Effects were rated as excellent/good in 97 percent of the cases. Seventeen patients received long-term prophylaxis to prevent bleeds in joints or the gastrointestinal tract and were dosed two to three times per week. Effects were excellent/good in 100 percent of cases. No side effects were observed.

Rivard et al [12] reported a retrospective study comprising 39 surgical patients, including nine with type 3 VWD. The patients were treated with FVIII/VWF concentrate (Alphanate®) in 61 procedures, 12 of which were major surgery. The maximum dose administered was 80 IU VWF:RC<sub>0</sub> per kg, with a total perioperative dose of 34 229 units for major surgery. Excellent/good effects were observed in 95.1 percent of the procedures on day one and 91.8 percent on the following day. One patient had a poor response in one major and one minor intervention. No serious side effects were observed.

Viswabandya et al [13], in a retrospective surgery study, reported experiences with FVIII/VWF concentrate (Koate DVI®). Ten of the 21 patients underwent ten major procedures. The mean dose was 35 UI FVIII per kg as an initial dose followed by 10 to 20 IU per kg daily for

seven days. In minor surgery, the doses were approximately half those for major surgery, and treatment time was two days. Adequate hemostasis was observed in all procedures. No adverse events such as wound infection or thrombosis were seen.

Berntorp and Windyga [14] presented 44 patients from four prospective studies, not reported elsewhere, treated with FVIII/VWF concentrate (Wilate<sup>®</sup>) for acute bleeding or given as long-term prophylaxis. In 1 095 bleeding episodes treated, the effects were rated as excellent/good in 96 percent of cases. Median dose was 26 IU FVIII:C per kg, and treatment averaged two days. The dose for gastrointestinal bleeding was higher at 44 units, and treatment time was longer at four days. Nineteen patients received prophylactic treatment over a long period (average 14.8 months) at a mean dose of 27.4 VWF:RC<sub>0</sub> per kg and an interval of 1.9 infusions per week. The bleeding frequency decreased significantly during prophylaxis, and no serious side effects were observed. Being prospective, this study has a relatively high clinical relevance.

### **Information from guidelines and reviews**

(Table 3.3.2)

Pasi et al [15] present the British UK Hemophilia Centre Doctors' Organisation (UKHCDO) recommendations and guidelines for the care management of VWD. They established that patients that do not respond to desmopressin should be treated with virus inactivated VWF concentrate.

Nichols et al [16] present guidelines from the US National Heart, Lung, and Blood Institute (NHLBI). The document summarises concentrate treatment for VWD in patients that do not respond to desmopressin. The need for further studies is asserted.

Mannucci et al [17] report guidelines from the Italian Association of Hemophilia Centres (AICE). They conclude that VWF containing concentrates is indicated for those that are unresponsive or insufficiently responsive to desmopressin. VWF concentrates devoid of FVIII may

be considered for short-term prophylaxis in elective surgery or for long-term prophylaxis.

Berntorp et al [18] present a systematic review of Haemate P<sup>®</sup>/Humate P<sup>®</sup>. This product to treat VWD has been on the market in Europe for more than 25 years and presents extensive documentation for treating VWD. The evidence grade is low for most of the studies included in this document.

## Discussion

Few of the patients with von Willebrand disease experience no, or insufficient, treatment effects from desmopressin and are therefore dependent on replacement therapy with concentrate containing von Willebrand factor (VWF). Since in addition to its platelet activity VWF also serves as a carrier protein for FVIII, patients with more severe forms of VWD have low FVIII even if their ability to produce FVIII is intact. In infusing VWF, the endogenous FVIII level increases, but it takes 12 to 22 hours to reach the therapeutic level if primarily it is very low, as in type 3 VWD. Most concentrates used in treating VWD contain both VWF and FVIII and create an immediate increase in plasma for both these factors. The ratio between VWF and FVIII varies between different products, and for Haemate P<sup>®</sup>/Humate P<sup>®</sup> it is approximately 2.5 and for Wilate<sup>®</sup> it is approximately 1.0. Since these two concentrates have not been compared, it is difficult to report on the importance of the different VWF content. Furthermore, the quality of VWF differs among the products.

The studies presented in Table 3.3.1 are retrospective or prospective observational studies without controls, and they present a low grade of evidence. The effects of concentrate are generally reported to be very good and cause few side effects. This and major economic obstacles against comparing products, makes it difficult to conduct studies that offer higher grades of evidence.

Prophylactic treatment of VWD is sometimes indicated, particularly for type 3 VWD. Sweden has considerable experience in this regard [8], but to a lesser extent so do Italy [11] and other European countries [14]. Available evidence indicates high clinical efficacy. International retrospective and prospective studies measuring bleeding frequency, joint outcome, and quality of life, are in progress.

To summarise, treatment of certain types of VWD with concentrate has good clinical effects in acute bleeding episodes, surgery, and long-term prophylaxis. The different concentrates available vary considerably in content and have not been compared with each other from a standpoint of clinical effectiveness. Strict, evidence-based guidelines are lacking, and indications, doses, and dosing intervals must be more thoroughly assessed.

### **Summary**

Treatment with FVIII/VWF concentrate has effects on acute bleeding episodes and surgical bleeding in patients with type 1 and type 2 von Willebrand disease (VWD) that does not respond to treatment with desmopressin. Treatment also has effects in type 3 VWD. Although the scientific evidence is mainly based on retrospective clinical studies without controls, the reported effects are generally high and of clinical relevance.

Scientific evidence supporting the prophylactic use of FVIII/VWF in patients with VWD is limited to retrospective studies. The results indicate good effects, but further studies are needed to confirm the findings.

**Table 3.3.1** Clinical studies on treatment with VWF/FVIII at acute bleeding, surgery and as prophylaxis in VWD patients not responding to desmopressin.

Author Year Reference Country	Study design	Population Number Female/male Age	Intervention	Outcome measures	Drop-outs	Results	Study quality and relevance
Goudemand et al 1998 <sup>a</sup> [1] France	Retrospective cohort study <sup>b</sup> 1989–1997  Hospital treatment	75 patients  Type 1: n=42 Type 2A: n=11 Type 2B: n=5 Type 2N: n=06 Type 3: n=4 Acquired: n=7	LFB VHP VWF  Spontaneous bleeds, minor (n=31) and major surgery (n=23)  Bleeding: 47 U/kg VWF:RCo, 40 U if needed every 12 hours  Surgery: 51–55 U/kg Postoperatively: 30–35 U every 12–24 hours	Not defined	Not reported	No bleeding compli- cation during surgery	Low
Nitu-Whalley et al 2001 <sup>a</sup> [2] UK	Retrospective study <sup>b</sup> Review period (1988–1997) One centre	Subjects with VWD n=65 with VWD and 103 surgical procedures identified  27 patients: 35 surgical pro- cedures covered with desmopressin  38 patients: 68 surgical pro- cedures treated with intermediate purity FVIII con- centrates rich in VWF Clothing factor concentrate (CFC) (BPL 8Y <sup>®</sup> or Haemate P <sup>®</sup> )	Major surgery median CFC dose: Pre-operative 54 IU/kg (range 41–77) and postoperative: 43 IU/kg (range 25–78)  Minor surgery Median CFC dose: Pre-operative 48 IU/kg (range 14–70) and postoperative 37 IU/kg (range 13–58)  Tranexamic acid in many mucocutaneous procedures	Hemostatic efficacy  Excellent, moderate, poor	One type 3 patients excluded because of severe bleeding needing daily treat- ment for 5 weeks	Hemostasis rated: Excellent in 31 events (91%) with DDAVP and in 56 events (82%) with CFC  Moderate in 6 (9%) Poor in 6 (9%) signi- ficant bleeding needing additional treatment	Low

