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Clotting factor concentrates for preventing bleeding and bleeding-related complications in previously treated individuals with haemophilia A or B (Review)

Olasupo OO, Lowe MS, Krishan A, Collins P, Iorio A, Matino D

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[Intervention Review]

Clotting factor concentrates for preventing bleeding and bleeding-related complications in previously treated individuals with haemophilia A or B

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ABSTRACT

Background

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

Objectives

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

Search methods

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

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

Selection criteria

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

Data collection and analysis

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

Main results

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

Comparison of two or more prophylactic regimens

For trials comparing one prophylaxis regimen to another, given the heterogeneity of the data, none of the data were pooled for this comparison. Considering the individual trials, three trials reported the primary outcome of joint bleeding, and none showed a dfference between dosing regimens (low-certainty evidence). For the secondary outcome of total bleeding events, prophylaxis with a twice-weekly regimen of FIX likely results in reduced total bleeds compared to a once-a-week regimen of the same dose, mean difference (MD) 11.2 (5.81 to 16.59) (one trial, 10 participants, low-certainty evidence).

Transient low-titer anti-FVIII inhibitors were reported in one of the trials. Blood-transmitted infections were not identified. Other adverse events reported include hypersensitivity, oedema, and weight gain. These were, however, rare and unrelated to study drugs (very low-certainty evidence).

Comparison of prophylactic and on-demand regimens

Four of the trials (258 participants) had arms that compared prophylaxis to on-demand treatment. Prophylaxis may result in a large decrease in the number of joint bleeds compared to on-demand treatment, MD -30.34 (95% CI -46.95 to -13.73) (two trials, 164 participants, low-certainty evidence). One of these trials (84 participants) also reported the long-term effects of prophylaxis versus on-demand therapy showing improved joint function, quality of life, and pain; but no differences between groups in joint structure when assessed by magnetic resonance imaging (MRI).

In one trial (84 participants) validated measures for joint health and pain assessment showed that prophylaxis likely improves joint health compared to an on-demand regimen with an estimated change difference of 0.94 points (95% CI 0.23 to 1.65) and improves total pain scores, MD -17.20 (95% CI -27.48 to -6.92 (moderate-certainty evidence).

Two trials (131 participants) reported that prophylaxis likely results in a slight increase in adverse events, risk ratio 1.71 (1.24 to 2.37) (moderate-certainty evidence). No inhibitor development and blood-transmitted infections were identified.

Overall, the certainty of the body of evidence was judged to be low because of different types of bias that could have altered the effect.

Authors' conclusions

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

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

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

PLAIN LANGUAGE SUMMARY

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

Review question

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

Background

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

Search date

Date of last search: 24 February 2021.

Study characteristics

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

Key results

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

Certainty of the evidence

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

SUMMARY OF FINDINGS

Summary of findings 1. Comparison of two prophylaxis regimens

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

Patient or population: children or adults with hemophilia A or B

Settings: outpatient

Intervention: secondary prophylaxis

Comparison: secondary prophylaxis

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Certainty of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Prophylaxis regimen	Prophylaxis regimen				
Number of joint bleeding episodes per year (AJBR) Follow-up: 12 months	No difference was seen between prophylaxis regimens in any of the studies. Thrice-weekly higher dose prophylaxis regimen compared to a twice-weekly lower dose regimen, MD -1.70 (95% CI -5.06 to 1.66) (LEOPOLD II 2015). PK-guided prophylaxis targeting trough levels of 8% to 12% compared to targeting trough levels of 1% to 3%, MD -1.50 (95% CI -3.54 to 0.54) (n = 115 participants) (PROPEL III 2020). Low frequency prophylaxis (100 IU / kg once a week) compared to standard frequency regimen (50 IU / kg twice a week, MD of 1.70 (95% CI -1.09 to 4.49) (Valentino 2014).		N/A	219 participants (3 trials)	⊕⊕⊖⊖ **low** [a]	We were unable to combine results in a meta-analysis due to the different prophylaxis regimens used in each trial.
Number of total bleeds per year (ABR) Follow-up: 12 months	There was no difference in total number of bleeds between prophylactic regimens in five trials (Aronstam 1977; LEOPOLD II 2015; PROPEL III 2020; Valentino 2012; Valentino 2014). A twice-a-week regimen (7.5 IU/kg) was favoured over a once-a-week regimen (15 IU/kg), MD 11.20 (5.81 to 16.59) (Morfini 1976) and a prophylaxis group with dosing producing at least 0.25 IU/mL of factor VIII showed a significant reduction in overall bleed-		N/A	310 participants (7 trials)	⊕⊖⊖⊖ **low**[b,c]	Due to heterogeneity of intervention and design, none of the trials we were unable to combine data from any of the trials (LEOPOLD II 2015).

	ing frequency compared to a dosing regimen producing at least 0.01IU/mL once weekly, MD 3.44 (95% CI 2.42 to 4.46) (Aronstam 1976).				
Treatment-related adverse events Follow-up: 32 weeks to 12 months	One trial reported no difference in total treatment-emergent adverse events, MD 1.00 (95% CI 0.54 to 1.84) at 32 weeks (Valentino 2014). A further trial reported no difference between treatment regimens in mean rates of adverse events (Valentino 2012). In the study targeting different trough levels, no serious adverse event was treatment-related in the arm targeting trough levels of of 1% to -3%, and in the arm targeting trough levels of 8% to -12%, one serious adverse event was estimated to be treatment-related (PROPEL III 2020).	N/A	223 participants (3 trials)	⊕⊖⊖⊖ **very low** [a,d]	Three trials did not report the rate of adverse events by treatment groups (Aronstam 1977; LEOPOLD II 2015; Morfini 1976). The LEOPOLD II trial reported three treatment related adverse events but gave no further detail (LEOPOLD II 2015). There was no reported inhibitor development reported in six of the trials in this comparison (Aronstam 1976; Aronstam 1977; LEOPOLD II 2015; Morfini 1976; Valentino 2012; Valentino 2014).

