Clotting factor concentrates given to prevent bleeding and bleeding-related complications in people with hemophilia A or B (Review)

Iorio A, Marchesini E, Marcucci M, Stobart K, Chan AKC

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[Intervention Review]

Clotting factor concentrates given to prevent bleeding and bleeding-related complications in people with hemophilia A or B

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ABSTRACT

Background

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

Objectives

To determine the effectiveness of clotting factor concentrate prophylaxis in the management of people with hemophilia A or B.

Search methods

We searched the Cochrane Cystic Fibrosis and Genetic Disorders Group's Coagulopathies Trials Register. In addition, we searched major electronic databases (MEDLINE, EMBASE, CENTRAL), handsearched relevant journals and abstract books and reference lists of relevant articles.

Last search of Group's Coagulopathies Trials Register: 07 April 2011.

Selection criteria

Randomised controlled trials and quasi-randomised controlled trials evaluating people with severe hemophilia A or hemophilia B receiving prophylactic clotting factor concentrates.

Data collection and analysis

Two authors independently reviewed studies for eligibility, assessed risk of bias and extracted data.

Main results

Six studies (including 142 participants) were eligible for inclusion. Two compared three-times-a-week prophylactic administration with on-demand treatment in children with hemophilia. Pooled results from these two studies showed a rate ratio of 0.30 (95% confidence interval; 0.12 to 0.76) for all bleedings and 0.22 (95% confidence interval 0.08 to 0.63) for joint bleedings favouring prophylaxis. Results on the number of patients with preserved joints after three to seven years of follow-up were not pooled due to significant heterogeneity. Three of the remaining four studies evaluated hemophilia A; one showed a statistically significant decrease in frequency of joint bleeds with prophylaxis compared to placebo, with a rate difference of -10.73 (95% confidence interval -16.55 to -4.91) bleeds per year. Two studies compared two prophylaxis regimens, failing to demonstrate an advantage of one regimen over the other in terms of bleeding frequency. The fourth study evaluated hemophilia B and showed fewer joint bleeds with weekly (15 IU/kg) versus bi-weekly (7.5 IU/kg) prophylaxis, rate difference -3.30 (95% confidence interval -5.50 to -1.10) bleeds per year. Non-significant increases in both inhibitor and infectious complications were observed in patients on prophylaxis, which occurred more often when using long-term venous access.

Authors' conclusions

There is strong evidence from randomised controlled trials and observational trials that prophylaxis preserves joint function in children with hemophilia as compared to on-demand treatment. There is insufficient evidence from randomised controlled trials to confirm the observational evidence that prophylaxis decreases bleeding and related complications in patients with existing joint damage. Well-designed randomised controlled trials and prospective observational controlled studies are needed to establish the best prophylactic regimen and to assess the effectiveness of prophylactic clotting factor concentrates in adult patients.

PLAIN LANGUAGE SUMMARY

Regular clotting factor replacement therapy to prevent joint disease in people with severe hemophilia A or B

Hemophilia A and B are X-linked inherited bleeding disorders, in which the major clinical problem is repeated bleeding into joints. As this disorder progresses, joints become deformed and movement limited. Current therapy for treating and preventing bleeding includes plasma-derived or recombinant clotting factor concentrates. This review includes six randomised controlled trials. Two compare the regular use of clotting factor concentrates to prevent joint bleeds with their use 'on demand'. Four compare different regimens of regular use in children and adults with hemophilia. It was clearly evident that preventative therapy, as intravenous infusion of factor concentrate repeated more times a week and started early in childhood was able to reduce joint deterioration as compared to treatment administered after bleeding occurred. This favourable effect is due to a consistent reduction in total bleeds and hemarthrosis (bleeding into joints) and leads to a significant improvement in quality of life. Preventative therapy is linked to an increased factor usage and cost of treatment. We found weaker evidence (due to lack of data) to show preventative therapy reduced joint deterioration when treatment is started after joint damage has been established. Further studies are needed to establish the best preventative regimen, i.e. for example starting time, dosage frequency, minimally effective dose.

BACKGROUND

Hemophilia is an X-linked bleeding disorder due to a coagulation factor deficiency (factor VIII for Hemophilia A and factor IX for Hemophilia B) and is classified according to clotting factor level: severe (with a baseline coagulation factor level of less than 1% of normal); moderate (with clotting factor levels of 1% to 5%); and mild (with a clotting factor greater than 5%).

People with moderate and mild haemophilia bleed rarely, and often only after trauma or in association with invasive procedures.

The frequency and severity of bleeding is greatest in people with severe hemophilia A or B, in which recurrent and often spontaneous bleeding into joints and soft tissues (since early childhood) is the hallmark of severity. The consequence of recurrent joint bleeding is the development of different degrees of haemophilic arthropathy.

The availability of clotting factor concentrates has radically changed the treatment of people with hemophilia, with a sig-

nificant improvement of morbidity, mortality and quality of life (QoL) (Lusher 1997). Since the introduction of clotting factor concentrates, the early on-demand treatment for acute bleeding episodes is now common practice. This has resulted in a decrease in the number of joint deformities with respect to untreated or minimally-treated patients (Ahlberg 1965; Hilgartner 1974).

However, observation of the natural history of haemophilic arthropathy in people on long-term on-demand treatment shows that this regimen is clearly sub-optimal. A milestone study in 1994 reported the results of a longitudinal observation of 477 males under 25 years of age with severe hemophilia A without inhibitors who were followed up for six years (Aledort 1994). Patients treated on demand showed a progressive deterioration of their joint function in some or all of the joints examined. Repeated bleeding in the joints has been indicated as the mechanism which, through abnormal proliferation of the synovial tissue, leads to joint disruption. At the time of this report's publication, the preventive use of clotting factor concentrates given at regular intervals had already been adopted for several decades in Sweden (Nilsson 1976). Then in 1994, the Medical and Scientific Advisory Council (MASAC), of the United States of America's National Hemophilia Foundation reviewed the Swedish experience with prophylaxis and issued guidelines stating that prophylaxis should be considered the optimal therapy for children with severe hemophilia A and B (NHF 1994).

In the meanwhile, the focus of managing an individual with hemophilia has changed from treating an acute bleeding episode to the comprehensive care of the individual, including the administration of clotting factor concentrate outside the hospital or treatment centre, as subsequently theorized and better defined (Teitel 2004).

In fact, the efficacy of prophylaxis is expected to be higher if started early, i.e. before the establishment of any degree of joint deterioration, and continued as much as possible, as only home care treatment allows.

In this perspective, currently agreed definitions of prophylaxis are those proposed by the European Paediatric Network for Haemophilia Management (Berntorp 2003; Ljiung 2000). In particular, prophylaxis was defined as:

- primary A (determined by age) if regular continuous treatment is started after the first joint bleed and before the age of two years;
- primary B (determined by first bleed) if regular continuous treatment is started before the age of two years without previous joint bleeds;
- secondary A if regular continuous (long-term) treatment is started after two or more joint bleeds or at an age of over two years;
- secondary B if intermittent regular (short-term) treatment is applied, based on frequent bleed events.

Primary prophylaxis (A or B) and secondary A regimens require at least three doses per week for 42 weeks per year.

Despite the above recommendations, prophylaxis has not been universally adopted because of medical, psychosocial, and cost controversies (Blanchette 2004). In fact, the use of clotting factor concentrates is the single largest predictor of overall cost in the care of people with hemophilia (Miners 2004; Miners 2009), and it prevents its extensive application worldwide. Furthermore, there is no general agreement on the optimal prophylaxis regimen, and some schemes differ from that proposed by the European Paediatric Network which has been recently proven to be feasible (Feldman 2006; Collins 2009). In addition, evidence is accumulating about the efficacy of secondary prophylaxis started in adulthood to slow the progression of hemophilic arthropathy in already damaged joints or to relieve symptoms, or both, and improve QoL (Fisher 2003; Hay 2007).

In order to help clarify the open issues and provide optimal treatment recommendations for as many people with hemophilia as possible, we aim to systematically appraise the available evidence for the effectiveness of prophylactic administration of factor concentrates

OBJECTIVES

The objective of this review is to evaluate whether the preventive use of clotting factor concentrates in people with hemophilia A or B improves short- and long-term outcomes as measured by one or more of the following:

Short-term

1. number of bleeding episodes per year or bleeding frequency
2. clotting factor concentrate plasma levels

Long-term

1. clinical joint function
2. orthopedic joint score
3. radiologic joint score
4. QoL measurements

METHODS

Criteria for considering studies for this review

Types of studies

Randomised or quasi-randomised clinical trials. All identified trials, unpublished or published as an article, an abstract or a letter, without any language limitations, were eligible.

Types of participants

Children and adults with congenital hemophilia A or B, including all ages and all degrees of severity. People with factor VIII or IX inhibitors were excluded.

Types of interventions

Trials included were those where intravenous clotting factor concentrates were administered as prophylactic treatment in any formulation (fresh frozen plasma, cryoprecipitate, lyophilised plasma derived clotting factor concentrate, or recombinant clotting factor concentrate), any concentration, any frequency and any dose were compared with no treatment, or on-demand treatment, or with one or more different prophylaxis regimens. The duration of treatment was greater than a single treatment. At least one treatment had to be a clotting factor concentrate.

Therefore the comparison groups are as follows:

1. prophylaxis versus placebo;
2. prophylaxis versus on-demand treatment;
3. prophylaxis versus alternative prophylaxis.

Types of outcome measures

Primary outcomes

1. Number of bleeding episodes or bleeding frequency

Secondary outcomes

1. Pain scores
2. Radiologic joint score or radiologic measurements or descriptions of joint damage
3. Orthopedic joint score or clinical joint function
4. QoL
5. Clotting factor concentrate plasma levels
6. Time loss to school or employment
7. Integration into society
8. Scales recording feeling of well-being and global functioning
9. Cost effectiveness, cost benefit, cost utilization, cost minimization
10. Any reported adverse effects or toxicity of clotting factor concentrates will be recorded (e.g. inhibitors, reactions, transmission of infection)

Search methods for identification of studies

Electronic searches

Relevant trials were identified from the Group's Coagulopathies Trials Register using the term: prophylaxis and hemophilia* or haemophilia*.

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

Date of the most recent search of the Group's Coagulopathies Trials Register: 07 April 2011.

We performed additional searches on MEDLINE (from January 1966 to 14 February 2011), and EMBASE (from 1988 to 14 Feburary 2011) (both on the OVID platform) and CENTRAL (Issue 4, 2010). For the full search strategies, please refer to the appendices (Appendix 1; Appendix 2).

Searching other resources

The bibliographic references of all retrieved studies and reviews were assessed for additional reports of clinical trials. For the 2011 update, handsearching of the proceedings of the International Society for Thrombosis and Haemostasis bi-annual meeting and proceedings of the European Association for Haemophilia and Allied Disorders were performed for the years 2004 to 2010.

Data collection and analysis

Selection of studies

Two authors independently examined the titles and abstracts of trials generated from the database searches to identify potentially relevant studies. They retrieved complete manuscripts for all potentially relevant studies. With the full text manuscripts, the authors independently assessed the studies using a standardised form.

They resolved differences, regarding which studies to include, by consensus reached after discussion.

Data extraction and management

Using a structured data form the authors extracted the following information: characteristics of the study; study participants' demographics; the study intervention and co-interventions (including doses of clotting factor concentrate); study outcomes (including primary and secondary outcomes). Two authors extracted data independently and compared the results. They resolved differences by consensus and referral to the original paper.
Authors considered outcome data if recorded as either individual events or as events grouped by time periods.