The table continues on the next page

Table 3.3.1 continued

Author Year Reference Country	Study design	Population Number Female/male Age	Intervention	Outcome measures	Drop-outs	Results	Study quality and relevance
Federici et al 2002 <sup>a</sup> [3] Italy	Retrospective study <sup>y</sup>  Collection of data 8 centres  Chart review	Subjects with VWD n=22  Type 1: n=9 Type 2 B: n=7 Type 3: n=6  10 males and 12 females  Median age: 28.5 years (range 5–70 years)	Factor VIII/VWF con- centrate (Fanhdi <sup>®</sup> ) given to stop 12 bleed- ing episodes or to pre- vent excessive bleeding during 14 surgical or invasive procedures  Major surgery: n=7 Minor surgery: n=5 Tooth extractions: n=2	<u>Attending physician rating</u> 1: Excellent, hemo- stasis clinically not different from normal  2: Good, mildly abnor- mal hemostasis (partial or delayed control of spontaneous bleeding or slight transient oozing from surgical wounds)  3: Moderate, modera- tely abnormal hemo- stasis (bleeding not fully controlled but no need of additional therapy)  4: Poor, no improve- ment at all with conti- nuation of bleeding Recording of adverse events	Not reported and not relevant con- sidering the study design	<u>Bleeding episodes</u> Excellent to good in 92% of episodes  58% controlled using a single dose of 14–38 IU FVIII/kg  <u>Surgery</u> Excellent to good in 93%, including all major surgeries. A median dose of 51 IU/kg, range 34–100 was given during major surgery per day, and usually 36 IU/kg in the postoperative 7 days. Doses were lower for minor surgery (median 42 IU/kg during surgery per day and 34 IU in postoperative period)  No adverse events reported	Low
Mannucci et al 2002 <sup>b</sup> [4] Multinational	Prospective multicentre study <sup>y</sup>	VWD n=81 Type 1: n=15 Type 2: n=34 Type 3: n=32  50 female 31 male 72 white 6 black 3 hispanic  Median age: 34 years, range 7–75	Alphanate <sup>®</sup> 40–50 VWF:RCo IU/kg for bleeding. 60–75 IU for surgery	<u>Surgery</u> Bleeding volume in mL measured and related to estimated blood loss in a hypothetical control person  Bleeding events: Number of infusions	6 Drop-outs	<u>Surgery</u> Less bleeding than expected. 3 patients bled more than 50 mL above expected value  <u>Bleeding</u> Median (range) number of infusions per bleeding episode: Type 1: 1.0 (range 1–2) Type 2A: 1.0 (range 1–7) Type 3: 3.0 (range 1–6)  <u>Adverse events</u> 1 thrombophlebitis, 1 DVT during surgery	Low

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Table 3.3.1 continued

Author Year Reference Country	Study design	Population Number Female/male Age	Intervention	Outcome measures	Drop-outs	Results	Study quality and relevance
Cox Gill et al 2004 <sup>a</sup> [5] USA	Prospective, open-label, non randomised <sup>β</sup> 19 centres	Subjects with VWD n=41  Type 1 VWD n=9 Type 2 VWD n=16 Type 3 VWD n=12 Unspecified subtype n=4	More than 1.7 million IU VWF: RCo FVIII/ VWF concentrate (Humate-P <sup>®</sup> ) in 290 infusions administered for treatment of 53 emergent bleeding episodes. Median treatment duration was 3 days and median loading dose 67 IU/kg (range 25.7–143.2)	Hemostatic efficacy Excellent/good: Similar hemostasis as expected for a person without known bleeding disorder  Fair/poor: Less hemostatic effect than expected  None: Severe bleeding due to VWD despite FVIII/VWF concentrate (Humate-P <sup>®</sup> )	91% had complete follow-up, 5 patients discontinued for different reasons	98% were rated as excellent/good  One mild allergic reaction judged to be related to study drug	Low
Franchini et al 2003 <sup>a</sup> [6] Italy	Retrospective study <sup>β</sup> Three centres  Chart review	Subjects with VWD n=26  Type 1: n=19 Type 2B: n=7  12 males and 14 females  Median age: 41.5 years, (range 9–80)	FVIII/VWF concentrate (Humate-P <sup>®</sup> ) was given during 43 surgical interventions during 1996 and 2002; Major surgery n=14 Minor surgery n=11 Dental extractions n=11 Invasive procedures n=7	Treatment outcome was rated by local physician as: Excellent (achievement of normal hemostasis)  Good (mildly abnormal hemostasis requiring additional therapy)  Poor (hemostasis less than expected) as a measure of overall efficacy	Not given/not relevant	For major surgery loading dose was 61.2 IU VWF:RCo/kg (range 47.5–81.1); mean daily dose 39.3 VWF:RCo/kg (range 25–52.5) and days of treatment 9.7 (range 5–23). All but one were rated as excellent/good. Patients undergoing minor surgery, dental extractions, or invasive procedures needed less dosing and fewer treatment days. No adverse events recorded or seen	Low

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Table 3.3.1 continued

Author Year Reference Country	Study design	Population Number Female/male Age	Intervention	Outcome measures	Drop-outs	Results	Study quality and relevance
Thompson et al 2004 <sup>6</sup> [7] USA	Prospective, open-label, non randomised study  Multi-centre 28 centers	Subjects with VWD n=39  Type 1: n=16 Type 2A: n=4 Type 2B: n=5 Type 3: n=8 Unspecified: n=6	FVIII/VWF concentrate (Humate-P <sup>®</sup> ) in subjects with VWD undergoing urgent or emergent non-elective surgery  Major: n=25 Minor: n=17  Loading dose 60–80 IU VWF:RCo (range 27–36 IU VIII:C) per kg body weight, followed by 40–60 IU VWF:RCo (range 18–27 IU FVIII:C) daily for up to 7 days	Local investigator's rating of hemostatic efficacy (excellent/good, fair/poor, or none)	Of 42 surgical events 3 were excluded	All 39 events were rated as excellent/good for overall efficacy 100%; (95% CI 89 to 100)  4 serious adverse events, none considered related to study drug. 7 adverse events possibly related. Study medication withdrawn in one event because of pseudo-thrombocytopenia in a subject with type 2B VWD, still clinical efficacy good to excellent  Median average daily dose VWF:RCo per infusion (maintenance) was 52.8 IU/kg (range 24.2–196.5). Medium number of infusions per event was 6 (range 1–67 infusions)	Low

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**Table 3.3.1** continued

Author Year Reference Country	Study design	Population Number Female/male Age	Intervention	Outcome measures	Drop-outs	Results	Study quality and relevance
Berntorp et al 2005 <sup>a</sup> [8] Sweden	Retrospective study <sup>b</sup>  Chart review	35 patients with VWD  Type 2A: n=2 Type 2B: n=4 Type 3: n=28  18 females and 17 males	Fraction 1–0 (AHF- Kabi®) before mid- 1980s and since then FVIII/VWF concentrate (Humate-P®) at a mean dose of 24 IU FVIII per kg (range 12–50) given one to three times weekly  Mean age at start of prophylaxis in patients below 20 years was 4 years (range 2–13 years). In the 17 patients now older than 15 years, mean age at start of prophylaxis was 27 years (range 3–57)	Bleeding frequency	Not relevant	Substantial reduction of bleeds, in many patients symptoms have virtually ceased. Indication for prophylaxis were: Nose/mouth bleeds, joint bleeds, gastrointestinal bleeds and heavy menstrua- tions. Sometimes mixed indications. Three patients developed inhibitors	Low

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Table 3.3.1 continued

Author Year Reference Country	Study design	Population Number Female/male Age	Intervention	Outcome measures	Drop-outs	Results	Study quality and relevance
Borel-Derlon et al 2007 <sup>6</sup> [9] Multieuropean	Prospective cohort study <sup>y</sup> 17 centres  Merge of a European and a French study	50 patients  Type 1: n=5 Type 2A: n=16 Type 2B: n=9 Type 2M: n=1 Type 2N: n=1 Type 3: n=18  32 females and 18 males  Median age 37 years (range 5–81)	Plasma-derived VWF concentrate (Wilfactin <sup>®</sup> ) given as only therapy except for clinical situations requiring a priming dose of FVIII. The clinical situations were:  1: Treatment of spontaneous bleeding episodes 2: Prevention of bleedings during surgery 3: Short-term prophylaxis in non-surgical situations with increased risk of bleeding 4: Secondary long- term prophylaxis in patients with frequently recurring bleeding episodes	Treatment outcome was assessed using a four-grade scale (excellent, good, moderate, none) by the patient or their custodians if treated at home and attending physicians if treated at hospital	Three patients lost to follow-up after surgery and did not complete	<u>Spontaneous bleeding episodes</u> 25 patients received 733 infusions over 565 exposure days for 139 bleeding episodes (121 treated at home)  60% of episodes occur- red in type 3 patients. Median infusion dose 41.8 IU VWF:RCo/kg (range 14.2–74.5) and treatment required a median number of three infusions per episode (range 1–46) over 3 exposure days (range 1–37). Tranexamic acid prescribed for 54 of 139 episodes  The percentage of excellent/good respon- ses to treatment 6 and 24 hours postinfusion was 88% and 89%, respectively <i>Continues</i>	Low