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

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

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

Summary of findings 2. Prophylaxis with standard therapeutic factor concentrate compared to pegylated liposome FVIII formulation

Prophylaxis with standard clotting factor concentrate compared with pegylated liposome FVIII formulation for previously treated individuals with haemophilia A

Patient or population: children or adults with hemophilia A

Settings: outpatient

Intervention: prophylaxis using investigational BAY 79-4980

Comparison: standard secondary prophylaxis

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Certainty of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Prophylaxis using investigational BAY 79-4980	Standard prophylaxis				
AJBR Follow-up: 12 months	The mean number of joint bleeding in the prophylaxis arm using investigational drug BAY 79-4980 was 12.2.	The mean number of joint bleeding in the standard prophylaxis regimen (5.0), was 7.20 lower (11.01 lower to 3.39 lower)	MD -7.20 (-11.01 to -3.39)	143 participants (1 trial)	⊕⊕⊖⊖ **low** a,b	More participants withdrew consent in the investigational drug arm. The trial was prematurely discontinued by the sponsor based on the recommendation of an independent data and safety monitoring board.
ABR Follow-up: 12 months	The mean number of total bleeds in the prophylaxis arm using investigational drug BAY 79-4980 was 15.	The mean number of total bleeds in the standard prophylaxis regimen (5.8), was 9.20 lower (13.07 lower to 5.33 lower)	MD -7.20 (-13.07 to -5.33)	143 participants (1 trial)	⊕⊕⊖⊖ **low** a,b	More participants withdrew consent in the investigational drug arm. The trial was prematurely discontinued by the sponsor based on the recommendation of an independent data and safety monitoring board.
Any reported adverse effects Follow-up: 12 months	No specific information was given about the presence/absence of adverse events in the BAY 70-4980 group.	One participant in the prophylaxis group reported three serious adverse events, which were deemed to be drug related.	Not estimable	143 participants (1 trial)	⊕⊕⊖⊖ **low** a,b	

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

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

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

Summary of findings 3. Prophylaxis regimen versus on-demand treatment

Prophylaxis regimen compared with on-demand treatment for previously treated individuals with haemophilia A or B

Patient or population: children and adults with haemophilia A or B

Settings: outpatient

Intervention: secondary prophylaxis

Comparison: on-demand treatment

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Certainty of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	On-demand treatment	Prophylaxis regimen				
Number of joint bleeding episodes or joint bleeding frequency Follow-up: 12 months	The mean number of joint bleeding episodes in the on-demand treatment group was 34	The mean number of joint bleeding episodes in the prophylaxis regimen group was 30.34 lower (46.95 lower to 13.73 lower)	MD -30.34 (-46.95 to -13.73)	164 (2 trials)	⊕⊕⊖⊖ **low** [a,b]	The data from the A-LONG trial suggests the same; however, these data were reported with medians, hence could not be included in the analysis.
Number of total bleeds per year	The mean number of total bleeds in the	The mean number of total bleeds in the prophylaxis regimen group was	MD -40.24 (-64.04 to -16.44)	164 (2 trials)	⊕⊕⊖⊖ **low** [a,b]	The data from the A-LONG trial suggests the same effect; however, these data were reported

or bleeding frequency Follow-up: 12 months	on-demand treatment group was 44	40.24 lower (64.04 lower to 16.44 lower)				with medians, hence could not be included in the analysis (A-LONG 2014). When comparing the overall bleeding frequency in 9 participants in the Aronstam cross-over trial, there was a significant reduction in the overall bleeding frequency in the prophylaxis group
Any reported adverse events Follow-up: 12 months	415 per 1000 (27 per 65)	712 per 1000 (47 per 66) The number of participants with adverse events in the prophylaxis regimen group was 1.71 times higher (1.24 times higher to 2.37 times higher)	RR 1.71 (1.24 to 2.37)	131 (2 trials)	⊕⊕⊕⊖ **moderate** [a]	The 2 trials were open-label trials with unclear risk of bias for randomised sequence generation (A-LONG 2014; SPINART 2013). The LEOPOLD II trial did not give the distribution of adverse events across groups, but there were 3 reported treatment-related adverse events while no participant developed an inhibitor during the course of treatment (LEOPOLD II 2015). In the 1976 Aronstam trial, one participant developed antigen-negative hepatitis and was removed from the remaining duration of the trial (Aronstam 1976).

*Th\e basis for the assumed risk (e.g. the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).
CI: confidence interval; **RR**: risk ratio; **MD**: mean difference

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

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

BACKGROUND

Description of the condition

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

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

Description of the intervention

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

Factor concentrates are generally administered according to two treatment regimens:

1. on-demand (also termed episodic) treatment, where individuals receive clotting factor only in response to a bleeding event; or
2. prophylaxis treatment, where individuals receive regular infusions of clotting factor with the aim to prevent bleeds.

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

How the intervention might work

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

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

Why it is important to do this review

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

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

OBJECTIVES

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

Short-term outcomes

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

Long-term outcomes

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

METHODS

Criteria for considering studies for this review

Types of studies

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

Types of participants

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

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

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

Types of interventions

We compared intravenous clotting factor concentrates administered as prophylactic treatment in any formulation (e.g. fresh frozen plasma, cryoprecipitate, lyophilised plasma-derived clotting factor concentrate, or recombinant clotting factor concentrate), any concentration, any frequency and any dose, with no treatment, placebo, on-demand treatment, or with one or more different prophylaxis regimens. We did not include trials of a single treatment and at least one treatment must have been a clotting factor concentrate.

Therefore the anticipated comparison groups were as follows:

- prophylaxis versus prophylaxis with a different regimen;
- prophylaxis versus on-demand treatment;
- prophylaxis versus no treatment;
- prophylaxis versus placebo.

Types of outcome measures

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

Primary outcomes

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

Secondary outcomes

1. Number of total bleeding episodes or total bleeding frequency during the trial period
2. Pain scores
3. Radiologic joint score or radiologic measurements or descriptions of joint damage
4. Clotting factor concentrate plasma levels
5. Time loss to school or employment
6. Integration into society (i.e. absenteeism)
7. Scores on scales recording feeling of well-being and global functioning
8. Economic data: cost-effectiveness, cost-benefit, cost-utilisation, cost-minimisation
9. Any reported adverse effects or toxicity of clotting factor concentrates (e.g. inhibitors, reactions, transmission of infection)

Search methods for identification of studies

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

Electronic searches

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

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

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

We also searched the following databases and trial registries:

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

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

Searching other resources

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

The following conference proceedings were also hand searched:

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

Data collection and analysis

Selection of studies

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

Data extraction and management

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

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

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

Assessment of risk of bias in included studies

The authors used the tool in RevMan 5.4 to measure the risk of bias and to produce summary figures (RevMan 2020).