Assessment of risk of bias in included studies

The authors used the standard built-in tool in RevMan 5.1 to measure the risk of bias and to produce summary figures (RevMan 2011).
The authors assessed the risk of bias using the 'Risk of bias' assessment tool as documented in section 8.5 of the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2011). The following domains were assessed as having either a low, high or unclear risk of bias:

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

Results of the risk of bias assessment are displayed in the risk of bias tables in the 'Characteristics of included studies' tables.

Measures of treatment effect

We expected rates of events to be the measures reported for the primary outcome. We expected rate of events or mean and standard deviations (SD) to be the measures reported for most of the secondary outcomes. Consequently, and taking also into account the high number of events expected for the primary outcome, the authors chose the rate difference as the measure of treatment effect for the primary outcome and risk difference or the mean difference (MD) for the secondary outcomes. The authors accounted for any deviation from this plan in the text.

Unit of analysis issues

Hemophilia lends itself to cross-over study design, as it is a chronic incurable genotypically-stable disease, and treatment with clotting factor concentrate has a rapid onset and short duration as the factor VIII and IX physiological half-lives are 12 and 24 hours respectively. Thus, we expected at least some of the studies to be cross-over in design. As a pre-planned analysis we stated that we would use the generic inverse variance (GIV) method when individual patient data were available or after obtaining the relevant data. If such data were available, we would have analysed any parallel group studies the same way to allow pooling of data. Otherwise, we used the standard RevMan method for parallel group trials (RevMan 2011).

Dealing with missing data

We contacted two authors to obtain additional data, but to date, none have been received (Gringeri 2011; Manco-Johnson 2007).

Assessment of heterogeneity

If we had included a sufficient number of studies in any meta-analysis, then we would have assessed clinical heterogeneity by visual and statistical analysis. For future updates, if we include a sufficient number of studies, we will use the I^2 method to assess for heterogeneity in meta-analysis. If I^2 is equal to or greater than 50% we will consider this indicative of heterogeneity. We have reported both I^2 and Cochran Q chi -squared values.

Assessment of reporting biases

We planned to look for publication bias, checking open trial registries (www.clinicaltrials.gov) and using visual inspection of the funnel plot graph (if there were 10 or more included studies). Given the rarity of the disease and its chronic course, we believe publication bias is unlikely to occur since any similar trials would have been openly planned and run in the small hemophilia community. We investigated outcome reporting bias by looking for differences between trial reports and the original protocols or challenging any relevant unreported outcome data.

Data synthesis

Due to the low number of available studies, we have conducted the meta-analyses of the primary data using a random-effects model.

Sensitivity analysis

We undertook a *post hoc* sensitivity analysis for adverse events (central venous catheter (CVC) patients) (Analysis 2.6)

RESULTS

Description of studies

See: Characteristics of included studies; Characteristics of excluded studies.

Results of the search

In the study search for the first edition of this systematic review, using the above search strategies, 890 unique references were identified. The authors assessed the titles and abstracts, from which 119 unique new articles were retrieved, 29 studies were considered for inclusion and 4 were finally included. One additional study was identified by contacting the primary author of an identified congress abstract. The original selection and extraction was performed by KS and AI.

Study selection and data extraction for the 2011 update were performed in duplicate by EM and MM. A total of 569 new references were retrieved, from which 82 unique references were identified by title and abstract scanning and 9 unique articles were identified as being potentially relevant. Three new references (to two studies) were finally included. Data about the 'Joint Outcome Study (JOS)' were provided by two of these references (Manco-Johnson 2007), while data about the ESPRIT study were retrieved in one reference (Gringeri 2011). Additional details about these two studies were requested from the authors (Gringeri 2011; Manco-Johnson 2007). For the JOS study we requested additional details about inhibitors (distributions into the two treatment arms and inhibitor levels); the data were partially provided by dr Manco-Johnson.

Included studies

Six studies, with a total of 142 participants, were identified as being relevant and included in the data analysis (Aronstam 1976; Aronstam 1977; Carlsson 1997; Gringeri 2011; Manco-Johnson 2007; Morfini 1976). There was no disagreement between the two authors with respect to study relevance. The six studies were heterogeneous as each study used a different intervention. Given the available data, a meta-analyses could be performed for two studies (Gringeri 2011; Manco-Johnson 2007).

One study was performed in the USA (Manco-Johnson 2007) and five studies were conducted in Europe. Two studies were conducted in Italy (Gringeri 2011; Morfini 1976), one in Sweden (Carlsson 1997) and two in England (Aronstam 1976; Aronstam 1977). The four participants in the second English study had participated in the earlier one. There were approximately six months between the completion of the first study and the commencement of the second. All studies were published in English.

Two studies were randomised controlled open studies (Gringeri 2011; Manco-Johnson 2007). Four were cross-over in design (Aronstam 1976; Aronstam 1977; Carlsson 1997; Morfini 1976), and all six used bleed frequency as the primary outcome measure. The interventions were not similar between the studies, leading to heterogeneous results and an inability to perform an overall meta-analysis. The two more recent studies allowed us to pool data for some of the outcomes (Gringeri 2011; Manco-Johnson 2007).

Types of Participants

The JOS study included patients on primary prophylaxis (Manco-Johnson 2007); the ESPRIT study included patients in primary and secondary prophylaxis (Gringeri 2011); the remaining four trials reported data about secondary prophylaxis (Aronstam 1976; Aronstam 1977;.Carlsson 1997; Morfini 1976).

In one study the participants were people with severe hemophilia B (factor IX less than 1%) (Morfini 1976). In three studies the participants were people with severe hemophilia A (factor VIII less than 1%) (Aronstam 1976; Aronstam 1977; Gringeri 2011). One study included people with clinically severe hemophilia, where one participant had a pharmacological moderate level of factor VIII (1.5%), but behaved clinically as a person with severe hemophilia A (Carlsson 1997). The JOS study included people with severe and moderate-severe hemophilia A with factor VIII level below than 2% (Manco-Johnson 2007).The age range of participants was from 1 year to 45 years. All participants were male, and none had inhibitors. The studies varied in sample size with 9, 4, 14, 40, 65 and 10 participants respectively (Aronstam 1976; Aronstam 1977; Carlsson 1997; Gringeri 2011; Manco-Johnson 2007; Morfini 1976).

Types of Interventions

Four studies were cross-over in design (Aronstam 1976; Aronstam 1977; Carlsson 1997; Morfini 1976). The order of the intervention was randomised, and all participants received both the control and active treatment. Different interventions were used in the four studies. The treatment arm was either a larger amount (Aronstam 1976; Aronstam 1977) or a more frequent dosing schedule (Morfini 1976) of clotting factor concentrate than the control arm, or a modified prophylaxis dose of clotting factor concentrate based on individual pharmacokinetic data (Carlsson 1997). The control arm was either a non-physiologic effective dose of clotting factor concentrate (Aronstam 1976), a physiologic effective clotting factor concentrate dose (Aronstam 1977; Morfini 1976), or a standard prophylaxis schedule of clotting factor concentrate (Carlsson 1997). In the Carlsson study, upon enrolment in the clinical trial, each patient received a single standard dose of clotting factor concentrate (factor VIII 25 to 40 IU/kg), and a pharmacokinetic evaluation was calculated by standard "model-independent" procedures; the individual's pharmacokinetic data were used to fit computer-simulated multiple-dose activity curves of factor VIII for each case, to clinically achieve a factor VIII trough level above 1% (Carlsson 1997).

One study compared a regimen of clotting factor concentrate to increase the factor VIII dose to 25% of the normal compared to 1% of the normal (Aronstam 1976). A second study compared bi-weekly dosing of clotting factor concentrate to raise factor VIII to 30% of normal, versus 15% of normal (Aronstam 1977). The study by Morfini compared the same total dose of factor IX clotting factor concentrate per week, administered either weekly (15 IU/kg) or bi-weekly (7.5 IU/kg) (Morfini 1976). The study by

Carlsson compared standard dose prophylaxis (25 to 40 IU/kg/dose) given three times per week with the dose and interval based on individual pharmacokinetic data (Carlsson 1997). In all four studies, the clotting factor concentrate dosing interval allowed a physiological washout period of treatment effect before the cross-over intervention was undertaken.

The two new studies at the 2011 update were open randomised controlled trials (Gringeri 2011; Manco-Johnson 2007).These studies compared a prophylaxis treatment group versus an on-demand treatment group. One study compared a prophylaxis group with a factor VIII infusion of 25 IU/kg of body weight every other day versus on-demand treatment with 40 IU/kg of body weight at the time of joint haemorrhage followed by 20 IU at 24 hours and 72 hours after the first dose (Manco-Johnson 2007). When hemarthroses occurred in the prophylaxis group, patients were treated with 40 IU/kg at the time of joint haemorrhage. The second trial compared prophylactic treatment with 25 IU/kg of body weight three-times weekly versus on-demand treatment with 25 IU/kg of body weight until complete healing (Gringeri 2011).

Types of Outcomes

The primary outcome of interest, bleeding events or bleed frequency, was reported in all six studies. All outcomes were standardized to event rates per year.

Range of motion of affected joints was collected in one study, but the data were collected at the completion of the study, after the participants had experienced both interventions in a cross-over fashion (Morfini 1976). Data about long-term joint deterioration and adverse events (inhibitors rate, and infection) were reported in two studies (Gringeri 2011; Manco-Johnson 2007).

A secondary outcome reported in one study was 'morbidity', and it was defined as "time spent in the college sick bay or at hospital, where more than three hours under medical care was noted as one day" (Aronstam 1976). A further secondary outcome that was reported in three studies was the quantity of clotting factor concentrate administered (Carlsson 1997; Gringeri 2011; Manco-Johnson 2007). Quality of life data were reported in one study (Gringeri 2011).

Excluded studies

Thirty-one studies were excluded because they were not RCTs. We classified these as controlled observations and included them in an additional table because of their potential use in estimating the baseline risk and variability of treatment effect size in different populations (Table 1). Twenty-five studies were excluded after the first search, an additional reference to one of these studies was identified during a later search (Feldman 2006). Six other studies were excluded from the analysis at the 2011 update and details are presented in the additional tables (Collins 2010; Fischer 2005; Nemes 2007; Schobess 2008; Tagliaferri 2008; Wu 2011) (Table 1).

Risk of bias in included studies

An overall graphical representation of the risk of bias assessment is provided in the figures (Figure 1; Figure 2). It was noted in particular, in relation to blinding, the risk of bias was found to be high in two studies (Carlsson 1997; Morfini 1976). In relation to 'other potential sources of bias', one trial was assessed as having a high risk of bias due to a significant number of patients crossing over the allocated treatment arms (Gringeri 2011).