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**Table 3.3.1** continued

Author Year Reference Country	Study design	Population Number Female/male Age	Intervention	Outcome measures	Drop-outs	Results	Study quality and relevance
Continued Borel-Derlon et al 2007 <sup>5</sup> [9] Multieuropean	See previous page	See previous page	See previous page	See previous page	See previous page	<p>Continues 45 patients were treated to prevent bleeding in 67 surgical and 43 invasive procedures. 14 were in VWD type 3 patients. 95 procedures were scheduled and thus performed without administration of FVIII. Median infusion dosage VWF:RCo was 45.5 IU/kg (range 11.1–100.0)</p> <p>Number of days 3.0 (range 1–57) and median number in fusions 3.0 (range 1–65). Excellent/good response at discharge was 100%</p> <p>Prophylaxis: a total of 10 type 3 patients underwent prophylaxis of whom 4 as long-term. Median dose was usually around 40 IU VWF:RCo/kg 2–3 times per week over 66.5 cumulative months. 3 of 17 bleeds occurred within the first 48 post-infusion hours</p> <p>No thromboembolic complications or development of antibodies against VWF or FVIII</p>	

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Table 3.3.1 continued

Author Year Reference Country	Study design	Population Number Female/male Age	Intervention	Outcome measures	Drop-outs	Results	Study quality and relevance
Lethagen et al 2007 <sup>o</sup> [10] Europe	Prospective, open-label European multicenter study <sup>y</sup> 12 centres	29 patients with VWD undergoing elective surgery  20 females 9 males  Ages: 5–16 years n=2 17–64 years n=22 ≥65 years n=5  Type 1 VWD: n=10 Type 2A: n=10 Type 2M: n=1 Type 3: n=8	FVIII/VWF concentrate (Humate-P®) during surgery. Minor surgery: n=11 Major surgery: n=16  Loading dose according to pharmacokinetic profile. Median VWF:RCo dose was 62.4 IU/kg (Interquartile range 50.1–87.0)  Maintenance dose was at discretion of the investigator and was lower by a median of 19.4 IU/kg and given up to >6 days	Assessment of hemo- static efficacy was based on laboratory assays, bleeding time, transfusion require- ments, and rating of hemostasis by the investigator on a four- point scale of excel- lent, good, moderate, or none	Of 29 enrolled subjects, 27 under- went surgery	On the day of surgery hemostatic efficacy was: Excellent for 81.5% of the subjects, good for 14.8% and moderate for 3.7%  On the first postopera- tive day, 92.6% received a rating of excellent and 7.4% good. At final evaluation, hemostatic efficacy was rated as excellent in all subjects  5 adverse events (1 serious adverse event) probably related to study drug  One subject with multiple risk factors developed pulmonary embolism which was resolved	Low

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**Table 3.3.1** continued

Author Year Reference Country	Study design	Population Number Female/male Age	Intervention	Outcome measures	Drop-outs	Results	Study quality and relevance
Federici et al 2007 <sup>a</sup> [11] Italy	Retrospective cohort study <sup>b</sup> 10 centres  Data from patient records	100 patients  Type 1: n=23 Type 2: n=40 Type 3: n=37  Median age: 41.5 years (range 2–87) followed for 36 months	59 patients were treated with FVIII/ VWF concentrate (Humate-P <sup>®</sup> ) because of 280 spontaneous bleeding episodes using 1 003 infusions with a median daily dose of 72 (range 27–135) VWF:RCo IU/kg. 56 patients underwent 73 procedures, major surgery n=17, minor surgery n=28, invasive procedures n=9 or dental procedures n=19, with a total consump- tion of 1.97 x 10 <sup>6</sup> IU through 366 infusions and a median daily dose of 80 (range 27–146) VWF:RCo IU/kg 12 patients underwent 17 long-term secondary prophylactic regimens to prevent recurrent bleeds into joints (35%) or GI tract (47%). Patients received FVIII/ VWF concentrate (Humate-P <sup>®</sup> ) three times or twice a week	Assesment of hemostatic efficacy was evaluated as follows: not different from normal (excellent), mildly abnormal (good) moderately abnormal but no need for addi- tional therapy (moderate), no improvement and need for additional or alternative therapies (poor)	Not relevant	Spontaneous bleeds: 95% excellent/good  Surgery: 97% excellent/good  Prophylaxis: excellent/good in 100%  No adverse events including thrombosis seen	Low

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Table 3.3.1 continued

Author Year Reference Country	Study design	Population Number Female/male Age	Intervention	Outcome measures	Drop-outs	Results	Study quality and relevance
Rivard et al 2008 <sup>6</sup> [12] US and UK	Retrospective study <sup>β</sup> 5 centres  Data from patient records	39 patients with VWD  Type 1: n=18 Type 2: n=12 Type 3: n=9  Mean age: 39.2 years	Patients were treated during surgery with FVIII/VWF concentrate (Alphanate <sup>®</sup> )  61 procedures 12 major surgeries, 49 minor invasive procedures. Maximum dose was 80 IU/kg VWF:RC <sub>0</sub> . Total pre-operative dose: Major surgery mean 34 229 (SD 21 892), minor surgery 18 327 (SD 15 333) and invasive procedures 9 117 (SD 13 581)	Primary endpoint was the overall clinical efficacy of the FVIII/VWF product assessed by the investigators: excellent, good, poor, no response	Not relevant	Excellent/good hemo- stasis rated for 95.1% of the procedures on day of surgery, and 91.8% on the subsequent day. One patient had poor response during one major and one minor procedure  7% of subjects had non- serious adverse events related to study product	Low
Viswabandya et al 2008 <sup>a</sup> [13] India	Retrospective study <sup>β</sup> Single centre  Data from patient records	21 patients with VWD. Type 1: n=3 Type 2: n=11 Type 3: n=7	Patients were treated during surgery with FVIII/VWF concentrate (Koate DVI <sup>®</sup> ). Major surgery: 10 patients and pro- cedures, mean age 34 years, (range 18–54) Pre-operative dose was mean 35 IU/kg FVIII followed by 10–20 IU/kg per day for a mean of 7 days. Minor surgeries 11 patients and 16 pro- cedures, mean age 26 years (range 3–55) 10–20 IU/kg were given pre-operatively and factor was given for 2 days	Clinical hemostasis (no rating scale used) was assessed and factor levels measured  Factor levels measured. Infection and throm- bosis registered	Not relevant	Adequate hemostasis in all procedures. Mean factor levels in major surgery were for days 1, 3, and 7 respectively: FVIII:C 70, 79, 65. VWF:Ag 80, 60, 40.5 VWF:RC <sub>0</sub> 37.3, 28.5, 30.4  One postoperative bleeding after major and minor surgery control- led by an extra dose  No adverse events such as wound infection or thrombosis	Low

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Table 3.3.1 continued

Author Year Reference Country	Study design	Population Number Female/male Age	Intervention	Outcome measures	Drop-outs	Results	Study quality and relevance
Berntorp et al 2009 <sup>6</sup> [14] Sweden	Prospective, multicentre <sup>β</sup>  Compilation of four prospective, open labeled, non-rando- mised phase II or III trials. No placebo control	44 patients with VWD (20 males and 24 females)  Type 1: n=8 Type 2A: n=6 Type 2B: n=4 Type 2N: n=2 Type 3: n=24	FVIII/VWF concentrate (Wilate <sup>®</sup> ) was given at a general dose recommendation of 20–50 IU per kg body weight for the treat- ment or prevention of spontaneous or trauma- induced hemorrhages. A total of 36 batches was used	Response to treat- ment was rated by the investigator or patient or parent using a 4-point verbal scale (excellent, good, moderate, none)	Not reported	1 095 bleeding episodes were treated with an overall efficacy rating of excellent or good in 96%  The median dose per treatment day was 26 IU FVIII:C per kg (roughly the same dose in VWF:RCo)  81% of bleeds stopped within 1 or 2 days. Gastrointestinal bleeds needed higher doses (mean 44 IU per kg) and longer treatment (mean 4 days). Data from 8 children of 12 years or less in age did not differ from the overall study population  19 patients were treated prophylactically for more than 3 months (mean 14.8, range 3–46) with a mean prophylactic dose of 27.4 IU per kg and a mean frequency of 1.9 infusions per week. A drop of bleeding frequency from a mean of 4.5 to 1.4 bleeds per month was observed (p<0.01). <i>Continues</i>	Low