The authors assessed the risk of bias using the 'Risk of bias' assessment tool as documented in section 8.5 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2017). The following domains were assessed as having either a low, high, or unclear risk of bias:

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

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

Measures of treatment effect

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

Unit of analysis issues

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

Dealing with missing data

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

Assessment of heterogeneity

Given the small number of trials that were included in a meta-analysis in this review, we did not assess for heterogeneity in most of the analyses. However, where sufficient trials were included in a meta-analysis, we identified the presence of statistical heterogeneity using the Chi^2 value. We also reported the I^2 value as a measure of heterogeneity in the meta-analysis. We applied the following thresholds, as suggested in the *Cochrane Handbook for Systematic Reviews of Interventions* (Deeks 2021):

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

Assessment of reporting biases

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

Data synthesis

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

Subgroup analysis and investigation of heterogeneity

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

Sensitivity analysis

We were unable to aggregate data for a majority of outcomes in this review. However, if there are a sufficient number of eligible and included trials, we will undertake a sensitivity analysis by looking at trials with a low risk of bias versus a high risk of bias, as measured above.

Summary of findings and assessment of the certainty of the evidence

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

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

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

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

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

RESULTS

Description of studies

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

Results of the search

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

We excluded a further 251 references to 89 trials.

Included studies

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

Trial design

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

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

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

Types of participants

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

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

Types of interventions

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

Comparison between two prophylaxis regimens

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

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

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

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

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

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

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

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

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

Prophylaxis regimen compared to on-demand (episodic) treatment

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

SPINART 2013: on-demand treatment administered on the basis of investigator recommendations versus prophylaxis treatment administered at a dosage of 25 IU/kg three times per week. This amount could be increased to a maximum of 35 IU/kg over two years in participants with 12 or more bleeding episodes per year on the trial.

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

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

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

Types of outcomes

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

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

Excluded studies

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

We excluded 89 trials (251 references) from this review. A total of 40 trials were excluded because they were not randomised studies, including 22 prospective and 18 retrospective observational studies. 15 trials had an intervention arm that included non-clotting factors, e.g. concizumab (n = 9), emicizumab (n = 5), investigational RNA inteference therapeutic (n = 1). Six trials were excluded because they were conducted in participants with

inhibitors, 13 additional trials were not eligible because they included individuals on primary prophylaxis. 10 trials assessed pharmacokinetic parameters and four were reported in conference abstracts only and detailed descriptions of trial participants were not available. One trial was a feasibility study with no hypothesis testing, no useable results and concluded that the trial lacked feasibility.

Risk of bias in included studies

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

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

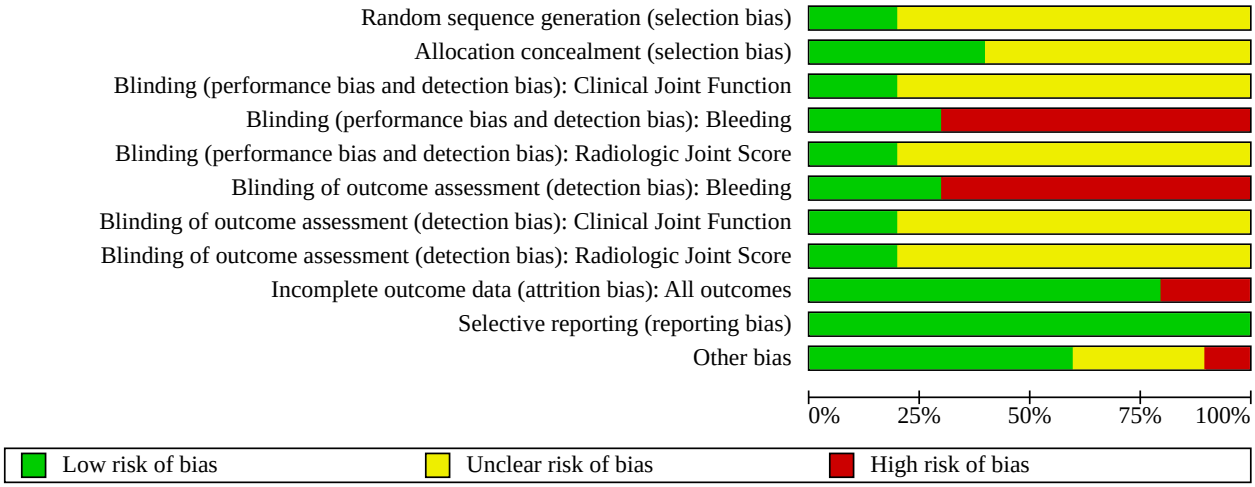
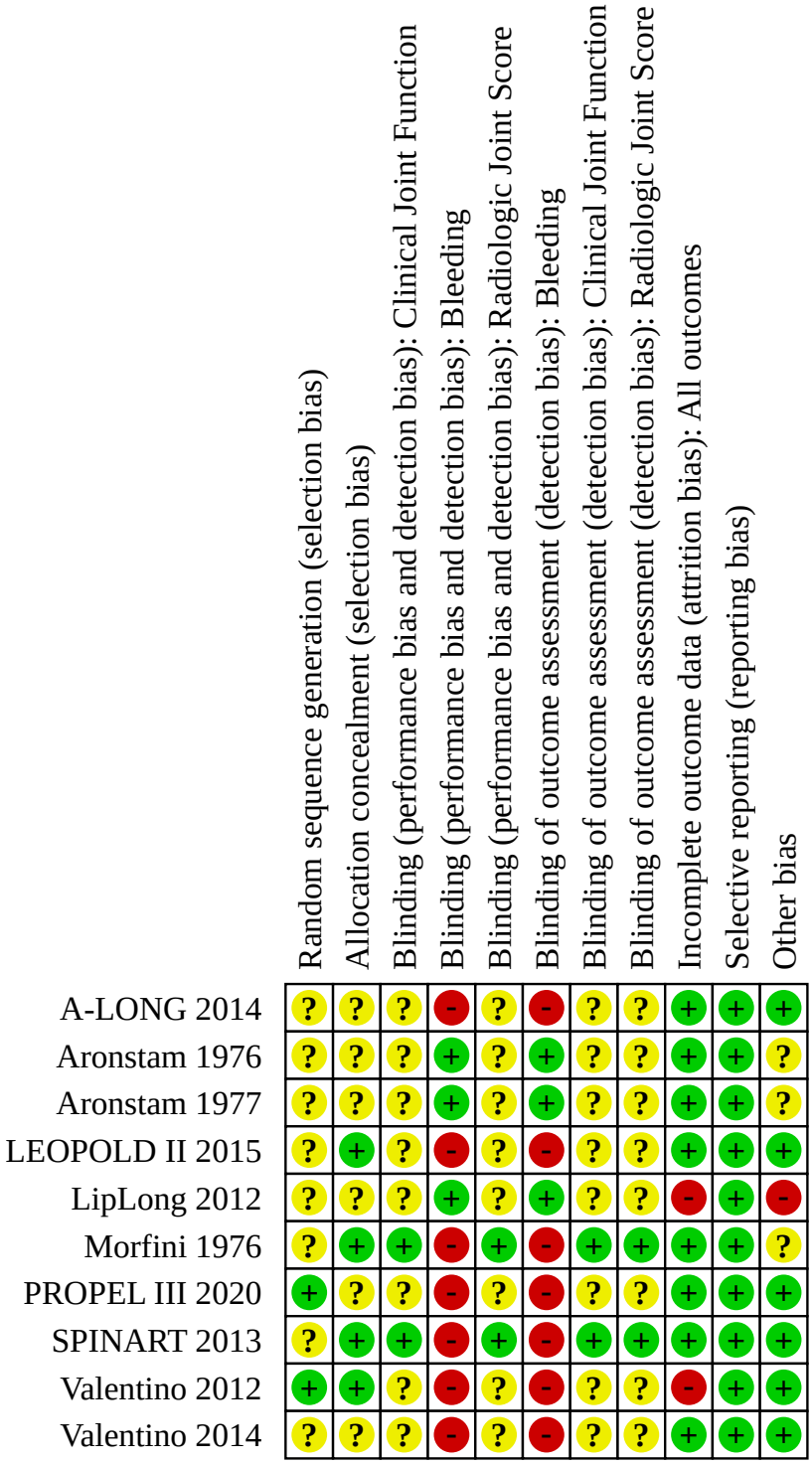