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

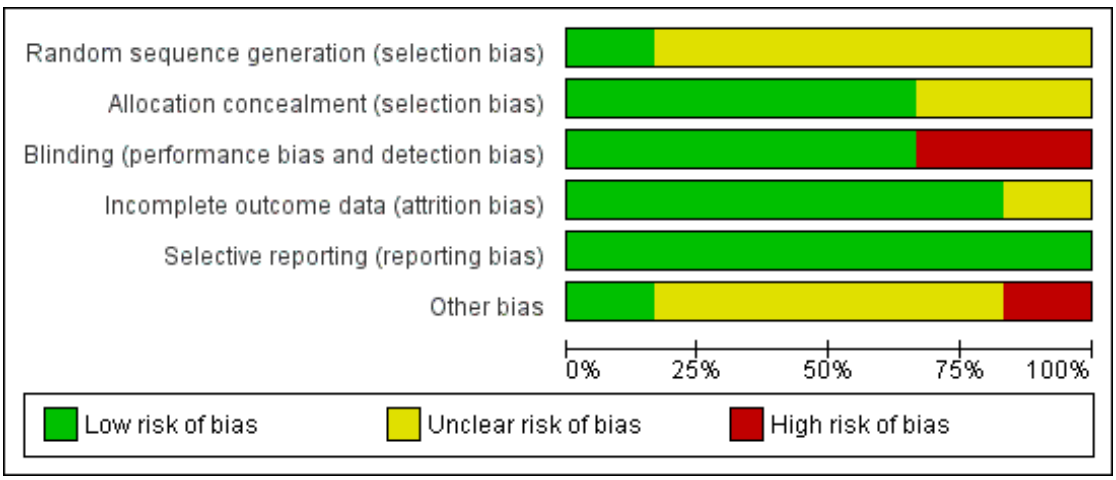
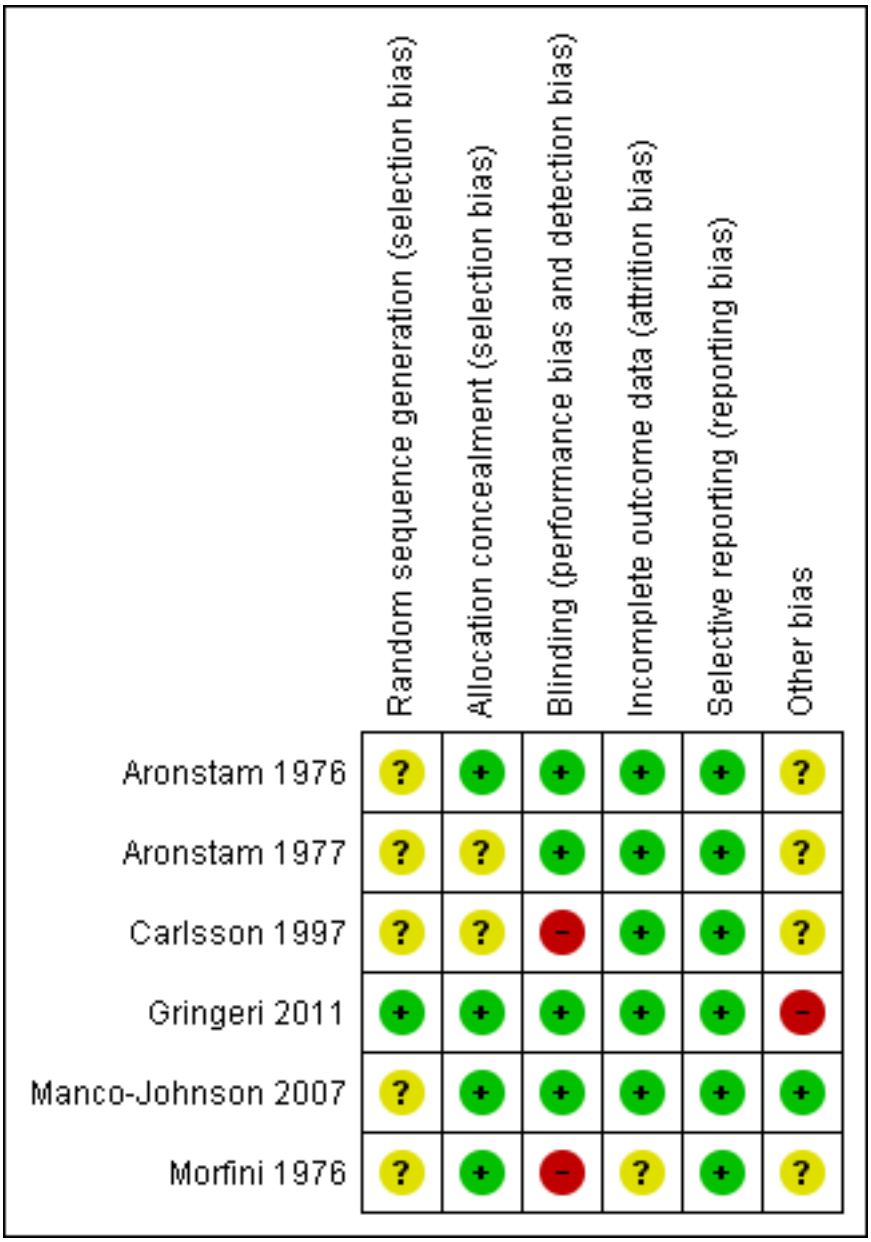


Figure 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.



Allocation

All six studies were described as being randomised, but none reported details about sequence generation. Four studies were judged as having suitable concealment (Aronstam 1976; Gringeri 2011; Manco-Johnson 2007; Morfini 1976). In the remaining two studies there was no allocation concealment (Aronstam 1977; Carlsson 1997).

Blinding

One study described an appropriate method of double blinding, where the physicians administering the study treatment were in a different institution from the physicians evaluating and treating bleeding episodes (Aronstam 1977). Two studies stated that the patients were unaware of the treatment administered by the physician (Aronstam 1976; Aronstam 1977). The ESPRIT study had a blinded assessment of orthopedic and radiographic scores (Gringeri 2011). The JOS study had blinded assessment of orthopedic and radiographic scores and of laboratory assessments (Manco-Johnson 2007). The remaining trials were unblinded.

Incomplete outcome data

All six studies discussed withdrawals. Two studies had no withdrawals (Morfini 1976; Aronstam 1977). One study had two withdrawals, these were voluntary discontinuations by two participants who bled soon after a low dose administration (Aronstam 1976). The fourth trial had seven withdrawals (four withdrew their consent, three had an unpredictable pharmacokinetic modified dosage schedule) (Carlsson 1997). The ESPRIT study was analysed by intention-to-treat, and recorded 8 withdrawals (4 in each arm) (Gringeri 2011). The JOS study reported 5 (out of 32) withdrawals in the prophylaxis group and 11 (out of 33) (3 for life-threatening haemorrhages) in the on-demand group (Manco-Johnson 2007). This study was analysed by intention-to-treat.

Selective reporting

Selective reporting was assessed only for trials with registered protocols. The only protocol found was for the JOS trial, registered at the end of enrolment (September 2005) on www.clinicaltrials.gov (NCT00207597) (Manco-Johnson 2007). All the outcomes reported in the protocol were analysed in the published paper. The main outcome was identical in the protocol and the published paper. For the remaining studies we assessed correspondence between methods and results sections. It was difficult to judge the occurrence of non reporting of clinically relevant for the older trials included in the review.

Other potential sources of bias

It was reported in three studies that they were sponsored by pharmaceutical companies (Carlsson 1997; Gringeri 2011; Manco-Johnson 2007). One study did not record sponsorship (Morfini 1976). Three studies received financial support from external sources (Aronstam 1976; Aronstam 1977; Carlsson 1997). A significant degree of cross-over between the two treatment arms was reported for ESPRIT trial (Gringeri 2011). The four studies designed as cross-over did not have a wash out period and did not take any other method to avoid or account for carry-over effect.

Effects of interventions

Standard prophylaxis regimen compared to a placebo regimen

One study was included in the comparison (Aronstam 1976). The characteristics of the included study were:

- **Type of prophylaxis:** secondary prophylaxis
- **Age range:** 13 years to 17 years old
- **Follow-up duration:** at least two school terms
- **Number of enrolled patients:** 9

Primary outcome

1. Bleeding frequency

The clinical trial found a statistically significant advantage for the higher dose of factor VIII as compared to a non-physiologic dose with a rate difference for bleeding frequency of -10.73 (95% CI -16.55 to -4.91) bleeds per year (Analysis 1.1).

Secondary Outcomes

1. Pain Scores

This outcome was not reported.

2. Radiologic joint score

This outcome was not reported.

3. Orthopedic joint score

This outcome was not reported.

4. QoL

This outcome was not reported.

5. Clotting factor concentrate levels

This outcome was not reported.

6. Time loss to school or employment

The study assessed morbidity, defined as "time spent in the college sick bay or at the hospital" (Analysis 1.2). The mean rate difference was statistically significant (P < 0.05), favouring treatment of children on the high-dose regimen (factor VIII 0.25 IU/kg), who spent less time confined to bed, rate difference 0.28 (95% CI 0.20 to 0.40). In this trial individual participant data were not provided, and therefore a logarithmic rate difference was calculated (Deeks 2011).

7. Integration into society

This outcome was not reported.

8. Well-being and global functioning

This outcome was not reported.

9. Cost effectiveness, cost benefit, cost utilization, cost minimization

This outcome was not reported.

10. Adverse events

The study summarized adverse events or complications at the end of the study, after participants had received both the treatment and control interventions. However, no participant developed a factor VIII inhibitor or became hepatitis B surface antigen positive during the clinical trial (Aronstam 1976).

Standard prophylaxis regimen compared to on-demand treatment

Two studies were included in the comparison (Gringeri 2011; Manco-Johnson 2007). The characteristics of the include studies were:

Gringeri 2011

- **Type of prophylaxis:** secondary and primary prophylaxis .
- **Age range:** less than seven years old
- **Follow-up duration:** median 82.5 months (range: 2 months to 163 months)
- **Number of enrolled patients: 40**

Manco-Johnson 2007

- **Type of prophylaxis:** primary prophylaxis
- **Age range:** less than 30 months
- **Follow-up duration:** mean 49 months (range: 48 to 58 months)
- **Number of enrolled patients: 65**

Primary outcome

1. Bleeding frequency

The comparison showed a significant statistical reduction of total bleeding in patients treated on prophylaxis versus those treated on demand. The rate difference was calculated for the JOS study only (Manco-Johnson 2007), since the SD for the main effect was not reported for the ESPRIT study (because of skewed data distribution) and not provided by the authors upon request (Gringeri 2011). The rate difference for the JOS study was -14.42 (SD 7.91) for bleed frequency and -4.16 (SD 2.71) for joint bleeds. To provide a pooled estimate of the effect on bleeding rate, the rate ratio was used, rate ratio 0.30 (95% CI 0.12 to 0.76), I^2 99% (Chi^2 196.78, P < 0.00001) (Analysis 2.1). A similar significant reduction was found when pooling results for joint bleeding, rate ratio 0.22 (95% CI 0.08 to 0.63), I^2 98% (Chi^2 63.31, P < 0.00001) (Analysis 2.2). The pooled estimates should be considered with caution due to the very high level of heterogeneity, very likely due to the different characteristics of the population in the two studies. The absolute bleeding rates in the control groups were for all bleedings 17.7 +/- 9.2 (events per patient per year, mean and SD) in the JOS study and 0.48 (events per patient per month, mean) in the ESPRIT study; for joint bleedings 4.9 +/- 3.6 (events per patient per year, mean and SD) in the JOS study and 0.24 (events per patient per month) in the ESPRIT study for joint bleeds.

Secondary Outcomes

1. Pain Scores

This outcome was not reported.

2. Radiologic joint score

We did not pool the data for this outcome due to two additional causes of variability in the two studies (duration of follow-up and the intensity of treatment in the control group (enhanced on-demand prophylaxis in the JOS study)). Only patients on primary prophylaxis in the ESPRIT study showed a statistically significant protection from joint damage with prophylaxis when this was compared to standard on-demand treatment (risk difference 0.70 (95% CI 0.39 to 1.01) while the difference in the JOS study was borderline significant, risk difference 0.15 (95% CI -0.01 to 0.31) (Analysis 2.3). The effectiveness of secondary prophylaxis was tested in the ESPRIT study only, resulting in a non-significant difference, risk difference for reduction in the progression of radiologic evidence of joint damage 0.32 (95% CI -0.07 to 0.70) (Analysis 2.3).

3. Orthopedic joint score

This outcome was not reported.

4. QoL

Only the ESPRIT trial reported data on QoL (Gringeri 2011). The Haemo-QoL questionnaire showed that overall QoL was of 22.2 (SD 8.2), in a scale from 0 to 100, where 100 indicates completely deteriorated QoL. When assessing the impact of treatment, a significant difference was found in children receiving on-demand treatment versus those receiving prophylaxis in the subscale exploring the dimension "family", which was more impaired in the on-demand treatment group, MD 32.73 (95% CI 22.30 to 43.16) (Analysis 2.4).