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**Table 3.3.1** continued

<b>Author Year Reference Country</b>	<b>Study design</b>	<b>Population Number Female/male Age</b>	<b>Intervention</b>	<b>Outcome measures</b>	<b>Drop-outs</b>	<b>Results</b>	<b>Study quality and relevance</b>
<i>Continued</i> Berntorp et al 2009 <sup>δ</sup> [14] Sweden	<i>See previous page</i>	<i>See previous page</i>	<i>See previous page</i>	<i>See previous page</i>	<i>See previous page</i>	<i>Continues</i> 5 310 infusions were given and tolerability was rated as good or very good in more than 99% rated infusions. 13 events in 5 patients were assessed to have possible or probable relationship to the drug. No thrombotic events	<i>See previous page</i>

<sup>α</sup> None of the authors declared any conflict of interest

<sup>β</sup> No reported support from pharmaceutical companies

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companies involved in the products

**Table 3.3.2** Systematic reviews and guidelines on the management of Von Willebrand disease.

Author Ref Year Country	Study design Review Consensus Guidelines	Title	Aim	Results
Pasi et al 2004 <sup>a</sup> [15] UK	Guideline <sup>β</sup>	Management of von Willebrand disease: a guideline from the UK Hemophilia Centre Doctors' Organization (UKHCD)	Establish guidelines about treatment, management, and products for VWD	<p>Patients non-responsive, or contra-indicated, to DDAVP should be treated with a virus-inactivated concentrate that contains either FVIII/VWF or very high purity VWF and which has been shown to be clinically effective (grade B, level III)</p> <p>Operative procedures that involve mucosal surfaces should also be covered with tranexamic acid (grade C, level IV)</p>
Nichols et al 2008 <sup>δ</sup> [16] USA	Guideline <sup>β</sup>	Von Willebrand disease (VWD): evidence-based diagnosis and management guidelines, the National Heart, Lung, and Blood Institute (NHLBI) Expert Panel report (USA)	Literature review of diagnosis and management	<p>Concentrate treatment when not responsive to DDAVP:                      Long-term prophylaxis grade C, level IV.                      Minor surgery or minor bleedings grade C, level IV. Major surgery or major bleedings grade B-C, level III-IV depending on clinical issue</p>
Berntorp et al 2008 <sup>δ</sup> [18] Sweden	Systematic review <sup>β</sup>	A systematic overview of the pasteurised VWF/FVIII medicinal product, Haemate P/ Humate-P <sup>®</sup> : History and clinical performance	Systematic review of clinical performance of Haemate P/Humate-P <sup>®</sup> with recommendations	Comprehensive review and recommendations using a specific product. Sponsored by the manufacturer
Mannucci et al 2009 <sup>a</sup> [17] Italy	Guideline <sup>β</sup>	Evidence-based recommendations on the treatment of von Willebrand disease in Italy	To give evidence-based recommendations	Observational studies and case series available. VWF/FVIII concentrates are effective in controlling bleeding in most cases. A number of issues are still open, such as the optimal control of menorrhagia, recurrent gastrointestinal bleeding, and the role of secondary prophylaxis

<sup>a</sup> None of the authors declared any conflict of interest

<sup>β</sup> No reported support from pharmaceutical companies

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## 3.4 Hemophilica – health economical aspects

### Evidence grading of the results

- The scientific evidence is insufficient to stipulate what strategy of intervention, on-demand or prophylaxis, is cost-effective.

### Introduction

Hemophilia is an inherited deficiency in clotting factors that results in bleeding in joints, body cavities including intracranial bleeds, and in soft tissues such as muscles. These hemorrhages can lead to severe pain, impaired quality of life, sickness, absence from work and even death. Therapeutic interventions with clotting factors are given in two ways. On-demand treatment is an intervention given as a factor concentrate replacement during an episode of acute bleeding. The second intervention, i.e. prophylactic clotting factor substitution, is given regularly several times a week. In Sweden, all individuals younger than 30 years of age with severe forms of hemophilia are included in prophylactic treatments.

Including economical aspects of hemophilia treatment based on a systematic review may increase the knowledge of medical management of a patient group in need of significant health care.

### Questions

For severe hemophilia:

- What strategy of intervention, i.e. on-demand treatment versus prophylaxis, is cost-effective?
- What factors predict high health care-costs?

## Methods

### Search of literature and method for assessment of studies

Starting from the medical headings used by medical experts for the structured search of literature in databases, the following search terms were added: "cost and cost analysis (including cost-effectiveness, cost-utility, cost-benefit, willingness to pay)". Specifications of search strategies are included in the Appendix see "Search strategies" [www.sbu.se/hemophilia](http://www.sbu.se/hemophilia).

The medical experts of the project group suggested that economic studies with a setting in health care from countries in Europe were to be included only, the reason being that the principles of treatment are fairly homogeneous in Europe but not worldwide.

The number of abstracts identified and studies in full text chosen were as follows:

Total number of abstracts identified	530
Chosen studies in full text	19
Excluded studies in full text	11
Included studies	8

Reasons for excluding studies were overview articles [1,2], one study on policies for interventions for Canada [3], four model studies from North America [4–7], two empirical studies using data from the USA and from Australia [8,9], and one longitudinal observational study using inconclusive economical methods [10]. Finally, a systematic review including mainly studies from countries outside Europe was excluded [11].

Studies including economical aspects on hemophilia were assessed for medical relevance by the medical experts, and assessed for study quality on economic aspects by using a check-list based on that proposed by Drummond [12]. Two economists made the assessments of study quality independently of each other.

Following the principles for health technology assessment as implemented at the SBU, empirical studies were included for statements regarding scientific support (evidence), but model studies only for discussions of economical consequences.

## Results

The included economic studies that were finally assessed for relevance and study quality were three model studies from a European setting [13–15] and five empirical studies [16–20].

### Empirical studies

A cross-sectional multi-centre study, undertaken in ten European countries, had a focus on resource utilisation in hemophilic treatment, i.e. effectiveness rather than efficacy [19]. The study design did not permit conclusions regarding any cause-effect relationship. On-demand treatment (n=399) was compared with prophylaxis (n=145). There was no significant difference as regards resource utilisation, although there was a significant difference of joint bleeds (8.8 vs 3.1;  $p < 0.001$ ) with on-demand and prophylaxis, respectively. A finding from a socio-economic point of view was that the unemployment rate was significantly higher in the on-demand group than in the prophylaxis group (14 vs 3.4%;  $p < 0.001$ ).

Costs for drugs and the outcome of activated prothrombin complex concentrate (aPCC) and recombinant factor VIIa (rFVIIa) were compared in a study based on a RCT cross-over study [18]. Prices from USA, Turkey, and Sweden were used. Costs per patient were analysed from patient-specific data (age, weight, previous bleeding, increased titration) and treatment-specific data (dose, treatment protocol). Since there was no significant difference as regards pain or bleeding frequencies, the drug with the lowest cost (price), i.e. in this study aPCC, was cost effective compared to rFVIIa.

In a prospective study at a French university hospital, a cohort of patients with hemophilia was followed during one year [16]. Direct hospital costs were analysed from a hospital perspective. Recombinant activated factor VII therapy was used at 20 percent of the hospital stays and accounted for 56 percent of the total anti-hemophilic drug costs. A multivariate analysis showed that five variables predicted high costs of anti-hemophilic drugs, of which the presence of a circulating inhibitor to coagulation factors was the most dominant (OR 16.9; 85% CI 4.3 to 66). However, including the variable “severity of hemophilia”, this variable predicted

the likelihood of higher anti-hemophilic drug expenditures (ORadj 3.7; 95% CI 1.6 to 8.6;  $p=0.001$ ), controlling for the effect of age, length of stay, and reason for hospitalisation.

A convenience sample of patients with hemophilia was included in a cross-sectional study comprising patients from 10 European countries [17]. On-demand intervention was compared with prophylactic intervention of factor replacement therapy. The economic aspects considered were utilisation of health resources and effects on employment and the quality of life were examined. Multiple regression analyses showed more frequent joint bleeds in the on-demand group compared to the prophylactic group of patients. However, costs were still higher for the prophylactic group than the on-demand group due to the higher utilisation of factor concentrate. As regards effects on employment and quality of life, the variables were highly skewed and not normally distributed, and therefore not studied in multivariate analyses.