Figure 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.



Allocation

Random sequence generation

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

Allocation concealment

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

Blinding

Performance and detection bias

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

Incomplete outcome data

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

Selective reporting

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

Other potential sources of bias

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

Effects of interventions

See: **Summary of findings 1** Comparison of two prophylaxis regimens; **Summary of findings 2** Prophylaxis with standard therapeutic factor concentrate compared to pegylated liposome FVIII formulation; **Summary of findings 3** Prophylaxis regimen versus on-demand treatment

Comparison between two prophylaxis regimens

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

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

Primary outcomes

1. Number of joint bleeding episodes or joint bleeding frequency

Three included trials reported on joint bleeding (LEOPOLD II 2015; PROPEL III 2020; Valentino 2014). The LEOPOLD II trial found no difference in joint bleed prevention when a thrice-weekly, higher-dose prophylaxis regimen was compared to a twice-weekly (at 12 months follow-up) lower-dose prophylaxis, MD -1.70 (95% CI -5.06 to 1.66) (59 participants) (moderate-certainty evidence) (Analysis 1.1) (LEOPOLD II 2015). Comparing a PK-guided prophylaxis regimen targeting trough levels of 8% to 12% or 1% to 3% in the PROPEL III trial, no difference was also found between the two prophylaxis arms (at 12 months follow-up); MD -1.50 (95% CI -3.54 to 0.54) (115 participants) (moderate-certainty evidence) (Analysis 1.2) (PROPEL III 2020). No difference was also seen in spontaneous joint bleeds between the two regimens, MD -1.50 (95% CI -3.22 to 0.22) (Analysis 1.3) (PROPEL III 2020). In the Valentino 2014 trial, no difference was also reported in annualized joint bleeding in the low-frequency prophylaxis arm (100 IU/kg once weekly) compared to the standard frequency regimen (50 IU/kg twice weekly); MD of

1.70 (95% CI -1.09 to 4.49) (50 participants) (Analysis 1.4) (Valentino 2014).

2. Orthopedic joint score or clinical joint function

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

3. QoL on validated scales

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

Secondary outcomes

1. Number of total bleeding episodes or total bleeding frequency

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

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

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

When comparing the overall bleeding frequency in nine participants in the Aronstam cross-over trial, there was a significant reduction in the overall bleeding frequency in the prophylaxis group with dosing producing at least 0.25 IU/mL of factor VIII compared to the dosing producing at least 0.01 IU/mL once weekly, MD 3.44 (95% CI 2.42 to 4.46) (Analysis 1.9) (Aronstam 1976).

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

2. Pain scores

None of the included trials reported this outcome.

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

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

4. Clotting factor concentrate plasma levels

One included trial (115 participants) assessed clotting factor concentrate plasma levels (PROPEL III 2020). In this trial, initial PK assessments showed mean (SD) plasma half-lives (t½) of 15.3 (4.2) and 14.7 (5.1) hour in the 1% to 3% and 8% to 12% arms to be respectively. FVIII activity was a median (Q1 to Q3) 17.30 (15.2-21.7) and 35.0 (29.2 - 40.9) IU/dL during the first six months, and 17.30 (14.5 - 22.4) and 30.9 (24.9 - 41.2) IU/dL during the second six months for the 1% to 3% and 8% to 12% arms, respectively. Observed FVIII activity trough levels during the second six months were within the intended ranges of 1% to 3% and 8% to 12%; with median FVIII troughs ranging from 2.1 to 3.0 IU/dL and 10.7 to 11.7 IU/dL.

5. Time loss to school or employment

None of the included trials reported this outcome.

6. Integration into society

None of the included trials reported this outcome.

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

None of the included trials reported this outcome.

8. Economic data

None of the included trials reported this outcome.

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

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

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

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

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

In the 2012 Valentino trial that compared standard prophylaxis to a PK-tailored regimen, there was no difference in mean rates of

adverse events between the two regimens at 12 months follow-up, MD 0.27 (95% CI -0.44 to 0.98) (Analysis 1.12) (Valentino 2012).

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

We assessed the certainty of the evidence as very low.

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

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

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

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

Primary outcomes

1. Number of joint bleeding episodes or joint bleeding frequency

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

2. Orthopedic joint score or clinical joint function

This outcome was not reported.

3. QoL on validated scales

This outcome was not reported.

Secondary outcomes

1. Number of total bleeding episodes or total bleeding frequency

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

2. Pain scores

This outcome was not reported.

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

This outcome was not reported.

4. Clotting factor concentrate plasma levels

This outcome was not reported.

5. Time loss to school or employment

This outcome was not reported.

6. Integration into society

This outcome was not reported.

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

This outcome was not reported.

8. Economic data

This outcome was not reported.