5. Clotting factor concentrate usage

The studies showed a significant increased consumption of factor VIII in the patients treated with prophylaxis as compared to those treated on demand. Monthly factor usage per patient on the ESPRIT trial was 8852 IU and 3981 IU in the prophylaxis group and in the on-demand group, respectively (Gringeri 2011) and in the JOS study they were 5880 IU and 1887 IU per patient per month in the prophylaxis group and in the on-demand group respectively, MD 5270 IU/month per patient (95% CI 4230 to 6320), I^2 0% (Chi^2 0.24, P = 0.62) (Analysis 2.5).

6. Time loss to school or employment.

The outcome was not reported.

7. Integration into society

The outcome was not reported.

8. Well-being and global functioning

The outcome was not reported.

9. Cost effectiveness, cost benefit, cost utilization, cost minimization

In the ESPRIT study a cost analysis was performed (Gringeri 2011). Cost evaluation was based on the annual FVIII consumption. A societal perspective was adopted (third party payer, i.e. the Italian National Health Service), and all the health care resources absorbed by the care of patients were specifically considered. With an average price per IU of recombinant factor VIII concentrates of EUR 0.75, the cost for one year of prophylaxis was EUR 79,668 compared to EUR 35,829 for one year on on-demand therapy. The incremental cost-efficacy ratio per bleeding events avoided in patients on prophylaxis was EUR 7537. The incremental cost-efficacy ratio for maintaining all joints unaffected over the whole treatment period was EUR 201,601.12.

10. Adverse events

Both studies reported the rate of infections per treatment group. When all the enrolled patients were considered, a non-significant difference against prophylaxis was observed, risk difference 0.14 (95% CI -0.14 to 0.42), I^2 75% (Chi^2 4.04, P = 0.04) (Analysis 2.6). Analysis of the inhibitor rate was complicated by suboptimal reporting of inhibitor incidence in both studies. In the Gringeri study, the incidence of inhibitors was reported without providing the distribution in high or low-responding/transient inhibitors (Gringeri 2011). In the JOS study, the assignment to treatment group of seven low-responding/transient inhibitors was not provided (Manco-Johnson 2007). Both authors were contacted to obtain additional data, but to date, none have been received. When compared using the data as reported in the publications, the inhibitor rate was not significantly higher in patients on prophylaxis, risk difference 0.06 (95% CI -0.03 to 0.15) I^2 0% (Chi^2 0.06, P = 0.81) (Analysis 2.6).

Adverse events in central venous catheter (CVC) patients (sensitivity analysis)

Since both infections and inhibitor development are reported to be more common in patients with CVC, we also analysed adverse events in this subgroup of patients. Data allowing the comparison were available from the JOS study only (Manco-Johnson 2007), since in the ESPRIT study only patients on prophylaxis had CVC placed (6 out of 10) (Gringeri 2011), and no infection or incidence of inhibitors were recorded in patients without a central vein access. A non-significant difference was observed, risk difference -0.03 (95% CI -0.26 to 0.19) (Analysis 2.6). In a further sensitivity analysis, we calculated the number of patients with CVC and events in the two studies (6/10 additional patients in the ESPRIT prophylaxis group), ending with 12/39 and 6/25 infections during prophylaxis or on-demand treatment in CVC patients, respectively, and recalculated an unadjusted risk difference of 0.07 (95% CI -0.15 to 0.29). Similarly for inhibitor rate we found a non-significant excess of inhibitors in CVC patients on prophylaxis versus those on demand (1 out of 29 versus 1 out of 25, respectively with a risk difference of -0.01 (95% CI -0.11 to 0.10)) (Analysis 2.6), unadjusted risk difference 0.06 (95% CI -0.06 to 0.18).

Standard prophylaxis regimen compared to an alternative prophylaxis regimen

Three studies were included in this comparison but could not be aggregated as one study compared bi-weekly dosing of clotting factor concentrate given at a dose to raise factor VIII to 30% of normal, versus a dose to get 15% of normal factor VIII concentrate post-infusion level (Aronstam 1977), a second study was on people with hemophilia B (Morfini 1976), and the third compared standard dose prophylaxis (25 to 40 IU/kg/dose) given three times

per week with a regimen in which the dose and interval were based on individual pharmacokinetic data (Carlsson 1997) .
The characteristics of the include studies were:
Aronstam 1977

- **Type of prophylaxis:** secondary prophylaxis
- **Age range:** 13 years to 17 years old
- **Follow-up duration:** at least two school term
- **Number of enrolled patients:** 4

Carlsson 1997

- **Kind of prophylaxis:** secondary prophylaxis
- **Age range:** 8 years to 42 years old
- **Follow-up duration:** one year
- **Number of enrolled patients:** 21 (14 included in the analysis)

Morfini 1976

- **Kind of prophylaxis:** secondary prophylaxis
- **Age range:** 5 years to 45 years old
- **Follow-up duration:** one year
- **Number of enrolled patients:** 10

Primary outcome

1. Bleeding frequency

Two studies did not find a statistical significant effect in the bleeding frequency: rate difference of -5.04 (95% CI -17.02 to 6.94) bleeds per year when comparing two different dosages (Aronstam 1977) (Analysis 3.1); and rate difference -0.14 (95%CI -1.34 to 1.05) bleeds per year when assessing a PK-based regimen (Carlsson 1997) (Analysis 4.1). The Morfini study showed a significant difference in favour of the bi-weekly versus the once weekly dosing group, rate difference of -3.30 (95% CI -5.50 to -1.10) bleeds per year (Morfini 1976) (Analysis 5.1).
Note: as the dosage and frequency of administration of the clotting factor concentrate was different in the three studies, it was not possible to combine the studies.

Secondary Outcomes

1. Pain Scores

No studies reported this outcome.

2. Radiologic joint score

The radiological assessments in people with factor IX deficiency were made at the completion of the study, not at the completion of the separate interventions. Therefore, it was not possible to attribute effectiveness of the treatment intervention in this cross-over design study (Morfini 1976).

3. Orthopedic joint score

The clinical orthopedic evaluations in people with factor IX deficiency were collected at the completion of the study, not at the completion of the separate interventions. Therefore, it was not possible to attribute effectiveness of the treatment intervention in this cross-over design study (Morfini 1976).

4. Quality of life

This outcome was not reported.

5. Clotting factor concentrate levels

One study reported clotting factor concentrate usage (Carlsson 1997). There was a significant difference in favour of the pharmacokinetic-optimised dosing group, mean difference of -3300 IU per month (95%CI -1420 to -5180) (Analysis 4.2).

6. Time loss to school or employment

This outcome was not reported.

7. Integration into society

This outcome was not reported.

8. Well-being and global functioning

This outcome was not reported.

9. Cost effectiveness, cost benefit, cost utilization, cost minimization

One study reported savings with a PK-based regimen as compared to a standard prophylaxis regimen (Carlsson 1997). Savings for 14 patients over 6 months were USD 418,000 or GBP 270 (as calculated in 1997).

10. Adverse events

Two studies summarized adverse events or complications at the end of the study, after participants had received both the treatment and control interventions. The development of factor VIII inhibitors or positivity to hepatitis B surface antigen was collected at the completion of the study, but no participants developed an inhibitor or became newly hepatitis B surface antigen positive (Aronstam 1977; Morfini 1976).

DISCUSSION

This systematic review included six studies with a total of 142 participants with a different degree of arthropathy at baseline and

variable types of interventions, which allowed only partial aggregation of data for clotting factor concentrate usage for the prevention of bleeding in people with hemophilia. On the whole, these studies provided evidence that prophylactic administration of clotting factor concentrates is effective in significantly preventing or slowing down the progression of hemophilic arthropathy. As a caveat, performing primary prophylaxis (i.e. started before a significant number of bleeds has occurred) in small children often requires clinicians to implant a venous access device. The use of these devices is complicated by local infection in a significant number of cases. Similarly, patients on prophylaxis in these studies developed more inhibitors than those receiving on-demand therapy, although the difference was not statistically significant and potentially associated with venous access implants or infection rather than to the prophylactic regimen.

The clinical management of people with hemophilia has changed over the past three decades, i.e. since the oldest clinical studies included in this review were undertaken. Hemophilia care is now provided under a comprehensive health care model and with prophylactic or on-demand treatment for the majority of bleeds given at home, i.e. outside the treatment centre.

The dates of publication of the earlier studies and the events that have occurred in the intervening years is worthy of comment. Three of the included studies were performed as early as the 1970s. Subsequently, the unfortunate events of the blood-borne infectious disease epidemic precluded the design and implementation of well-designed clinical trials in the 1980s. Later on, the introduction of recombinant human clotting factor concentrates removed any residual risk of infection. However, the ability to undertake a RCT on the effectiveness of prophylaxis was overshadowed by more than 20 years experience of primary prophylaxis with clotting factor concentrate compared to historical controls (Nilsson 1992; Petrini 1991; Brackmann 1992; Manco-Johnson 1994; van den Berg 2002). Although not RCTs, the observational studies indicated clear benefits in the reduction of bleed frequency and joint deformity. It has therefore been very difficult for investigators to decide if there was true equipoise in the choice between prophylactic and on-demand treatment. Essentially, coupled with this established pattern of practice, there are 30 unique observational studies reporting data from 1960 people with hemophilia undergoing clotting factor concentrate prophylaxis in comparison with 1312 people with hemophilia treated on-demand. Detailed characteristics of these observational studies are listed in an additional table (Table 1). These non-RCT observational studies have been used by healthcare providers to justify the use of clotting factor concentrate in primary prophylaxis in several countries throughout the world. Finally, and notwithstanding all the evidence above, two independent groups in the USA (Manco-Johnson 2007) and Italy (Gringeri 2011) found it ethically and scientifically sound to compare the widely-used thrice-a-week prophylaxis regimen with on-demand treatment. Both groups confirmed the superiority of administering prophylactic factor concentrates, by showing a reduction in the bleeding rate and progression of arthropathy. Both studies, however, demonstrated that hemophilia patients develop some degree of joint deterioration even when receiving prophylaxis. Furthermore, prophylaxis was found to be associated with a significant increase in the amount of resources used.

Why were the results of these two more recently performed studies positive and at variance with the four older studies? Bleeding episodes within and between people with hemophilia can vary considerably over a period of months. Furthermore, the pathologic process which leads to hemophilic arthropathy requires several years to produce clinically evident modifications in the affected joints. Only the two more recent of the six studies observed patients for 10 years (Gringeri 2011) and 4 years (Manco-Johnson 2007), time-spans that can be considered long enough to establish a significant difference. Of the remaining four studies included in the analysis, two observed participants for one year, and two for two or four "English school" terms. The bleeding frequency period studied may have been too short to be clinically meaningful, and the cross-over design could have been suboptimal in assessing differences in the setting of chronic disease, where information about effectiveness and optimal duration of the washout period are largely unknown. Carryover effect from on-demand treatment to prophylaxis might have negatively biased the effect of prophylaxis, while carryover from prophylaxis to on-demand treatment may have positively inflated the effectiveness of on-demand treatment. Furthermore, it has been repeatedly shown that prophylaxis exerts its effect mostly in patients whose joints are still unaffected joints (i.e. after one or at maximum two clinically relevant bleeding episodes). Most of the participants in the older studies had already presented with some degree of hemophilic arthropathy (Aronstam 1976; Aronstam 1977; Carlsson 1997; Morfini 1976), while the patients in the JOS study (Manco-Johnson 2007) and some of those in the ESPRIT study (Gringeri 2011) qualified to be considered as receiving primary prophylaxis. Of note, even the two more recent studies, though focused on prophylaxis in children, presented a high degree of heterogeneity, most likely due to the difference in either the characteristics of the population included or the different treatment scheme used for the on-demand control group (Gringeri 2011, Manco-Johnson 2007). Thus, the overall estimates of the meta-analyses should be considered with caution, and it may even have been inappropriate to pool the results of the two studies to give a point estimate. In addition to the estimate of the mean effect size, it is important that the clinical reader, when estimating the reduction in the bleeding frequency expected for a given patient, considers the appropriate value in the range of the confidence intervals, assuming that the baseline risk and the reduction are likely to be inversely correlated with the age and joint deterioration of the patient.The heterogeneity between the studies is most evident when considering the long-term effect of prophylaxis. In fact, only patients on primary prophylaxis in the ESPRIT study, where the control was standard on-

demand treatment, showed a statistically significant protection of the joint function, while the difference in the JOS study, where enhanced prophylaxis was used as a comparator and the follow-up was shorter, was borderline significant (Analysis 2.3).