Costs of on-demand and prophylactic treatment for severe hemophilia in Norway and Sweden were analysed in an 11-year retrospective study based on panel data [20]. The aim was to calculate annual costs and variation of costs from a societal perspective. The mean direct cost per patient-year for an adult individual was 51 518 euros for on-demand treatment, compared to 147 939 euros for prophylaxis. Factor concentrate was the major source of costs, 74 percent and 94 percent, for on-demand and prophylaxis, respectively. Costs of care increased with age and body weight. Although indirect costs were higher for on-demand treatment than for prophylactic treatment, the total costs were still higher for prophylactic than for on-demand treatment.

### **Model studies**

A representative sample of the Swedish population was asked about its willingness to pay for patients with severe hemophilia to receive on-demand treatment and prophylaxis, respectively [15]. The response rate was about 60 percent, and the order of bidding, i.e. willingness to pay, was randomised as concerns starting of the bidding, i.e. on-demand or prophylaxis, respectively. From bidding was estimated that the willingness to pay was 39 euros for on-demand treatment, compared to 65 euros

for prophylaxis. The willingness to pay as expressed by the biddings actually exceeded the average level of costs of health care of hemophilia as shared by each taxpayer. Thus, from the point of view of a societal-ethical perspective, the biddings give an estimate of the acceptance, or justification, of the costs of the treatment options for patients with hemophilia.

The incremental cost-effectiveness of on-demand treatment compared with prophylaxis was estimated for Germany, the United Kingdom, the Netherlands, and Sweden using a decision tree model [13]. The perspective was that of third-party payer, the time horizon one year, including direct medical costs only. Estimates for clinical data were based on original patient data from 506 patients. Quality adjusted life-years (QALY) were estimated from algorithms using Short Form-6D. End-points were avoided bleeds and QALYs gained. Prices of resources used were specific for each country. For Sweden, the incremental cost per avoided bleed of patients 30 years old or more, comparing prophylaxis with on-demand treatment, was 14 138 euros. For patients with HIV status, the incremental cost per QALY was estimated at 107 446 euros. The comparison of strategies, on-demand versus prophylaxis, for patients younger than 30 years of age was not relevant for Sweden since all patients of that age-group receive prophylaxis.

In a Markov model study, the cost effectiveness of primary prophylaxis was compared with on-demand treatment for severe hemophilia from a British health-care perspective [14]. Since data on the impact of treatments on health-related quality of life is scarce for this group of patients, estimates of utility levels of different interventions were included. Age-adjusted patient data were based on results from a London-based treatment centre. Over a 70-year horizon, the costs of treatment were estimated at £644 000 and £858 000 for on-demand and prophylaxis, respectively. The net gain of QALYs was estimated to correspond to 13.95 and 19.58, respectively, thus higher for prophylaxis than on-demand. The incremental cost effectiveness ratio was estimated as £38 000 per QALY. However, compared to an assumed threshold of £30 000 per QALY in the health care sector, the probability that prophylaxis was cost effective was estimated to 13 percent, thus of limited likelihood of

being cost-effective. Reducing the discount rate on utilities (i.e. QALYs) increased this probability to 60 percent, at a discount rate of 1.5 percent. The level of discount rate also had an impact on the expected value of perfect information, i.e. on the value of further research.

## Discussion

All studies included had a setting in European countries with similar strategies of interventions for hemophilia. However, the study designs differed, as concerning empirical studies there was one prospective study [16], one retrospective study [15], one study added retrospectively to a RCT [18], and two cross-sectional studies [17,19]. The included model studies also had different designs, i.e. one Markov model, one decision tree model, and one enquiry to the public on willingness to pay for interventions of different strategies.

The possibilities of differences of internal validity due to the heterogeneity of study designs used in included studies, reduces the assessment of study quality, but also the possibility of grading of evidence. Furthermore, the included studies had divergent aims, thus making general conclusions difficult.

Seven of the included eight studies had a health care perspective, i.e. all but the study including patients from Norway and from Sweden, where a societal perspective was included [15]. In the study by Szucs et al [19] no significant difference of resource utilisation (i.e. out-patient visits, length of stay, days off work) was found between on-demand treatment and prophylaxis, but there were no calculations of costs of factor VIII included. However, such calculations of health-care costs including factor VIII, were included in the study by Steen Carlsson et al [15]. For on-demand therapy the annual cost of treatment was 51 518 euros for on-demand compared with 147 939 euros for prophylaxis.

The incremental cost per avoided bleed of patients older than 30 years of age, comparing prophylaxis with on-demand treatment, was estimated at 14 138 euros [13].

From the perspective of British health care, the incremental cost effectiveness ratio was estimated at £38 000 per QALY [14].

Thus, although almost all studies had a health-care perspective, the included studies had different outcomes for comparisons of costs. However, all included studies indicate that health-care costs of care are high for treatment of hemophilia A, and that the utilisation of factor VIII concentrates explains a large share of the variance of costs. Age and body weight will increase the specific resource utilisation of factor VIII.

## **Conclusions**

- Due to few studies of different aims and different study designs, evidence of cost-effective strategies of interventions of patients with hemophilia cannot be stated.
- Although there are few studies published, it is evident that the patient's weight is an important cost driver for the utilisation of factor concentrate and thus for costs of health-care intervention of hemophilia.

**Table 3.4.1** Economic aspects – empirical studies.

Author Year Reference Country	Study design Setting Perspective	Population Number Age	Intervention I	Intervention II	Drop- outs	Outcome effects	Outcome costs	Study quality
Galanaud 2003 <sup>a</sup> [16] France	Prospective obser- vational study  Cost analysis Referrals to a regional hospital in France Health care perspective <sup>b</sup>	Patients with hemophilia n=96 (type A=84, B=12)  Ages 1.5 to 85 years	Recombinant activated factor VII (rFVIIa) therapy	NA	None	NA	In multivariate analysis, controlling for effects of age, length of stay, reason for hospitalisation, the “severity of hemophilia” predicted high anti-hemophilic drug expenditure (OR 3.7 CI 95%: 1.6 to 8.6)	Limited
Schramm 2002 <sup>a</sup> [17] 10 countries	Multicentre cross-sectional  Hospitals in 10 countries  Convenience samples  On-demand vs prophylactic cost-analysis health care perspective <sup>y</sup>	Patients with hemophilia n=1 042 hemophilia subjects (type A=837, B=166)  On-demand n=670 Prophylactic n=335  Ages 11–83 years	Factor VIII On-demand	Factor VIII Prophylactic	n=37	On-demand signifi- cantly more likely to experience a joint bleed than those on a prophylactic regimen <30 years: 7.55 (p<0.001) 30 years: 3.33 (p<0.001)	Sweden: Direct costs: Prophylaxis mean cost 3 348 euros  On-demand mean cost 902 euros of which Factor VIII 2 283 vs 439 euros (p<0.001)  Indirect costs: 381 vs 51 euro	Limited
Steen Carlsson 2004 <sup>a</sup> [20] Sweden	11 years retrospective On-demand vs prophylactic treatment. Health care and societal perspective <sup>y</sup>	Patients with hemophilia A or B Children n=80 Adults n=118	Factor concentrate On-demand	Factor concentrate Prophylactic	No informa- tion	NA	For 30-year old patients, Direct costs (mean, 1 <sup>st</sup> quartile): On-demand 33 358 euros Prophylaxis 99 742 euros  Indirect costs: On-demand 31 096 euros Prophylaxis 13 004 euros	Moderate
Steen Carlsson 2008 <sup>a</sup> [18] Sweden	Open label RCT Cross-over Cost-effectiveness 3 countries Health care and patient perspective <sup>y</sup>	Patients aged 2 years and older n=48	Activated prothrombin complex con- centrate (aPCC)	Recombinant factor VIIa (rFVIIa)	None	No difference of joint bleeds VAS N.S.	Determinants for costs: prescribed dose, bodyweight, treatment in addition to pro- tocol. The extra cost per 1 VAS unit better pain reduction by rFVIIa was USD 6 405	Moderate

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Table 3.4.1 continued

Author Year Reference Country	Study design Setting Perspective	Population Number Age	Intervention I	Intervention II	Drop- outs	Outcome effects	Outcome costs	Study quality
Szucs 1998 <sup>a</sup> [19] Germany	Cross sectional Hemophilic patients attending 16 treatment centres in 10 European countries Resource utilisation Health care perspective <sup>β</sup>	Consecutive patients  On-demand n=399 (type A n=335)  Prophylactic n=145 (type A n=112)  Ages mean 35.3 years	Factor VIII On-demand	Factor VIII Prophylactic	No information	Joint bleeds per patient during the 6-month observation period On-demand 8.8 Prophylactic 3.1 (p<0.001) (95% CI 4.33 to 7.07)	On-demand vs prophylactic  Resource utilisation: Outpatient visits 2.9 vs 2.5 Hospitalisation length 1.0 vs 0.7 Days off work 3.5 vs 4.0  No estimate of costs of factor VIII	Limited

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**Table 3.4.2** Economic aspects – model studies.