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

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

Prophylaxis regimen compared to on-demand (episodic) treatment

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

Four trials were reported on this comparison (A-LONG 2014; LEOPOLD II 2015; SPINART 2013; Valentino 2014). In the Valentino 2012 trial, while comparing prophylaxis and on-demand treatments, the comparison was not across the randomised allocation and hence was not included in the following analyses (Valentino 2012). Of note, this trial found that any type of secondary prophylaxis (standard versus PK-adjusted) was significantly protective for total bleeding and joint bleeding when compared to episodic treatment ($P < 0.0001$). Also, this trial reported a significant improvement in QoL for the bodily pain (4.1, $P = 0.0007$) and physical component score (PCS) (3.6, $P = 0.0002$) domains as measured on the SF36v1 scale for prophylaxis (any type) versus on-demand treatment (Valentino 2012).

Primary outcomes

1. Number of joint bleeding episodes or joint bleeding frequency

All trials reported this outcome.

Data from two combined trials suggest that the use of a prophylaxis regimen significantly decreases the number of joint bleeds when compared to on-demand treatments, MD -30.34 (95% CI -46.95

to -13.73) (low-certainty evidence) (Analysis 3.1) (LEOPOLD II 2015; SPINART 2013). Considerable heterogeneity was seen in this analysis (I^2 = 87%). The data from the A-LONG trial suggest the same effect; however, these data were reported with medians, hence could not be included in the above analysis (A-LONG 2014).

2. Orthopedic joint score or clinical joint function

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

3. QoL on validated scales

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

Secondary outcomes

1. Number of total bleeding episodes or total bleeding frequency

Data from two combined trials suggest that the use of a prophylaxis regimen is significantly more protective than on-demand treatment when preventing bleeding episodes, MD -40.24 (95% CI -64.04 to -16.44) (low-certainty evidence) (Analysis 3.3) (LEOPOLD II 2015; SPINART 2013). Considerable heterogeneity was also seen in this analysis (I^2 = 93%). Total bleeding rates in the A-LONG trial also suggest a similar effect and were also not included in this analysis as data were reported as medians (A-LONG 2014).

2. Pain scores

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

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

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

4. Clotting factor concentrate plasma levels

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

5. Time loss to school or employment

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

6. Integration into society

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

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

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

8. Economic data

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

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

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

DISCUSSION

Summary of main results

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

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

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

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

When considering the comparison between two prophylaxis regimens, no individual prophylactic treatment schedule investigated proved to be superior at preventing total bleeding events in people in haemophilia A. Finally, standard prophylaxis may be more effective at preventing joint and total bleeding events than the experimental drug BAY 79-4980 (low-certainty evidence). Individuals with hemophilia B were included in two trials (Morfini 1976; Valentino 2014). The Morfini trial showed that a twice-weekly regimen of prophylaxis may be superior to a once-weekly regimen in decreasing total bleeding incidence, but these results should be interpreted cautiously given the small number of participants, the extremely low dose used and the fact that none of the participants were blinded to their treatment allocation (low-certainty evidence). The results of the Valentino 2014 trial did not establish a superior prophylaxis regimen; however, this trial did show that prophylaxis at any dosing schedule was superior to on-demand treatment to prevent spontaneous bleeds and joint bleeding incidence (Valentino 2014). When considering these data, it must be kept in mind that the bleeding data were aggregated for only 16 weeks, and the annualized bleeding rates were extrapolated from this time period.

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

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

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

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

1. diversity in participant characteristics and treatment regimens; and
2. diversity in reporting methods.

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

Overall completeness and applicability of evidence

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

Quality of the evidence

Overall, we found the included trials to be at low risk or unclear risk of bias for most domains. In particular, while all trial reports indicated that the trial was randomised, only four of the 10 included trials indicated the method used for random sequence generation (LEOPOLD II 2015; PROPEL III 2020; SPINART 2013; Valentino 2012), with only two were assessed as having a low risk of bias for the domain (LEOPOLD II 2015; PROPEL III 2020). When considering the method for allocation concealment four trials were judged to be at low risk of bias for this domain (LEOPOLD II 2015; Morfini 1976; SPINART 2013; Valentino 2012). The remaining six trials had an unclear risk of bias (A-LONG 2014; Aronstam 1976;

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

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

Potential biases in the review process

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

Agreements and disagreements with other studies or reviews

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

AUTHORS' CONCLUSIONS

Implications for practice

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

Implications for research

Prophylaxis treatment is often considered the ideal treatment in high-resource countries. However, there are still knowledge gaps in the understanding of haemophilia treatment with respect to the ideal regimen and when to start prophylaxis. While the results of this review begin to shed light on the use of secondary prophylaxis in managing bleeding, there are still areas that require elucidation, namely the impact of late prophylaxis in people with varying degrees of arthropathy at baseline, the most cost-efficient dosage and frequency, the minimally effective dose and the role of individualised regimens to a person's bleeding pattern and activity. Further research should be undertaken to attempt to provide evidence-based data for these areas.

Future randomised controlled trials should address the following aspects:

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

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

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

A-LONG 2014

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

A-LONG 2014 *(Continued)*

	Number of participants randomised: 47.
Interventions	**Type of prophylaxis**: secondary prophylaxis; treatment arm A: sufficient dose to increase FVIII levels to >/= 0.25 IU/mL versus treatment arm B:sufficient dose to increase FVIII levels to >/= 0.1 IU/mL. 1. weekly prophylaxis: 65 IU/kg (n = 24). 2. episodic treatment: 10 - 50 IU/kg (n = 23). Trial visits occurred at screening (≤ 8 weeks), baseline, week 7, week 14, week 28, week 38, and week 52.
Outcomes	Annualised bleeding rate. Rate of inhibitor development. Adverse events.
Notes	Only randomised arms were included in this review. This trial also included an arm that used individualized prophylaxis regimen, which was not randomised. Dates of study: November 2010 - August 2012. Source of funding: Biogen Idec. ClinicalTrials.gov identifier: NCT01181128.

Risk of bias

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

A-LONG 2014 *(Continued)*

Clinical Joint Function		
Blinding of outcome assessment (detection bias) Radiologic Joint Score	Unclear risk	Not assessed.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Reasons for dropouts were discussed and were likely not due to allocated treatment.
Selective reporting (reporting bias)	Low risk	2 outcomes, which were listed in the protocol were not reported in the final paper: 1. participants with abnormal vital signs; and 2. participants with abnormal laboratory values.
Other bias	Low risk	Data analysis was conducted by the trial sponsor, Biogen Idec. As well, the initial draft was written by employees of the sponsor.