Prophylaxis has already been set as a standard in the western world, but there is still a lack of knowledge about several aspects of this treatment, as highlighted by the many outcomes that are considered relevant by hemophilia clinicians (and thus listed among the outcomes of interest for this review), but which have not been addressed or reported on by most of the studies. Furthermore, new randomised comparisons between different regimens to deliver prophylaxis are to be expected in the near future. In fact, during the course of the recent randomised studies and after their completion, several new issues about prophylaxis in hemophilia were raised, such as: optimal regimen (including both dose, frequency, individual tailoring by means of escalating-dose protocol or PK modelling); optimal starting point and regimen to preserve joint function and minimize inhibitor development (Kurnik 2010); whether or not to continue beyond childhood and the role of secondary prophylaxis in adult patients, etc. Similarly, several pharmacoeconomic evaluations have been published (Collins 2009; Miners 2009). Some of these studies have had a strong impact on the hemophilia community, and are likely to change the clinical practice in the western world. In low- and middle-income countries, studies are ongoing to evaluate the effectiveness of low-dose prophylaxis regimens.

AUTHORS' CONCLUSIONS

Implications for practice

There is evidence from RCTs and observational studies that the use of prophylactic clotting factor concentrate is effective in decreasing the frequency of joint bleeds and in partially preventing or slowing down the development of arthropathy.

Implications for research

Future randomised clinical trials should address the following aspects:

1. comparative efficacy, safety and effectiveness of different prophylactic regimens (escalating versus fixed-dose, pharmacokinetic-tailored versus fixed-dose);

2. optimal starting and ending age;

3. standardized clinical and radiological outcome measures of efficacy;

4. long-term cost-effectiveness.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Aronstam 1976

Methods	Cross-over study. Time unit: school term. Randomised clinical trial.
Participants	Country: England. Participants: males with hemophilia A. (factor VIII < 1%). Age Range: 13 - 17 years. Number enrolled: 9.
Interventions	Factor VIII concentrate. (Blood Products Laboratory - UK). Arm A: 0.25 U/kg once weekly. Arm B: 0.01 U/kg once weekly.
Outcomes	Bleeding events or frequency.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	The authors did not specify sequence generation methods but specified that it was generated by the Wessex Medical Information Unit
Allocation concealment (selection bias)	Low risk	Quote:"...the random allocation of trial subjects to the different regimens at the beginning of each trial term was made by the Wessex Medical Information Unit"
Blinding (performance bias and detection bias) All outcomes	Low risk	Patients were blinded to the assignment treatment; clinicians and assessors were unblinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data.
Selective reporting (reporting bias)	Low risk	The study protocol is not available but the published reports include all expected outcomes

Aronstam 1976 (*Continued*)

Other bias	Unclear risk	Cross-over study without washout period

Aronstam 1977

Methods	Cross-over study. Time unit: school term. Randomized clinical trial.
Participants	Country: England. Participants: males with hemophilia A (factor VIII < 1%). Age Range: 13 - 17 years. Number enrolled: 4. All patients completed the study.
Interventions	Cryoprecipitate (prepared by Wessex Regional Transfusion Centre) or Kryobulin (prepared by Serological Products, UK). Arm A: raise factor VIII to 15% twice weekly. Arm B: raise factor VIII to 30% twice weekly.
Outcomes	Bleeding events or frequency.
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	The authors reported they used a random sequence generation but did not give details about methods of sequence generation: Quote:" The boys were allocated to different treatment schedules at random at the start of the trial....."
Allocation concealment (selection bias)	Unclear risk	The authors did not specify methods of concealment.
Blinding (performance bias and detection bias) All outcomes	Low risk	Patients and clinicians were blinded to the assignment treatment
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data.
Selective reporting (reporting bias)	Low risk	The study protocol is not available but the published reports include all expected outcomes

Aronstam 1977 (*Continued*)

Other bias	Unclear risk	Cross-over study without washout period.

Carlsson 1997

Methods	Cross-over study. 1-year duration. Time unit: 6 months. Randomized clinical trial.
Participants	Country: Sweden. Participants: samples with clinically severe hemophilia A (factor VIII < 2%). Age range: 8 - 42 years. Number enrolled: 21. Number completed: 14.
Interventions	Factor VIII concentrate (monoclonal antibody plasma derived, high-purity plasma-derived, or recombinant)
Outcomes	Bleeding events or frequency.
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Published report specifies that is a random sequence generation but not defines methods of sequence generation
Allocation concealment (selection bias)	Unclear risk	The authors did not specify methods of concealment.
Blinding (performance bias and detection bias) All outcomes	High risk	No blinding.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Reason of withdrawal were provided.
Selective reporting (reporting bias)	Low risk	The study protocol is not available but the published reports include all expected outcomes
Other bias	Unclear risk	Cross-over study without washout period.

Gringeri 2011

Methods	10 years duration. Randomised clinical trial.
Participants	Country: Italy. Participants: male with severe hemophilia A (factor VIII level <1%) Median age: 4 years (age less than 7 years). Number enrolled: 40.
Interventions	Recombinant factor VIII concentrate (Recombinate). Arm A:25 IU per kilogram of body weight 3 times a week. Arm B: 25 IU per kilogram of body weight until complete healing
Outcomes	Joint deterioration, bleed frequency.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: " centralized allocation system based on a computer generated randomization list....."
Allocation concealment (selection bias)	Low risk	Quote: " patients were centrally randomised to be treated on prophylaxis with. ...."
Blinding (performance bias and detection bias) All outcomes	Low risk	Patients were unblinded, but the outcome assessors (for musculoskeletal and radiologic evaluation) were blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing data have been in managed intention-to-treat analysis by last observation carried forward technique. List of cause for withdrawal: 9 patients refused randomization; 3 patients suffered for more than 2 bleeding episodes in the same joints; 3 patients had not bled in the previous 6 months, 1 child had radiologic signs of arthropathy, 1 child belonged to an unreliable (dysfunctional) family
Selective reporting (reporting bias)	Low risk	The study protocol is not available but the published reports include all expected outcomes
Other bias	High risk	Significant degree of cross-over between treatment arms.

Manco-Johnson 2007

Methods	9 years duration. Time unit: mean 49 month (48-58 month). Multicentre, open-label trial randomised clinical trial.
Participants	Country: USA. Participants: male with severe and moderate-severe hemophilia A (factor VIII level <2%) Age: mean 1.6 years (age less than 30 month in all participants) Number enrolled: 65.
Interventions	Recombinant factor VIII concentrate (Kogenate or Kogenate Bayer) Arm A: 25 IU of factor VIII per kilogram of body weight every other day to prevent bleeding. When hemarthroses occurred during prophylaxis, patients were treated with 40 IU per kg at the time of joint haemorrhage Arm B: 40 IU per kg of body weight at the time of joint haemorrhage and 20 IU at 24 hours and 72 hours after the first dose
Outcomes	Primary outcome: preservation of index-joint structure. Secondary outcomes: number of bleeding events, number of infusion, total of factor VIII units administrated
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	No information provided.
Allocation concealment (selection bias)	Low risk	Quote: "randomisation was performed centrally and stratified by site in permuted blocks of 2, 4 or 6."
Blinding (performance bias and detection bias) All outcomes	Low risk	Quote: "The radiologists who reviewed joint images, the physiotherapists who performed assays were unaware of the patients' treatment assignments and status with respect to a history of bleeding"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing data have been managed in intention-to-treat analysis by last observation carried forward technique. Patients removed in by protocol analysis: 5/32 (list of causes for withdrawal: 2 patients developed high titre inhibitors; 1 patient had joint damage; 2 patients dropped out) in the prophylaxis group and 11/33 (list of causes for withdrawal: 3 for life threatening haemorrhage; 6 patients had joint damage;

Manco-Johnson 2007 (*Continued*)

		1 patient dropped out; 1 was lost to follow up) in the on-demand group
Selective reporting (reporting bias)	Low risk	The study protocol is published at the end of enrolment but the published reports include all expected outcomes and analysed data following protocol publication
Other bias	Low risk	No risk of bias.

Morfini 1976

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

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	No information provided.
Allocation concealment (selection bias)	Low risk	Quote:" allocation to treatment protocols was made on the basis of random envelopes. ...."
Blinding (performance bias and detection bias) All outcomes	High risk	No blinding.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No missing data.

Morfini 1976 (*Continued*)

Selective reporting (reporting bias)	Low risk	The study protocol is not available but the published reports include all expected outcomes
Other bias	Unclear risk	Cross-over study without washout period.

IU: international units

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Aledort 1994	Prospective observational study.
Astermark 1999	Retrospective observational study.
Brackmann 1992	Retrospective observational study.
Chuansumrit 1995	Retrospective observational study.
Collins 2010	Prospective observational cross-over study.
Courter 2001	Prospective observational study.
Dzinaj 1996	Prospective observational study.
Feldman 2006	Prospective observational single-arm dose-escalation study.
Fischer 2005	Retrospective observational study.
Kavakli 1997	Prospective observational study.
Kreuz 1998	Prospective observational study.
Liesner 1996	Retrospective observational study.
Lofqvist 1997	Retrospective observational study.
Manco-Johnson 1994	Prospective observational study.
Nemes 2007	Prospective observational single arm study.
Nilsson 1970	Retrospective observational study with historical control.

(*Continued*)

Nilsson 1976	Prospective observational study with historical control.
Nilsson 1992	Retrospective observational study.
Petrini 1991	Retrospective observational study.
Petrini 2001	Retrospective observational study.
Pettersson 1981	Retrospective observational study with historical control.
Ramsay 1973	Prospective observational study.
Royal 2002	Retrospective observational study with parallel groups.
Schimpf 1977	Prospective observational cross-over study.
Schobess 2008	Prospective observational study.
Smith 1996	Retrospective observational switch study.
Szucs 1996	Prospective observational study.
Tagliaferri 2008	Retrospective observational switch study.
Tusell 2002	Retrospective observational study.
Van den Berg 2001	Retrospective observational single-arm study.
Wu 2011	Prospective observation with historical control.