Author Year Reference Country	Study design Setting Perspective	Population Number Age Gender	Interven- tion I	Intervention II	Drop- outs	Outcome effects	Outcome costs	Study quality
Lippert 2005 <sup>α</sup> [13] Cross- national	Decision tree model On-demand vs prophylactic Cost-effectiveness Cross-sectional survey Health care perspective <sup>γ</sup>	n=506 (hemo- philia A=425) Ages 14–83 years	On-demand	Prophylactic treatment	Not included	Estimated for Sweden, on-demand vs prophylactic, incremental effectiveness  Estimated number of avoided bleeds 7.6	Incremental cost-effective- ness ratio (ICER) per avoided bleed 14 138 euros	Moderate
Miners 2009 <sup>α</sup> [14] UK	Markov model Health care perspective, UK 70 years perspective <sup>γ</sup>	Based on published study for the UK (Miners 1999)	On-demand	Prophylactic treatment	Not included	On-demand vs prophylactic, 13.95 vs 19.58 QALY	Over a 70 years horizon, the costs of treatment were estimated to £644 000 vs £858 000 for on-demand and prophylaxis, respectively ICER £38 000/QALY	Moderate
Steen Carlsson 2004 <sup>α</sup> [15] Sweden	Contingent valuation study on Willingness to Pay (WTP) Patient (public) perspective <sup>γ</sup>	Household panel n=1 080	On-demand vs prophylaxis	NA	n=471	NA	WTP: On-demand 39 euros (95% CI 31 to 47) Prophylaxis 65 euros (95% CI 55 to 73)	Moderate

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<sup>β</sup> No reported support from pharmaceutical companies

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## 4. Ethical aspects

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A major ethical concern about the use of plasma-derived products for replacement therapy in bleeding disorders has been that of transmission of blood-borne viral infections. In particular, the transmission of HIV but also of HCV has caused fear among treating physicians and patients that has negatively influenced the development of improved regimens for the treatment of the clotting disorders *per se*. With the possibility of screening of blood donors, effective methods for virus reduction, and the introduction of recombinant concentrates using recombinant DNA technology the problem of blood transmitted agents hopefully belongs to history and does not raise any ethical concerns today when treatment is started, typically, for a small child. The most obvious medical concern associated with treatment of hemophilia today is that of the risk of inhibitor development. This risk may be related to the type of coagulation factor concentrate used and the type of treatment regimen and may create an ethical conflict when decisions about treatment are taken. An example would be: a small child with severe hemophilia starts prophylaxis. Which concentrate to use – the recombinant devoid of human plasma constituent but perhaps with a somewhat higher risk of inhibitor development compared to the plasma-derived concentrate, which, on the other hand, has a somewhat higher risk of transmitting blood-borne agents? The statements are hypothetical but controversial and vigorously discussed internationally.

The cost of replacement therapy and inhibitor therapy is paramount and may cause ethical and priority concerns, especially regarding the aging hemophilia population and treatment of co-morbidities which may need even more intense substitution therapy to avoid bleeding.

In this chapter, more general aspects on ethics will be addressed and a case of a person with severe hemophilia, who may represent a growing problem for future hemophilia care, is discussed.

## Background

Currently, there are different conceptions among ethicists concerning the nature of medical ethics. There is thus a need for a more general introduction to express our opinion. First, the words "moral" and "ethics" are discussed. After that, our understanding of what is meant by "ethical conflict", and the underlying philosophical theories, are accounted for. In the end, *one* model for ethical analysis (among several existing) is presented and applied to a simple case.

### The words "ethics" and "moral"

According to Abelson [1] the word "ethics" is commonly used with three different meanings. To denote (1) a general pattern or "way of life", (2) a set of rules of conduct or "moral code", and (3) inquiry about ways of life and rules of conduct. In the first sense, we speak of Buddhist and of Christian ethics; in the second, we speak of professional ethics and of unethical behaviour. In the third sense, ethics is a branch of philosophy that is frequently given the special name of meta-ethics. There is a long tradition within ethics to use the word in the third sense, i.e. as "meta-ethics" or "moral philosophy". In 1902, the German physician Moll [2] wrote:

*Seit Aristoteles nennt man Ethik die Wissenschaft, die den sittlichen Wert und Unwert des menschlichen Wollen und Handelns untersucht.*

A similar definition of "ethics" is recommended by the committee for Norwegian research [3] and by Hermerén [4].

However, it is doubtful if such a definition is appropriate outside a group of philosophers. In everyday language, the two words are often used interchangeably. There is a tendency to use the word "moral" about commonly used norms and values, while the word "ethics" is reserved for a more elaborate system of professional codes. A similar meaning is mentioned in *Webster's New World Dictionary of the American Language* (1970). Under the entry "moral" it is written:

*Moral implies conformity with the generally accepted standard of goodness or rightness in conduct or character, sometimes, specif., in sexual conduct (a moral woman); ethical implies conformity with an elaborated, ideal code of moral principles, sometimes, specif., with the code of a particular profession (an ethical lawyer).*

## **Ethical conflicts**

An ethical conflict is a situation that satisfies four conditions: (1) there are good reasons for a person to do action A (2) there are good reasons for P also to do another action B (3) P has the ability to do A separately and B separately and (4) for logical or factual reasons P is not able to perform both A and B [5].

This definition can also be stated in words. Few, if any, would maintain that all actions fall within the field of ethics. With the exception of actions, which for ethical reasons ought to be carried out or not, there are actions for which there is no reason to perform or not to perform. They are ethically neutral and are called “adiophora” (indifferent matter).

Besides the distinction between ethical neutral actions and non-ethical neutral actions, it is also advisable to distinguish two different types of ethical motivated actions. The first actions are such that they realise *ethical demand*. Concerning these, Sinnott-Armstrong writes: “*a moral reason to keep a promise is a requirement, because failure to keep a promise is morally wrong unless it can be morally justified*” [5]. Other actions ought not to be performed. If such actions are performed, the actor deserves criticism. Beauchamp and Childress writes that such acts “*are wrong and prohibited*” and as an example they give “*murder*” [6].

Agreement on where the boundary between ethical ideals and ethical demands should be drawn does not currently exist. To participate in non-therapeutic research is, according to Ramsey [7], an action that is an ethical ideal. To participate should never be demanded of the individual because that is incompatible with the right to self-determination. To McCormick [8], on the other hand, it is a question of an ethical

demand. The individual has an obligation to be a research subject. According to McCormick, the demand of justice goes before the demand of self-determination.

Ethical reasons are commonly conceived as comparable. Those reasons that speak in favour of one alternative can be compared to those reasons that speak for another alternative. Conflicts depending on comparable demands are therefore (in most cases) solvable. For instance, the demand to speak the truth may usually have less weight than the demand not to kill. According to Mill [9], Ross [10], and Hare [11] all ethical conflicts are solvable.

However, competent moral philosophers maintain that there are (or could be) unsolvable ethical conflicts [5,12,13]. According to Sinnott-Armstrong [5], there are two types of unsolvable conflicts. The first occur when the reasons are symmetrical and comparable, when those reasons speaking in favour of one alternative and those speaking in favour of another alternative have the same force. The second occur when the reasons are incomparable, when those reasons speaking for one alternative cannot be weighted against another alternative.