Aronstam 1976

Study characteristics	
Methods	Single-centre RCT. Cross-over trial. Boys were studied for a total of 27 boy-school terms. A 'boy-school term' is defined as the whole or any part of any school term during which an individual boy was under observation; the whole study took place during five school terms. Note: there are 3 school terms per annum in the UK.
Participants	Country: England. Participants: males with haemophilia A (factor VIII < 1%). Age range: 13 - 17 years. Number enrolled: 9.
Interventions	Factor VIII concentrate. (Blood Products Laboratory - UK). Arm A: sufficient dose to increase FVIII levels to at least 0.25 IU/mL once weekly. Arm B: sufficient dose to increase FVIII levels to no more than 0.01 IU/mL once weekly. Follow-up duration: at least 2 school terms.
Outcomes	Bleeding events or frequency.
Notes	Source of funding: National Fund for Research into Crippling Diseases, the Lord Mayor Treloar Trust and the Department of Health and Social Security.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Specifics about random sequence generation methods were not given.

Aronstam 1976 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Participants were allocated, "... at the beginning of each trial term.. by the Wessex Medical Information Unit." but no specific details were given.
Blinding (performance bias and detection bias) Clinical Joint Function	Unclear risk	Not assessed.
Blinding (performance bias and detection bias) Bleeding	Low risk	Participants were blinded to the allocation. Further, concentrate products were made to be indistinguishable, and were covered during infusion. Staff interacting with participants were also unaware of allocation.
Blinding (performance bias and detection bias) Radiologic Joint Score	Unclear risk	Not assessed.
Blinding of outcome assessment (detection bias) Bleeding	Low risk	Clinicians assessing bleeding were unaware of allocation.
Blinding of outcome assessment (detection bias) Clinical Joint Function	Unclear risk	Not assessed.
Blinding of outcome assessment (detection bias) Radiologic Joint Score	Unclear risk	Not assessed.
Incomplete outcome data (attrition bias) All outcomes	Low risk	There were no missing outcome data - all participants were included in analyses and there were no losses to follow-up.
Selective reporting (reporting bias)	Low risk	While the study protocol was not available, all expected outcomes were reported for all participants.
Other bias	Unclear risk	Unclear washout period between trial arms.

Aronstam 1977

Study characteristics	
Methods	Single-centre RCT. Cross-over trial. Trial conducted over 2 school terms. Note: there are 3 school terms per annum in the UK.
Participants	Country: England. Participants: males with haemophilia A (factor VIII < 1%). Age range: 13 - 17 years. Number enrolled: 4 All participants completed the trial.

Aronstam 1977 *(Continued)*

	Those boys who had been on the first double-blind controlled trial (Aronstam 1976) and were still available for a further 2 terms were selected. There were 4 such boys, patients 1, 3, 8, and 9 of that trial. The boys selected had each had at least one full school term off prophylaxis before entering the second trial.
Interventions	Cryoprecipitate (prepared by Wessex Regional Transfusion Centre) or Kryobulin (prepared by Serological Products, UK). Type of prophylaxis: 2 prophylaxis arms; Arm A: raise factor VIII to 15% twice weekly. Arm B: raise factor VIII to 30% twice weekly. Follow-up duration: 2 school terms
Outcomes	Bleeding events or frequency.
Notes	Source of funding: Sir William Coxon Trust and the Lord Mayor Treloar Trust.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	While authors indicated that random sequence generation was used to allocate participants to groups, no details were given.
Allocation concealment (selection bias)	Unclear risk	No details on allocation concealment were given.
Blinding (performance bias and detection bias) Clinical Joint Function	Unclear risk	Not assessed.
Blinding (performance bias and detection bias) Bleeding	Low risk	Participants and personnel were unaware of allocation.
Blinding (performance bias and detection bias) Radiologic Joint Score	Unclear risk	Not assessed.
Blinding of outcome assessment (detection bias) Bleeding	Low risk	Outcome assessors were blinded to allocation.
Blinding of outcome assessment (detection bias) Clinical Joint Function	Unclear risk	Not assessed.
Blinding of outcome assessment (detection bias) Radiologic Joint Score	Unclear risk	Not assessed.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Outcome data are present for all participants.
Selective reporting (reporting bias)	Low risk	While the trial protocol was not available, all expected outcomes were reported for all participants.

Aronstam 1977 *(Continued)*

Other bias	Unclear risk	Washout period between arms is unclear.

LEOPOLD II 2015

Study characteristics	
Methods	Multicentre RCT. Open label. Cross-over trial (see 'Notes'). Trial period:12 months. Conducted at 30 centres in 11 countries in Europe, South Africa, North America, South America, and Asia.
Participants	Males aged 12 – 65 years with severe haemophilia A who had not received regular prophylaxis treatment for > 6 consecutive months in the previous 5 years. Number randomised: 83; number included in the analysis: 80.
Interventions	1. Twice-weekly prophylaxis (20 – 30 IU/kg). 2. Thrice-weekly prophylaxis (30 – 40 IU kg). 3. On-demand treatment with BAY 81-8973: a recombinant factor VIII product. Participants were randomised to 1 of 6 treatment arms (2 low-dose prophylaxis groups, 2 high-dose prophylaxis groups, and 2 on-demand treatment groups; participants received treatment based on CS/EP or CS/ADJ for 6 months each with an intra-individual cross-over after 6 months. Follow-up duration: 3 to 8 weeks of screening and 52 weeks of follow-up on either high- or low-dose prophylaxis.
Outcomes	Annualised number of all bleeding events and adverse events.
Notes	ClinicalTrials.gov identifier: NCT01233258. This is not a traditional cross-over trial. Participants were randomised to receive on demand or prophylactic therapy with FVIII (2 different regimen); patients were crossed-over within their treatment groups but only with respect to the methods for measuring the content of FVIII in the vials (CS/EP or CS/ADJ) therefore this study has been treated as a parallel trial for the analysis, "Study drug was labeled using the chromogenic substrate assay per European Pharmacopoeia (CS/EP) or adjusted by a predefined factor to mimic results obtained with the one-stage assay (CS/ADJ). Because of differences in the detection of FVIII activity between the two potency assays, the difference in the actual amount of FVIII received for prophylaxis injections in the CS/EP and CS/ADJ periods was ~20–25%, with higher amounts received during the CS/ADJ period. Patients received treatment based on CS/EP or CS/ADJ for 6 months each with an intraindividual crossover after 6 months (Fig. 1)." Date of trial: Between January 2011 and December 2012. Source of funding: Bayer HealthCare AG, Leverkusen, Germany.