DATA AND ANALYSES

Comparison 1. Standard prophylaxis versus placebo (factor VIII concentrate (post-infusion level)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Bleed frequency	1		Rate difference (Fixed, 95% CI)	Totals not selected
2 Morbidity (length of stay)	1		Rate difference (Fixed, 95% CI)	Totals not selected

Comparison 2. Standard prophylaxis versus on-demand treatment (factor VIII concentrate)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Bleed frequency	2		Rate Ratio (Random, 95% CI)	0.30 [0.12, 0.76]
2 Joint bleeding	2		Rate Ratio (Random, 95% CI)	0.22 [0.08, 0.63]
3 Joint function protection	2		Risk Difference (M-H, Fixed, 95% CI)	Totals not selected
3.1 Primary prophylaxis	2		Risk Difference (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.2 Secondary prophylaxis	1		Risk Difference (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
4 Quality of Life	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
5 Factor concentrate usage [x1000 IU]	2	105	Mean Difference (IV, Fixed, 95% CI)	5.27 [4.23, 6.32]
6 Adverse events	2		Risk Difference (M-H, Random, 95% CI)	Subtotals only
6.1 Infections (All patients)	2	105	Risk Difference (M-H, Random, 95% CI)	0.14 [-0.14, 0.42]
6.2 Inhibitors (All patients)	2	105	Risk Difference (M-H, Random, 95% CI)	0.06 [-0.03, 0.15]
6.3 Infections (Patients with CVC)	1	54	Risk Difference (M-H, Random, 95% CI)	-0.03 [-0.26, 0.19]
6.4 Inhibitors (Patients with CVC)	1	54	Risk Difference (M-H, Random, 95% CI)	-0.01 [-0.11, 0.10]

Comparison 3. Standard prophylaxis versus alternative prophylaxis (factor VIII concentrate (post-infusion level)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Bleed frequency	1		Rate difference (Fixed, 95% CI)	Totals not selected

Comparison 4. Standard prophylaxis versus alternative prophylaxis (factor VIII concentrate)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Bleed frequency	1		Rate difference (Fixed, 95% CI)	Totals not selected
2 Clotting factor concentrate usage [x1000]	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only

Comparison 5. Standard prophylaxis versus alternative prophylaxis (factor IX concentrate)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Bleed frequency	1		Rate difference (Fixed, 95% CI)	Totals not selected

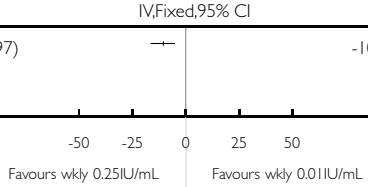
Analysis 1.1. Comparison 1 Standard prophylaxis versus placebo (factor VIII concentrate (post-infusion level), Outcome 1 Bleed frequency.

Review: Clotting factor concentrates given to prevent bleeding and bleeding-related complications in people with hemophilia A or B

Comparison: 1 Standard prophylaxis versus placebo (factor VIII concentrate (post-infusion level)

Outcome: 1 Bleed frequency

Study or subgroup	Wkly 0.25IU/mL N	Wkly 0.01IU/mL N	Rate difference (SE)	Rate difference IV,Fixed,95% CI	Rate difference IV,Fixed,95% CI
Aronstam 1976	9	9	-10.73 (2.97)		-10.73 [-16.55, -4.91]



Analysis 1.2. Comparison 1 Standard prophylaxis versus placebo (factor VIII concentrate (post-infusion level), Outcome 2 Morbidity (length of stay).

Review: Clotting factor concentrates given to prevent bleeding and bleeding-related complications in people with hemophilia A or B

Comparison: 1 Standard prophylaxis versus placebo (factor VIII concentrate (post-infusion level)

Outcome: 2 Morbidity (length of stay)

Study or subgroup	Wkly 0.25IU/mL N	Wkly 0.01IU/mL N	log [Rate difference] (SE)	Rate difference IV,Fixed,95% CI	Rate difference IV,Fixed,95% CI
Aronstam 1976	9	9	-1.26 (0.1703)		0.28 [0.20, 0.40]

Analysis 2.1. Comparison 2 Standard prophylaxis versus on-demand treatment (factor VIII concentrate), Outcome 1 Bleed frequency.

Review: Clotting factor concentrates given to prevent bleeding and bleeding-related complications in people with hemophilia A or B

Comparison: 2 Standard prophylaxis versus on-demand treatment (factor VIII concentrate)

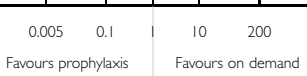
Outcome: 1 Bleed frequency

Study or subgroup	log [Rate Ratio] (SE)	Rate Ratio IV,Random,95% CI	Weight	Rate Ratio IV,Random,95% CI
Gringeri 2011	-0.7309 (0.0436)		50.0 %	0.48 [0.44, 0.52]
Manco-Johnson 2007	-1.6882 (0.0525)		50.0 %	0.18 [0.17, 0.20]
Total (95% CI)			**100.0 %**	**0.30 [0.12, 0.76]**

Heterogeneity: $Tau^2 = 0.46$; $Chi^2 = 196.78$, df = 1 ($P<0.00001$); $I^2 = 99\%$

Test for overall effect: $Z = 2.53$ ($P = 0.012$)

Test for subgroup differences: Not applicable



Analysis 2.2. Comparison 2 Standard prophylaxis versus on-demand treatment (factor VIII concentrate), Outcome 2 Joint bleeding.

Review: Clotting factor concentrates given to prevent bleeding and bleeding-related complications in people with hemophilia A or B

Comparison: 2 Standard prophylaxis versus on-demand treatment (factor VIII concentrate)

Outcome: 2 Joint bleeding

Study or subgroup	log [Rate Ratio] (SE)	Rate Ratio IV,Random,95% CI	Weight	Rate Ratio IV,Random,95% CI
Gringeri 2011	-0.9746 (0.0678)		50.4 %	0.38 [0.33, 0.43]
Manco-Johnson 2007	-2.0492 (0.1168)		49.6 %	0.13 [0.10, 0.16]
Total (95% CI)			**100.0 %**	**0.22 [0.08, 0.63]**

Heterogeneity: $Tau^2 = 0.57$; $Chi^2 = 63.31$, df = 1 ($P<0.00001$); $I^2 = 98\%$

Test for overall effect: Z = 2.81 (P = 0.0050)

Test for subgroup differences: Not applicable

Analysis 2.3. Comparison 2 Standard prophylaxis versus on-demand treatment (factor VIII concentrate), Outcome 3 Joint function protection.

Review: Clotting factor concentrates given to prevent bleeding and bleeding-related complications in people with hemophilia A or B

Comparison: 2 Standard prophylaxis versus on-demand treatment (factor VIII concentrate)

Outcome: 3 Joint function protection

Study or subgroup	Prophylaxis n/N	On demand n/N	Risk Difference M-H,Fixed,95% CI	Risk Difference M-H,Fixed,95% CI
1 Primary prophylaxis				
Gringeri 2011	8/8	3/10		0.70 [0.39, 1.01]
Manco-Johnson 2007	27/28	22/27		0.15 [-0.01, 0.31]
2 Secondary prophylaxis				
Gringeri 2011	7/13	2/9		0.32 [-0.07, 0.70]

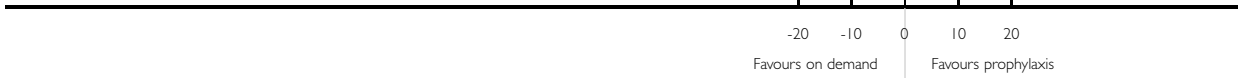
Analysis 2.4. Comparison 2 Standard prophylaxis versus on-demand treatment (factor VIII concentrate), Outcome 4 Quality of Life.

Review: Clotting factor concentrates given to prevent bleeding and bleeding-related complications in people with hemophilia A or B

Comparison: 2 Standard prophylaxis versus on-demand treatment (factor VIII concentrate)

Outcome: 4 Quality of Life

Study or subgroup	On demand		Prophylaxis		Mean Difference	Mean Difference
	N	Mean(SD)	N	Mean(SD)	IV,Fixed,95% CI	IV,Fixed,95% CI
Gringeri 2011	21	44 (22.6)	19	11.27 (8.7)		32.73 [22.30, 43.16]



Analysis 2.5. Comparison 2 Standard prophylaxis versus on-demand treatment (factor VIII concentrate), Outcome 5 Factor concentrate usage [x1000 IU].

Review: Clotting factor concentrates given to prevent bleeding and bleeding-related complications in people with hemophilia A or B

Comparison: 2 Standard prophylaxis versus on-demand treatment (factor VIII concentrate)

Outcome: 5 Factor concentrate usage [x1000 IU]

Study or subgroup	Prophylaxis N	Mean(SD)	On demand N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Gringeri 2011	21	8.852 (3.774)	19	3.98 (2.301)		29.8 %	4.87 [2.95, 6.79]
Manco-Johnson 2007	32	8.018 (3.419)	33	2.57 (1.1488)		70.2 %	5.44 [4.20, 6.69]
Total (95% CI)	**53**		**52**			**100.0 %**	**5.27 [4.23, 6.32]**

Heterogeneity: $Chi^2 = 0.24$, df = 1 (P = 0.62); $I^2 = 0.0\%$

Test for overall effect: Z = 9.88 (P < 0.00001)

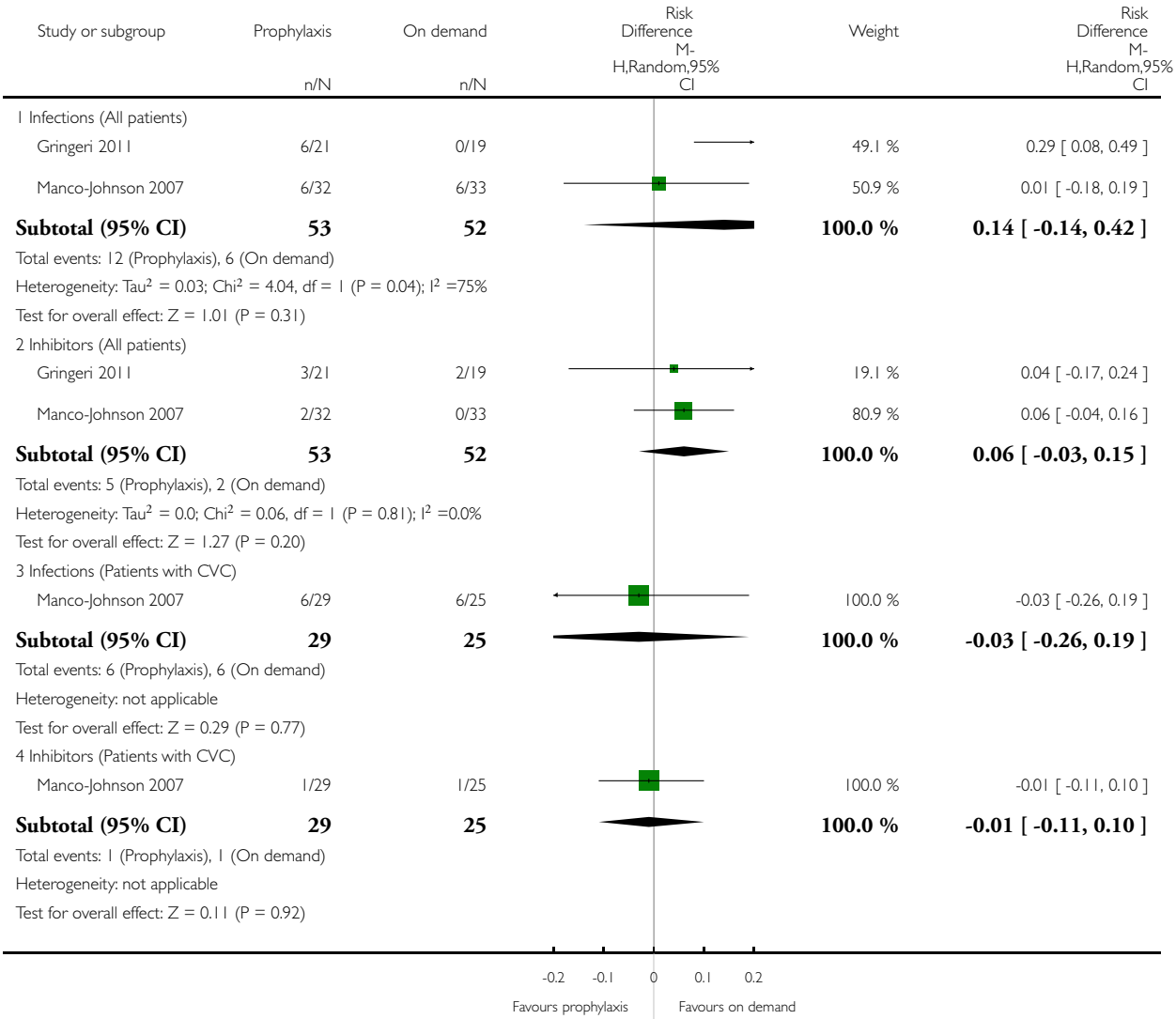
Test for subgroup differences: Not applicable

Analysis 2.6. Comparison 2 Standard prophylaxis versus on-demand treatment (factor VIII concentrate), Outcome 6 Adverse events.