## The relevant philosophical theories

It is, however, more complicated. A person's ethics can be teleological or duty-oriented. *The common feature of all teleological theories of ethics is the subordination of the concept of duty, right conduct, or moral obligation to the concept of the good or human desirable. Duty is defined as that which conduces to the good, and any statement enjoining a particular course of conduct as duty or moral obligation is regarded as acceptable only if it can be shown that such conduct tends to produce a greater balance of good than do possible alternatives. Non-teleological theories, which hold that the concept of duty is logically independent of the concept of good and therefore deny the necessity of justifying duties by showing that they are productive of good, are called deontological theories [14].*

The concepts denote, to quote the British philosopher Broad, “rather ideal limits than real existents. Most actual theories are mixed, some being more predominantly deontological and others predominantly teleological” [15].

According to Tranøy [16], the same applies to medical ethics:

*It is obvious that medical ethics contains both consequentialist and deontological elements and it is difficult even to imagine that it could be otherwise. The basic aim and purpose of medicine – to fight disease and to promote health – is focussed on the consequences of medical intervention. But it is also clear that it is non-consequentialist principles which so radically changed the face of medical ethics – from the former profile of medical paternalism to a medical morality focusing on integrity, autonomy, and patient’s rights – all of them so obviously deontological notions.*

The distinction “deontological” and “teleological” is intersected by the distinction “pluralism” and “monism”. An ethic is *plural* if it contains two or more independent criteria for what is right or wrong. Sometimes these criteria are in conflict. To the duty-oriented this means that there are different fundamental principles, and to the consequentialist that there are different types of basic values. According to Frankena:

*There are at least two basic and independent principles of morality, that of beneficence or utility which tells us to maximise the total amount of good in the world (the balance of good over evil), and that of justice [17].*

According to the *monists* it is possible to reduce the morality of an individual and the ethics of a group to one criterion for what is right or wrong. To a monist that is duty-oriented there is only one fundamental ethical principle, and to the consequentialist that there is only one basic value.

The British philosopher Russell thought that the ethical principle of justice was not an independent ethical principle. He defines it as: *The main objection to an uneven distribution is that it causes envy and hatred in the less fortunate, leading to fear and correlative hatred in the more fortunate [18].*

Among others, Mill [9] has argued that every acceptable individual morality and every group ethics should start from only one criterion. For him a monist and teleological morality was the only alternative. *There must be some standard by which to determine the goodness or badness, absolute and comparative, of ends or objects of desire. And whatever that standard is, there can be but one; for if there were several ultimate principles of conduct, the same conduct might be approved by one of those principles and condemned by another, and there would be needed some more general principle as umpire between them.*

## A model

Different methods for ethical analyses exist in economy, philosophy, and political science. They are, for instance, pro/contra-analysis, decision-technique, cost/utility-analysis, cost/result-analysis, decision-tree-technique, decision-matrix, delphi-technique, and stakeholder-analysis (compare for instance [15,18,19]). Facing two alternatives – relatively superficial to present the great numbers of methods or more thoroughly discuss one – the latter alternative has been chosen. It is to give an account of and apply *one* such method for description and analysis of ethical conflicts, thereby combining stakeholder-analysis [4] with explicit formulated ethical value-premises according to decision-tree-technique [15].

### A case

A 70-year old person with severe hemophilia was admitted to the hospital in Sweden as he could not manage his condition, nor could his spouse. He was somewhat crippled because of joint bleeds but could walk. He had diabetes in need of insulin treatment and also mild dementia. He had been on prophylactic factor VIII treatment for years and it was known that he would have painful joint bleeds if the treatment was stopped. The alternative is treatment according to need, something that is practised in most other countries with adult patients. Should he be given prophylactic treatment for his hemophilia (which is expensive) or should he only be given treatment according to need (which is less expensive)?

## Presentation of the model

The first task is to identify and put together the individuals or the groups that are related to the treatment. Each individual or group ought to have a common interest, that is all involved or affected persons should belong to one group. To apply the model presupposes thorough knowledge about the situation and the possible alternatives. This implies for individuals or groups that are involved in or affected by the measure: (1) the patient, (2) the relatives, (3) the physician, (4) the hospital nurse, (5) the assistant nurse, and (6) other patients.

The second task is to identify the relevant ethical principles. They are:

- *The principle of autonomy*, with its demand for protection of those that cannot protect themselves, honesty, and confidentiality (or anonymity in certain questionnaires), informed and voluntary consent, or refusal to participate. The principle is duty-oriented.
- *The principle of utility*, with its demand not to harm, to reduce suffering, to prevent suffering, and to increase wellbeing. The principle is consequentialistic, and it is sometimes formulated as two requirements. The first requirement is often called "the principle of non-maleficence". The second, third, and fourth requirements are often called "the principle of beneficence".
- *The principle of justice*, with its demand that no one should be discriminated against (for instance by reference to age and sex), and the obligation to show solidarity with vulnerable individuals. To impartially respect the right of everyone is usually understood as a duty-oriented principle.

The third task is to assess the ethical costs and the ethical utility for the individuals or groups that are involved in or affected by the measures. Some examples may illustrate what is meant by "ethical costs" and "ethical utility". If ethically sensitive information is collected without the patient's (or proxy's) informed and voluntary consent, this is an ethical cost for the patient. However, if informed and voluntary consent is obtained from the patient (or the proxy), it is a question of an

ethical utility. In the latter case, there is no cost according to the autonomy principle. If any patient with hemophilia is harmed in a test of a new pharmaceutical, there is an ethical cost. If all the patients identify themselves with the group that (in the long run) can have any advantages of the product, it could be presumed that they carried a reasonable burden of the research. In this case there is no loss from the point of view of justice.

## **Analysis of the case**

The principles are the three mentioned earlier, which are related to autonomy, utility, and justice. The individuals or groups that are involved in or affected by the possible measures are:

- *The patient* probably wants the prophylactic treatment.
- *The relatives* want the prophylactic treatment.
- *The physician* believes that the prophylactic treatment should be given because that is what the physician believes to be in the best interest of the patient and that is what the relatives want. The physician is to decide and the decision made is to give the patient the prophylactic treatment.
- *The hospital nurse* disagrees and believes that the needs of the patient after a bleeding should be satisfied and nothing more – even if the patient suffers. The reasons given are the age of the patient and his dementia. He also has diabetes.
- *The assistant nurse* also disagrees and believes that the needs of the patient after a bleeding should be satisfied and nothing more. She gives the same reason as the hospital nurse.
- It could reasonably be seen by *the other patients* as a utility cost and an injustice to them to offer the demented and old patient the prophylactic treatment (if they were told about the consequences).

The ethical analysis can also be summed up in a simple figure:

**Figure 4.1** Ethical principles, individuals or groups involved in or affected by the conflict, and not relevant (/), utility (+) and costs (–) in the different rows.

Involved and affected	Relevant ethical principles		
	Autonomy	Beneficence	Justice
The patient	/	+	–
The relatives	+	+	–
The physician	+	+	–
The hospital nurse	–	–	+
The assistant nurse	–	–	+
Other patients	/	–	–

## Strategy for solution of any ethical conflict

Often it is enough to do an intuitive weighting of the ethical costs and the ethical utility. Sometimes, for instance, when one feels uncertain of what is the right thing to do, there is a reason to make an ethical analysis. This can be done according to the above analysis.

One idea is, for instance, to have a meeting at the hospital about a difficult case of hemophilia previous to the encounter with the patient and the relatives. At least the physician, the hospital nurse, and the assistant nurse should meet before the patient and the relatives are met. It is important that the same message is given to the patient from the hospital. The same holds true also for the relatives.

The model used is usually called “principlism” by ethicists. But with its emphasis on impartiality there is, however, a risk that the principles prohibit the best alternative for the patient. Principlism demands distance and health care demands closeness. Sometimes these demands can come into conflict [20].

However, one can supplement with analogous cases. By taking one uncontroversial case for granted and making explicit relevant similarities and dissimilarities, analogous cases can be used as arguments for or against a certain solution. In the literature this method is called "casuistry" (case-based reasoning). A problem with analogies as arguments is that the selection of a case for comparison may be controversial. The tendency is to select a comparison, which supports the conviction already had.

Another method is to supplement with virtue ethics (which emphasise the character of the person performing the act) or motive ethics (which emphasise the motive of the action).

## **A warning**

All costs are not equally important. Some costs can have a value that outweigh the utility, or vice versa. It is not possible to say in advance whether the utilities or the costs have the highest weight for a certain alternative. It is therefore not possible to say what the physician should choose in a particular case.