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**

LEOPOLD II 2015 *(Continued)*

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

LipLong 2012

Study characteristics	
Methods	Double-blind, 2-arm, parallel, RCT. Trial duration: 52 weeks.
Participants	Males aged 12 - 70 years with severe haemophilia A (< 1% FVIII) who were currently using on-demand treatment with any FVIII product. Number randomised = 143.
Interventions	1. Once-weekly prophylaxis with BAY 79–4980 (35 IU/kg).[N=70] 2. Thrice-weekly prophylaxis with FVIII-FS (25 IU/kg).[N=73]

LipLong 2012 *(Continued)*

Outcomes	1. total bleeding episodes. 2. joint bleeding episodes.
Notes	The study Sponsor halted the study prematurely based on the recommendations of the DSMB, indicating that the primary and secondary endpoints of non-inferiority with prophylaxis with rFVIII-FS 3 times/week would not be met. Dates of study: From June 30, 2008 through to October 5, 2010, consisting of a three- to eight-week screening period and a 52-week treatment period for each enrolled participant. Source of funding: Bayer HealthCare Pharmaceuticals, Inc.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method of randomisation is not stated.
Allocation concealment (selection bias)	Unclear risk	No details on allocation concealment were given.
Blinding (performance bias and detection bias) Clinical Joint Function	Unclear risk	Not assessed.
Blinding (performance bias and detection bias) Bleeding	Low risk	This was a double-blind trial. Investigators employed a similar looking solvent for the different prophylaxis products to blind participation and outcome assessors.
Blinding (performance bias and detection bias) Radiologic Joint Score	Unclear risk	Not assessed.
Blinding of outcome assessment (detection bias) Bleeding	Low risk	Outcome assessors were unaware of allocation.
Blinding of outcome assessment (detection bias) Clinical Joint Function	Unclear risk	Not assessed.
Blinding of outcome assessment (detection bias) Radiologic Joint Score	Unclear risk	Not assessed.
Incomplete outcome data (attrition bias) All outcomes	High risk	Efficacy outcome analyzed per protocol. Participants lost to follow-up (n = 36; 51.4% in the investigational drug arm and n = 32; 43.8% in the comparison arm) where described with higher consent withdrawal reported in the investigational drug arm (N = 8 vs N = 2).
Selective reporting (reporting bias)	Low risk	All reported outcomes in protocol were reported in paper.
Other bias	High risk	The trial was prematurely discontinued by the sponsor based on the recommendation of an independent data and safety monitoring board.

Morfini 1976

Study characteristics	
Methods	RCT. Cross-over trial. Trial period: 1 year. Time unit: 3-month cycles (A-B-A-B versus B-A-B-A).
Participants	Country: Italy. Participants: males with haemophilia B (factor IX < 1%). Age range: 5 - 45 years. Number enrolled: 10.
Interventions	Two secondary prophylaxis treatment arms. Factor IX concentrate (Bebulin). Arm A: 7.5 U/kg twice weekly. Arm B: 15 U/kg weekly. Follow-up duration: 6 months per arm.
Outcomes	Bleeding events or frequency, joint deterioration.
Notes	Study involved participants of the Research Committee of the Fondazione dell'Emofilia.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No information given.
Allocation concealment (selection bias)	Low risk	Quote: "Allocation to treatment protocols was made on the basis of random envelopes...".
Blinding (performance bias and detection bias) Clinical Joint Function	Low risk	The personnel involved in the orthopedic examinations was blinded.
Blinding (performance bias and detection bias) Bleeding	High risk	No blinding.
Blinding (performance bias and detection bias) Radiologic Joint Score	Low risk	Radiological examinations were carried out in a blinded fashion.
Blinding of outcome assessment (detection bias) Bleeding	High risk	Haematologists were aware of patients' treatment.
Blinding of outcome assessment (detection bias) Clinical Joint Function	Low risk	Quote: "Orthopedic and radiological examinations were carried out by staff who were unaware of the trial details."
Blinding of outcome assessment (detection bias)	Low risk	Quote: "Orthopedic and radiological examinations were carried out by staff who were unaware of the trial details."

Morfini 1976 *(Continued)*
Radiologic Joint Score

Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing data for primary outcome and minimal missing data for secondary outcomes.
Selective reporting (reporting bias)	Low risk	Protocol was not available but all expected outcomes were reported.
Other bias	Unclear risk	Washout period between arms was not clear.

PROPEL III 2020

Study characteristics	
Methods	Open-label, phase 3, prospective, randomized, multi-centre clinical study comparing the safety and efficacy of BAX 855 following PK-guided prophylaxis targeting two different FVIII trough levels in subjects with severe haemophilia A. Trial conducted at 62 study sites in 19 countries from November 2015 to August 2018. Participants underwent a 72- to 96-hour washout period followed by initial PK parameter evaluation. Blood samples were taken within 30 minutes before a single intravenous infusion of 60 ± 5 IU/kg rurioctocog alfa pegol and at 7 time points up to 96 ± 4 hours post-infusion.
Participants	Participants 12 - 65 years old with severe haemophilia A (FVIII level < 1%), and • an ABR ≥2 during the 12 months before study entry; • had either completed a previous rurioctocog alfa pegol study or were naïve to rurioctocog alfa pegol; and • had received prophylaxis or on-demand treatment (for breakthrough bleeds) with plasma-derived or recombinant FVIII for ≥ 150 documented exposure days. Number randomised: 115
Interventions	PwHA were randomly assigned (1:1) to 12 months of PK-guided prophylaxis with rurioctocog alfa pegol targeting FVIII troughs of either 1% - 3% (reference arm) or ~10% (8% - 12%). Targeting trough levels of 1% - 3%; N = 57. Targeting trough levels of 8% - 12%; N = 58.
Outcomes	1. Pharmacokinetic parameters 2. Hemostatic efficacy; • Presence or absence of any bleeds in the second 6-month study period reported as proportion of patients with zero total bleeds. • Proportions of PwHA who achieved zero spontaneous bleeds and zero spontaneous joint bleeds during the second 6-months. • Total ABR, spontaneous ABR, spontaneous joint ABR, joint ABR, ABR in joints with ≥ 4 spontaneous bleeds in 6 consecutive months, and injury-related ABR. • Total ABR during the 12-month trial period was compared with historical ABR during the 12 months before enrollment. • Change from baseline in the number of joints with ≥ 4 spontaneous bleeds. 3. Adverse events (inhibitor development, immunogenicity).