Review: Clotting factor concentrates given to prevent bleeding and bleeding-related complications in people with hemophilia A or B

Comparison: 2 Standard prophylaxis versus on-demand treatment (factor VIII concentrate)

Outcome: 6 Adverse events



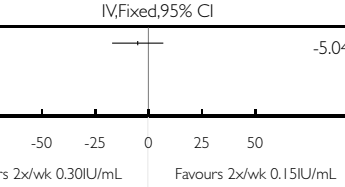
Analysis 3.1. Comparison 3 Standard prophylaxis versus alternative prophylaxis (factor VIII concentrate (post-infusion level), Outcome 1 Bleed frequency.

Review: Clotting factor concentrates given to prevent bleeding and bleeding-related complications in people with hemophilia A or B

Comparison: 3 Standard prophylaxis versus alternative prophylaxis (factor VIII concentrate (post-infusion level)

Outcome: 1 Bleed frequency

Study or subgroup	2x/wk 0.30 IU/mL N	2x/wk 0.15 IU/mL N	Rate difference (SE)	Rate difference IV,Fixed,95% CI	Rate difference IV,Fixed,95% CI
Aronstam 1977	4	4	-5.04 (6.11)		-5.04 [-17.02, 6.94]



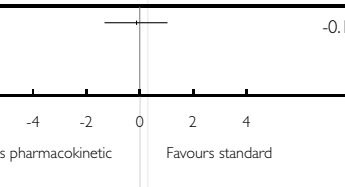
Analysis 4.1. Comparison 4 Standard prophylaxis versus alternative prophylaxis (factor VIII concentrate), Outcome 1 Bleed frequency.

Review: Clotting factor concentrates given to prevent bleeding and bleeding-related complications in people with hemophilia A or B

Comparison: 4 Standard prophylaxis versus alternative prophylaxis (factor VIII concentrate)

Outcome: 1 Bleed frequency

Study or subgroup	Pharmacokinetic N	Standard N	Rate difference (SE)	Rate difference IV,Fixed,95% CI	Rate difference IV,Fixed,95% CI
Carlsson 1997	14	14	-0.1429 (0.61)		-0.14 [-1.34, 1.05]



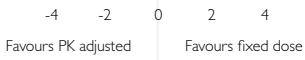
Analysis 4.2. Comparison 4 Standard prophylaxis versus alternative prophylaxis (factor VIII concentrate), Outcome 2 Clotting factor concentrate usage [x1000].

Review: Clotting factor concentrates given to prevent bleeding and bleeding-related complications in people with hemophilia A or B

Comparison: 4 Standard prophylaxis versus alternative prophylaxis (factor VIII concentrate)

Outcome: 2 Clotting factor concentrate usage [x1000]

Study or subgroup	Fixed dose proph		PK adjusted proph		Mean Difference	Mean Difference
	N	Mean(SD)	N	Mean(SD)	IV,Fixed,95% CI	IV,Fixed,95% CI
Carlsson 1997	14	10.3 (2.5)	14	7 (2.58)		3.30 [1.42, 5.18]
Subtotal (95% CI)	**0**		**0**			**0.0 [0.0, 0.0]**
Heterogeneity: not applicable						
Test for overall effect: Z = 0.0 (P < 0.00001)						
Test for subgroup differences: Not applicable						



Analysis 5.1. Comparison 5 Standard prophylaxis versus alternative prophylaxis (factor IX concentrate), Outcome 1 Bleed frequency.

Review: Clotting factor concentrates given to prevent bleeding and bleeding-related complications in people with hemophilia A or B

Comparison: 5 Standard prophylaxis versus alternative prophylaxis (factor IX concentrate)

Outcome: 1 Bleed frequency

Study or subgroup	Bi-weekly 0.075IU/mL	Weekly 0.15IU/mL	Rate difference (SE)	Rate difference	Rate difference
	N	N		IV,Fixed,95% CI	IV,Fixed,95% CI
Morfini 1976	10	10	-3.3 (1.12)		-3.30 [-5.50, -1.10]

ADDITIONAL TABLES

Table 1. Additional non-randomised observational clinical studies

Study ID	Methods	Participants	Interventions	Outcomes	Notes
Aledort 1994	Prospective observational study.	Country: Japan, USA, Europe. Cases: severe hemophilia A, under age 25 years. Enrolled 66; controls 411	Dose category in mcg/kg body weight per year.	Orthopedic joint score.	
Astermark 1999	Retrospective observational study.	Country: Sweden. Cases: severe hemophilia A and B. Hemophilia A = 108; Hemophilia B = 13	Clotting factor concentrates 25-40 IU/kg body weight. Hemophilia A: three times per week. Hemophilia B: 2 times per week	Bleeding episodes. Orthopedic joint score.	
Brackmann 1992	Retrospective observational study.	Country: Germany. Cases: severe hemophilia A, <16 years of age in 1978. Number enrolled: 90	Clotting factor concentrate: no details provided.	Bleeding episodes. Clinical joint score. Radiological joint score	
Chuansumrit 1995	Prospective observational study. Single arm.	Country: Thailand. Cases: moderate and severe hemophilia A. Number enrolled: 6	Clotting factor concentrate 8-10 U/kg body weight twice per week	Bleeding episodes. Days of hospitalisation.	
Collins 2010	Prospective observational study. Crossover study	Country: United States, UK. Case: severe hemophilia. Enrolled: 20	rFVIII-FS	Bleeding episodes, joint function, health related QoL, health economics and safety	
Courter 2001	Prospective observational label study.	Country: Multinational. Cases: severe hemophilia A. Previously untreated patients. Enrolled: 27	Coagulation recombinant factor BDDrFVIII. Prophylaxis or on-demand therapy	Bleeding episodes.	
Dzinaj 1996	Prospective observational study.	Country: Germany. Cases: early onset prophy-	Clotting factor concentrate (Humate P) 30-40	Radiologic joint score.	

Table 1. Additional non-randomised observational clinical studies (*Continued*)

		laxis versus late onset of prophylaxis in moderate or severe hemophilia A). Enrolled: Cases = 10. Controls = 7	IU/kg body weight three times per week		
Feldman 2006	Prospective observational study. Single arm dose escalation.	Country: Canada. Cases: severe hemophilia A. Enrolled: 25	Clotting factor concentrate. Step1 prophylaxis with 50 IU/kg/weekly Step 2 prophylaxis with 30 IU/kg twice a week if patients met excalation criteria Step 3 25 IU/kg on alternative days if patients met excalation criteria	Bleeding episodes.	excalation criteria: - target joint development - four or more bleeding episodes in a consecutive 3-month period - more than 5 joint bleeding in any period of time
Fischer 2005	Retrospective observational study.	Country: Netherlands. Cases: severe hemophilia A. Enrolled: 61	Clotting factor concentrate.	Joint bleeds. Radiological joint score.	
Kavakli 1997	Prospective observational study, both historically and parallel group controlled	Country: Turkey. cases: 6 with severe hemophilia A, 1 with severe hemophilia B. Controls = 10	Clotting factor concentrate. 20-50 IU/kg body weight twice weekly	Vital bleeds. Joint bleeds. Days hospitalised. Orthopedic score. Radiologic joint score. Life quality	
Kreuz 1998	Prospective observational study.	Country: Germany. Cases: previously untreated patients with moderate or severe hemophilia A. Enrolled: 21	Clotting factor concentrate.	Joint bleeding.	
Liesner 1996	Retrospective observational study. Single arm.	Country: UK. Cases: severe hemophilia A and B. Enrolled 24 and 3, respectively	Clotting factor concentrate. Prophylaxis regimen.	Number of bleeding episodes.	
Lofqvist 1997	Retrospective observational study.	Country: Sweden. Cases: severe hemophilia A	Clotting factor concentrate. Dose: 25-	Orthopedic joint scores. Radio-	

Table 1. Additional non-randomised observational clinical studies (*Continued*)

		or B. Enrolled: hemophilia A = 29. Hemophilia B = 5	40 IU/kg body weight. Hemophilia A three times per week. Hemophilia B twice per week	logic joint scores.	
Manco-Johnson 1994	Prospective observational study.	Country: USA. Cases: severe hemophilia A and B. Enrolled: hemophilia A = 13; hemophilia B = 1	Clotting factor concentrate. Dose: factor VIII 20 IU/kg body weight. factor IX 40 IU/kg body weight. Frequency: Factor VIII three times per week (n = 6), and every other day (n = 7). Factor IX twice per week	Bleeding episodes. Radiologic joint score.	
Nilsson 1970	Retrospective observational with historical control.	Country: Sweden. Cases: 24 with hemophilia A.	AHF freeze-dried concentrate.	Days of hospitalisation.	
Nilsson 1976	Retrospective observational with historical control.	Country: Sweden. Cases: 29 with hemophilia A.	AHF freeze-dried concentrate.	Orthopedic joint score.	
Nilsson 1992	Retrospective observational study.	Country: Sweden. Cases: severe hemophilia A or B. Enrolled: hemophilia A = 52. hemophilia B = 8	Clotting factor concentrate. Dose: Hemophilia A 24-40 IU/kg body weight three time per week. Hemophilia B 25-40 IU/kg body weight twice weekly	Orthopedic joint score. Radiologic joint score.	
Nemes 2007	Prospective, multicenter, 3-part clinical trial.	Country: Austria. Cases: severe hemophilia A. Enrolled: cases 49. Control 17	Immunate S/D. Dose: according to pharmacokinetics evaluation	Bleeding frequency.	Part 1:pharmacokinetics randomised double-blind; Part 2: prospective observational study. Subjects received infusions with Immunate S/D Part 3: pharmacokinetics evaluation after 14 weeks +/- 7 days

Table 1. Additional non-randomised observational clinical studies (*Continued*)

Petrini 1991	Retrospective observational study.	Country: Sweden. Cases: severe hemophilia A born in 1965 - 1972 treated initially on-demand. Controls: severe hemophilia A born 1976 - 1983 treated prophylactically. Enrolled: Cases: 7. Controls: 7	Clotting factor concentrate.	Bleed frequency. Limitation of joint movement. Ankle hemarthrosis	
Petrini 2001	Retrospective observational study. Historical control.	Country: Sweden. Cases: severe hemophilia A or B, born 1988-1998. Enrolled: 34	Clotting factor concentrate. Dose: 20-40 IU/kg body weight. Hemophilia A three times per week. Hemophilia B twice per week	Joint bleeds. Hemarthrosis.	
Pettersson 1981	Retrospective observational study. Historical control.	Country: Sweden. Cases: 44 with severe hemophilia A. 6 with severe hemophilia B	Hemophilia A: AHF-Kabi. Hemophilia B: Preconativ (KabiVitrum)	Radiological joint score.	
Ramsay 1973	Prospective observational study.	Country: UK. Cases: severe hemophilia A or B. Enrolled: Hemophilia A = 2, Hemophilia B =1	Clotting factor concentrate: cryoprecipitate.	Bleeding episodes.	
Royal 2002	Retrospective observational study. Parallel groups.	Country: Europe. Cases: prophylaxis regimen (varies between HTC). Controls: on-demand. Enrolled: Cases: 313. Controls: 590	Clotting factor concentrate in prophylactic or on-demand regimen	QoL Instrument: SF-36.	
Schimpf 1977	Prospective observational study. Crossover study.	Country: Germany. Cases: severe hemophilia A. Enrolled: 6.	Clotting factor concentrate. Treatment A: 1 x 36 U/kg body weight and week. Treatment B: 2 x 18 U/kg body	Bleeding episodes.	