This does not mean that principlism is without value. The effort to name the involved or affected, to formulate the principles, and then assess the ethical costs and utility, will not only improve knowledge of the different alternatives, it also counteracts the tendency to "forget" costs and utilities for those involved or affected. When, for instance, the physician believes that he or she knows the "right" answer to the ethical conflict, then the ability to judge the alternative without bias is easily lost.

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## 5. Lack of knowledge

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Hemophilia and the more severe forms of von Willebrand disease (VWD) are rare bleeding disorders. The current treatment strategies are mainly based on more or less well-controlled observational studies and trends in such studies easily give rise to different opinions depending on the view of the hemophilia treater. The level of evidence may be hampered by repetitive publications of the same, or almost the same, study cohort that has been followed for many years. Many of the treatments we use today can be judged as best practice than evidence-based medicine. The design of well-controlled, prospective studies is difficult, not to say impossible, to achieve for several reasons of which the major are: difficulties to recruit enough large study cohorts, the long-term follow-up needed, and financing. Trials in these rare disorders are very costly to perform as studies have to be multinational because of the rareness of the disorders. In addition, the products used are extremely expensive. The consequence is that industry funding is a prerequisite, which may introduce bias.

A number of items can be highlighted as areas where we lack real knowledge and where better studies are needed (but still very difficult to perform). Regarding hemophilia, such areas are:

### Prophylaxis in non-inhibitor patients

- When to start
- When/if to stop
- Dose regimens
- Long-term assessment of joint disease
- Health economy

### Inhibitors

- Genetic and environmental risk factors for inhibitor development
- ITI protocols
- Prophylaxis with bypass therapy

## Products

- Improved pharmacokinetics with longer biological half-life. Such products will have a potential to:
  - improve convenience
  - improve compliance
  - improve cost efficacy
- Increased potency
  - May be of importance for better treatment of inhibitor patients
- Development of products or tools so that intravenous injections can be avoided and be replaced by alternative routes of administration (subcutaneous, inhalation, per oral)
  - Puncture of veins is today a major obstacle for effective treatment of small children

For VWD the clinical problems are somewhat different, as especially the inhibitor problem is not of the same magnitude as in hemophilia, but on the other hand less well explored. Some areas can be highlighted for von Willebrand disease:

- At which plasma levels of FVIII/VWF is concentrate treatment necessary, i.e. when is desmopressin truly not giving enough hemostasis?
- The clinical importance of the heterogeneity of VWF concentrates
- Prophylaxis in von Willebrand disease: indications and dosing schedules
- Products used for treatment of VWD are still plasma-based and there is a need for recombinant technology as already is the case for hemophilia. One such product is currently in clinical trial and its feasibility remains to be proven.

Results from several prospective, randomised trials will be available in the near future and will hopefully give somewhat better insight in some of these issues. Examples are the International ITI Study where different

dosing used for immune tolerance induction is compared, the SIPPET study where previously untreated patients are randomised to be treated with plasma-derived or recombinant FVIII to address the question regarding product classes and inhibitor risk, and the VWD PN where prophylaxis in von Willebrand disease is studied both in a retro- and prospective fashion.

## **Amendment**

### **Studies published after the initial literature review**

The rigorous methodology that SBU uses in systematic reviewing the literature is – and needs to be – time-consuming. A dead-line for the literature search has to be set up when the list of selected studies that fulfilled the inclusion criteria is established. After this no further studies are included. This is necessary for both practical and scientific reasons. Hence there might be a considerable delay between the last date for literature search and publication of the final report because of reading, critical appraisal of the studies, data extraction, writing, external review, approval of the SBU scientific council and board, etc. During this period, of course, new studies are published, even such studies that might affect the report's conclusions. In order to partly deal with this problem, a new updated literature search according to previously defined search strategy was performed on October 23, in 2010. The search identified 106 abstracts (out of 440 new hits) that were judged as tentatively relevant. After careful perusal by two independent reviewers, 29 studies of the 106 studies were found to fulfill the previous defined inclusion and exclusion criteria for the systematic review and were investigated in full text format by two reviewers. Eleven of the articles were found to be congress abstracts and not published as full studies. However, we chose to include these to be sure not to miss anything of importance. Our conclusions based on the findings in the previous review were not affected by these new studies. Of note is that none of the added publications was a randomised trial.

The 29 articles are distributed as follows according to the report's sections:

- Hemophilia A and B (section 3.1.): 8
- Inhibitors (section 3.2): 15
- von Willebrand disease (section 3.3): 2
- Economy (section 3.4) 4

**Table 1** Studies published after the initial literature review.

	<b>Number of abstracts</b>	<b>Reference</b>
Case series	8	1, 2*, 8, 11*, 14, 19, 23*, 25
Case control studies	1	5*
Pharmacovigilance	1	6*
Surgery (case series)	4	7, 16, 17*, 18
Retrospective survey	2	10, 13*
Registry studies	2	21*, 22*
Economical aspects	4	26*, 27, 28, 29
Reviews	7	3*, 4, 9, 12, 15, 20, 24
<b>Total number of abstracts</b>	<b>29</b>	

\* Reference only available in abstract format

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## 6. Project Group

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Members of the group represent different perspectives on knowledge and comprised of the following experts:

*Erik Berntorp*

Professor, MD, PhD. Malmö Centre for Thrombosis and Hemostasis, Lund University, Skåne University Hospital, Sweden

*David Bergqvist*

Professor Emeritus MD, PhD. Department of Surgery, Uppsala University Hospital, Uppsala, Sweden

*Jan Astermark*

Associate Professor, MD, PhD. Malmö Centre for Thrombosis and Hemostasis, Lund University, Skåne University Hospital, Sweden

*Fariba Baghaei*

MD, PhD. Division of Hematology and Coagulation, Sahlgrenska University Hospital, Gothenburg, Sweden

*Margareta Holmström*

MD, PhD, Coagulation Unit, Hematology Centre Karolinska, Karolinska University Hospital, Stockholm, Sweden

*Bengt Ljungberg*

MD, PhD Senior expert, Medical Products Agency, Uppsala

*Tore Nilstun*

Professor Emeritus, Lund University, Lund, Sweden

*Pia Petrini*

MD, Coagulation Clinic, Hematology, Astrid Lindgren's Children's Hospital, Solna, Sweden

*Jan Palmblad*

Professor Emeritus, MD, PhD, Department of Medicine and Hematology, Karolinska Institute, Karolinska University Hospital, Huddinge, Stockholm, Sweden

*Lennart Stigendal*

MD, Chief Physician (retired), Division of Hematology and Coagulation, Sahlgrenska University Hospital, Gothenburg, Sweden

*Anders Norlund*

Health Economist, Senior Lecturer, Karolinska Institute, SBU, Stockholm, Sweden

*Annebeth Syversson*

Project Assistant, SBU, Stockholm, Sweden

*Juliette Säwe*

Project Manager, MD, PhD, Associate Professor, SBU, Stockholm, Sweden

### **Additional author (Section 3.1.1)**

*Rolf Ljung*

Professor, MD, PhD, Departments of Paediatrics and Malmö Centre for Thrombosis and Hemostasis, Lund University, Skåne University Hospital, Sweden

### **Scientific Reviewers**

*Anders Anell*

School of Economics and Management, Lunds University, Sweden

*Christine A Lee*

University of London, United Kingdom

*Michael Makris*

Department of Cardiovascular Science University of Sheffield, United Kingdom

*Geir E Tjønnfjord*

Department of Medicine, Oslo University Hospital Rikshospitalet,  
Norway

*Anders Wahlin*

Division of Hematology, Umeå University Hospital, Sweden

## **Conflict of interest**

SBU requires all participants in a project group to submit written declarations regarding potential linkages, or conflict of interest. Such conflicts of interest may exist if a member of the group receives financial compensation from parties with an interest in the group's findings. The chairman of the group and SBU then take a position on whether there are any circumstances that could be seen as potentially influencing an objective evaluation of the knowledge base or proposals for action based this evaluation.

In light of the fact that among the available experts in Sweden all declared some form of involvement in industry, such as being a member of an advisory board or receiving research support from pharmaceutical companies, SBU has extended the expert group with additional members that are not primarily involved in health care for hemophilic patients, nor have or have any commitments related to drug development or research in the area.

In accordance with SBU's requirements, the expert advisers as well as the external referees have submitted declarations of financial disclosures and potential conflict of interests. These documents are available at SBU.

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