Table 1. Additional non-randomised observational clinical studies (*Continued*)

			weight and week. Treatment C: 3 x 12 U/kg body weight and week		
Schobess 2008	Prospective observational study.	Country: Germany. Cases: Preaviously untreated patients with severe hemophilia A. Enrolled: 109 (42 primary prophylaxis: 67 secondary prophylaxis)	At discretion of the participating centre. Median 40 IU/kg twice a week	Bleeding episodes Joint preservation Development of target joint	
Smith 1996	Retrospective observational switch study.	Country: USA. Cases: episodic infusions. Controls: prophylactic infusions. Enrolled: 27. Controls = 70	Clotting factor concentrate.	Bleeding episodes. Incremental cost effectiveness.	
Szucs 1996	Prospective observational study.	Country: Germany. Cases: moderate or severe hemophilia. Number enrolled: moderate = 4, severe = 46	Clotting factor concentrate. Treatment programs: (i) on-demand; (ii) pure prophylaxis; (iii) modified prophylaxis	Joint bleeds. QoL (SF-36). Cost of care. Cost effectiveness.	
Tagliaferri 2008	Retrospective observational switch study.	Country: Italy. Cases: adolescents and adults severe hemophilia patients.Number enrolled= 84	Clotting factor concentrate.	Joint bleeds. Orthopedic and radiologic score, QoL, days lost from work/school, usage of clotting factor concentrates	
Tusell 2002	Retrospective observational study.	Country: Spain. Cases: severe hemophilia A or B. Enrolled: Hemophilia A = 423. Hemophilia B = 88	Clotting factor concentrate.	Bleeding episodes.	
Van den Berg 2001	Retrospective observational study. Single arm.	Country: Netherlands. Case: severe hemophilia A or B. Enrolled:	Clotting factor concentrate.	Bleeding episodes.	

Table 1. Additional non-randomised observational clinical studies (*Continued*)

		hemophilia A = 70. hemophilia B = 5			
Wu 2011	Prospective observational study. Single arm.	Country: China. Case: severe and moderate hemophilia. Enrolled: Hemophilia A = 34	Clotting factor concentrate. Low dose (10 IU/kg/x2 week)	Bleeding episodes. Cost effectiveness.	

IU: international units
QoL: quality of life

APPENDICES

Appendix 1. Search strategies for current version of the review

Database	Strategy
The Cochrane Central Register of Controlled Trials (CENTRAL) Issue 4, 2010	#1 hemophilia #2 haemophilia #3 (#1 or #2)
MEDLINE (Ovid) 2003 -14th Feb 2011	1 (inherit$ or heredit$ or congenital or severe).mp. (778243) 2 (blood adj5 disorder).mp. (1569) 3 (hemophili$ or haemophili$).mp. (19425) 4 bleed$.mp. (107960) 5 exp blood coagulation disorders/ (72445) 6 exp coagulation protein disorders/ (25400) 7 coagulation factor deficien$.mp. (180) 8 christmas disease$.mp. (215) 9 or/2-8 (174132) 10 1 and 9 (25842) 11 (factor adj3 concentrat$).mp. (7116) 12 plasma.mp. (594094) 13 cryoprecipitat$.mp. (1977) 14 lyophilized plasma.mp. (76) 15 (recombinant adj3 factor$).mp. (6770) 16 or/11-15 (605334) 17 prevent$.mp. (730741) 18 exp primary prevention/ (95951)

(*Continued*)

	19 prophyla$.mp. (104804) 20 or/17-19 (878004) 21 ("factor 8" or "Factor 8" or "f viii" or "f VIII" or "F VIII" or fviii or fVIII or FVIII or f-viii or f-VIII or F-VIII or "factor viii" or "factor VIII" or "Factor VIII" or "factor 9" or "Factor 9" or "f ix" or "f IX" or "F IX" or fix or fIX or FIX or f-ix or f-IX or F-IX or "factor ix" or "factor IX" or "Factor IX").mp. (27545) 22 and/10,16,20-21 (279) 23 22 (279) 24 limit 23 to yr="2003 -Current" (145)
EMBASE (Ovid) 2003 - 14th Feb 2011	1 (hemophili$ or haemophili$).mp. (24152) 2 blood disease/ (4208) 3 blood disorder$.mp. (711) 4 blood clotting disorder/ (19027) 5 "blood coagulation disorder".mp. (65) 6 "coagulation protein disorder".mp. (0) 7 exp blood clotting factor deficiency/ (33506) 8 coagulation factor deficien$.mp. (255) 9 exp congenital blood clotting disorder/ (27042) 10 christmas disease$.mp. (194) 11 bleed$.mp. (232718) 12 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 (275630) 13 (inherit$ or heredit$ or congenital or severe).mp. (1157640) 14 12 and 13 (39178) 15 exp blood clotting factor concentrate/ (531) 16 coagulation factor deficien$.mp. (255) 17 fresh frozen plasma.mp. (7327) 18 exp plasma/ (51835) 19 plasma.mp. (696927) 20 cryoprecipitat$.mp. (3260) 21 lyophilized plasma.mp. (97) 22 exp recombinant blood clotting factor 8/ (1707) 23 exp recombinant blood clotting factor 9/ (445) 24 recombinant factor$.mp. (2207) 25 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 (701280) 26 exp prevention/ (731271) 27 exp primary prevention/ (19405) 28 prevent$.mp. (1008998) 29 exp prophylaxis/ (535291) 30 prophyla$.mp. (156872) 31 26 or 27 or 28 or 29 or 30 (1524847) 32 ("factor 8" or "Factor 8" or "f viii" or "f VIII" or "F VIII" or fviii or fVIII or FVIII or f-viii or f-VIII or F-VIII or "factor viii" or "factor VIII" or "Factor VIII" or "factor 9" or "Factor 9" or "f ix" or "f IX" or "F IX" or fix or fIX or FIX or f-ix or f-IX or F-IX or "factor ix" or "factor IX" or "Factor IX").mp. (35580) 33 exp blood clotting factor 8/ (15240)

(*Continued*)

	34 exp blood clotting factor 9/ (5758) 35 32 or 33 or 34 (35580) 36 14 and 25 and 31 and 35 (473) 37 limit 36 to yr="2003 -Current" (329)

Appendix 2. Search strategies for previous versions of the review

Database	Strategy
The Cochrane Central Register of Controlled Trials (CENTRAL) 1948-2003	#1 Therapeutics #2 Intervention studies #3 (therap* or intervention* or treat*) #4 (#1 or #2 or #3) #51 hemophilia #62 haemophilia #73 (#51 or #62) #8 (#4 and #7)
MEDLINE (Ovid) Jan 1966-May 2003	1. (inherit$ or heredit$ or congenital).mp. 2. (blood adj5 disorder).mp. 3. (hemophili$ or haemophili$).mp. 4. bleed$.mp. 5. exp blood coagulation disorders/ 6. exp coagulation protein disorders/ 7. coagulation factor deficien$.mp. 8. christmas disease$.mp. 9. or/2-8 10. 1 and 9 11. (factor adj3 concentrat$).mp. 12. plasma.mp. 13. cryoprecipitat$.mp. 14. lyophilized plasma.mp. 15. (recombinant adj3 factor$).mp. 16. or/11-15 17. prevent$.mp. 18. exp primary prevention/ 19. prophyla$.mp. 20. or/17-19 21. ("factor 8" or "f viii" or fviii or "factor viii" or "factor 9" or "f ix" or fix or "factor ix").mp. 22. and/10,16,20-21
EMBASE (Ovid) 1988- May 2003	1. (hemophili$ or haemophili$).mp. 2. blood disease/ 3. blood disorder$.mp. 4. blood disorder$.mp.

(*Continued*)

	5. blood clotting disorder/ 6. "blood coagulation disorder".mp. 7. "coagulation protein disorder".mp. 8. exp blood clotting factor deficiency/ 9. coagulation factor deficien$.mp. 10. exp congenital blood clotting disorder/ 11. christmas disease$.mp. 12. bleed$.mp. 13. or/1-12 14. (inherit$ or heredit$ or congenital).mp. 15. 13 and 14 16. exp blood clotting factor concentrate/ 17. coagulation factor deficien$.mp. 18. fresh frozen plasma.mp. 19. exp plasma/ 20. plasma.mp. 21. cryoprecipitat$.mp. 22. lyophilized plasma.mp. 23. exp recombinant blood clotting factor 8/ 24. exp recombinant blood clotting factor 9/ 25. recombinant factor$.mp. 26. or/16-25 27. exp prevention/ 28. exp primary prevention/ 29. prevent$.mp. 30. exp prophylaxis/ 31. prophyla$.mp. 32. or/27-31 33. ("factor 8" or "f viii" or fviii or "factor viii" or "factor 9" or "f ix" or fix or "factor ix").mp. 34. exp blood clotting factor 8/ 35. exp blood clotting factor 9/ 36. or/33-35 37. and/15,26,32,36

WHAT'S NEW

Last assessed as up-to-date: 9 July 2011.

Date	Event	Description
10 July 2011	New search has been performed	Two new trials have been incorporated into the review (Gringeri 2011; Manco-Johnson 2007).

(*Continued*)

10 July 2011	New citation required and conclusions have changed	The conclusions of the review have changed from there being insufficient evidence assessing the use of prophylactic clotting factor concentrates, to there being evidence that the use of these concentrates is effective in decreasing the frequency of joint bleeds and in partially preventing or slowing down the development of arthropathy The number of participants included in the review has increased from 37 to 142, with two new studies added Alfonso Iorio (previously a co-author) is now lead author on this review and Kent Stobart (previously lead-author) is now a co-author. John Wu has stepped down from the review and Emanuela Marchesini, Maura Marcucci and Anthony Chan are new co-authors

HISTORY

Protocol first published: Issue 1, 2002

Review first published: Issue 2, 2005

Date	Event	Description
7 October 2009	Amended	Please note: We are aware that the update of this review is overdue. The original review team has stepped down and a new review team is in place and working on the update. The updated version of this review will be published in 2010
31 October 2008	Amended	Converted to new review format.
1 February 2006	New search has been performed	The text of the Reviewers' Conclusions in the abstract has been altered to make clear that there is a lack of evidence from randomised controlled trials for the use of prophylaxis. No new references were found in the latest search for this review

CONTRIBUTIONS OF AUTHORS

Kent Stobart: protocol development; study selection; data extraction; data entry; development of final review.

Alfonso Iorio: study selection; data extraction; development of final review.

John K. Wu (previous author): protocol development.

New roles in the update

Alfonso Iorio: updated manuscript drafting; development of final review.

Emanuela Marchesini: study selection; data extraction; updated manuscript drafting; development of final review.

Maura Marcucci: study selection; data extraction.

Anthony Chan: development of final review.

Kent Stobart: development of final review.

DECLARATIONS OF INTEREST

None known.

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Internal sources

- Alberta Research Centre for Child Health Evidence, Canada.

This support was received for the firs edition of this systematic review

External sources

- Association of Hemophilia Clinic Directors of Canada, Canada.

This support was received for the firs edition of this systematic review

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

In the 2011 update we undertook a *post hoc* sensitivity analyse for adverse events.

INDEX TERMS

Medical Subject Headings (MeSH)

Blood Coagulation Factors [*therapeutic use]; Factor VIII [*therapeutic use]; Hemarthrosis [*prevention & control]; Hemophilia A [*complications]; Hemophilia B [*complications]; Randomized Controlled Trials as Topic

MeSH check words

Humans