PROPEL III 2020 *(Continued)*

Notes	ClinicalTrials.gov NCT02585960; EudraCT 2014-005477-37 Dates of study; November 2015 to August 2018 Source of funding: Baxalta US Inc., a Takeda company, and Baxalta Innovations GmbH, a Takeda company, Vienna, Austria.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Randomization was stratified according to pre-study treatment regimen and ABR (prophylaxis with ABR < 5 vs prophylaxis with ABR ≥ 5 vs on-demand) and was independent of the patient's PK profile."
Allocation concealment (selection bias)	Unclear risk	"The investigator and patient chose the dosing interval and dose was selected from the sponsor's dosing recommendation table."
Blinding (performance bias and detection bias) Clinical Joint Function	Unclear risk	Not assessed.
Blinding (performance bias and detection bias) Bleeding	High risk	An open-label trial.
Blinding (performance bias and detection bias) Radiologic Joint Score	Unclear risk	Not assessed.
Blinding of outcome assessment (detection bias) Bleeding	High risk	Outcome assessment was by patient self-report. "Each patient was provided with a diary in electronic/paper format to record details of their infusions, bleeds and response to treatment, physical activity, unexpected events, and patient reported outcomes."
Blinding of outcome assessment (detection bias) Clinical Joint Function	Unclear risk	Not assessed.
Blinding of outcome assessment (detection bias) Radiologic Joint Score	Unclear risk	Not assessed.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Reasons for dropouts were discussed and were likely not due to allocated treatment. Both intention-to-treat (full analysis set) and per protocol analysis done.
Selective reporting (reporting bias)	Low risk	While the original protocol was not assessed (authors provided a 3-month time frame to make this assessible), all expected outcomes were reported in the trial results.
Other bias	Low risk	No other potential sources of bias identified.

SPINART 2013

Study characteristics	
Methods	Open-label, parallel, multicentre RCT. Conducted in 31 centres (USA, 23; Bulgaria, 3; Romania, 3; Argentina, 2). Treatment period: 1 year (of a planned 3-year trial).
Participants	Males aged 12 – 50 years (aged 18 – 50 years in Bulgaria and Romania) with severe haemophilia A with no prophylaxis for > 12 consecutive months in the past 5 years and 6 – 24 bleeding episodes in the preceding 6-month period. Number randomised: 84.
Interventions	1. rFVIII-FS prophylaxis thrice weekly (25 IU/kg) (n = 42). 2. on-demand treatment (n = 42).
Outcomes	Total number of bleeding episodes.
Notes	ClinicalTrials.gov identifier: NCT00623480. Dates of trial: March 2008 to September 2011 Source of funding: Bayer HealthCare AG, Leverkusen, Germany.

Risk of bias

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

SPINART 2013 *(Continued)*

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

Valentino 2012

Study characteristics	
Methods	Open-label, multicentre, randomised, 2-arm, parallel trial. Enrolled participants at 9 USA and 21 European sites between January 2006 and June 2010. Participants completed the 6-month on-demand period and were randomised to a 12-month prophylaxis period (32 on standard and 34 on PK-tailored prophylaxis).
Participants	Participants aged 7 to 65 years with moderately severe or severe haemophilia A, receiving on-demand treatment. Baseline FVIII: < 1% Number of participants enrolled: 82. Number of participants randomised: 66.
Interventions	2 secondary prophylaxis arms: 1. Standard prophylaxis (20 – 40 IU/kg) every other day.(N = 32) 2. PK-tailored prophylaxis (20 – 80 IU/kg) every third day.(N = 34) Follow-up duration: 6 months on-demand treatment followed by 12 months prophylaxis
Outcomes	Annualized bleeding rate.
Notes	Of note, this trial had a non-randomised longitudinal cross-over portion that compared prophylaxis versus on demand. Dates of trial: January 2006 to June 2010 Source of funding: Baxter Healthcare Corporation.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "The randomization sequence was created using SAS version 8.2 (Cary, NC, USA), stratified by 0, 1–2 or ‡ 3target joints (defined as a joint in which ‡ 4 hemorrhages occurred within a period of 6 months, or > 20 lifetime hemarthroses)...".
Allocation concealment (selection bias)	Low risk	Quote: "...1:1 allocation to treatment regimens using a random block size of 2, and provided to the investigator via an automated assignment system as the subject neared completion of on-demand treatment."

Valentino 2012 *(Continued)*

Blinding (performance bias and detection bias) Clinical Joint Function	Unclear risk	Not assessed.
Blinding (performance bias and detection bias) Bleeding	High risk	An open-label trial.
Blinding (performance bias and detection bias) Radiologic Joint Score	Unclear risk	Not assessed.
Blinding of outcome assessment (detection bias) Bleeding	High risk	An open-label trial.
Blinding of outcome assessment (detection bias) Clinical Joint Function	Unclear risk	Not assessed.
Blinding of outcome assessment (detection bias) Radiologic Joint Score	Unclear risk	Not assessed.
Incomplete outcome data (attrition bias) All outcomes	High risk	Unbalanced dropout rate across groups (N = 2 in standard prophylaxis arm; N = 11 in PK-tailored prophylaxis arm). Reasons for dropout were included.
Selective reporting (reporting bias)	Low risk	Outcomes reported in protocol are present in report.
Other bias	Low risk	No other potential sources of bias identified.

Valentino 2014

Study characteristics	
Methods	Randomised, multicentre, open-label, four-period cross-over trial. Trial conducted between May 2007 and October 2010 at 18 centres in the USA, Canada and Europe. Treatment period: 56 weeks.
Participants	Males aged 6 – 65 years with severe or moderately severe haemophilia B with 12 or more bleeding episodes in the prior 12 months. Baseline FIX: < 2% Number randomised = 47. 50 participants were included in the ITT analysis (including three who dropped out prior to randomisation)
Interventions	1. On demand (2 separate periods). 2. Prophylaxis with FIX once weekly (100 IU/kg). 3. Prophylaxis with FIX twice weekly (50 IU/kg). Participants received nonacog alfa (BeneFIX®; Pfizer, Philadelphia, PA, USA) as on-demand treatment for 16 weeks (Period 1), followed by randomisation to a prophylaxis regimen (Period 2) comprising

Valentino 2014 *(Continued)*

	nonacog alfa at 100 IU kg^{-1} once weekly or 50 IU kg^{-1} twice weekly for 16 weeks. During the following 8-week period, participants received on-demand treatment only (Period 3). Participants then crossed over to the alternate prophylaxis treatment regimen for 16 additional weeks (Period 4). Follow-up duration: total 59 weeks/participant to complete the entire study course.
Outcomes	Annualised bleeding rate.
Notes	Dates of trial: between May 2007 and October 2010. Source of funding: Pfizer.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Specific methods used to conduct randomisation are unclear: "Randomization to treatment sequence utilized an electronic assignment system."
Allocation concealment (selection bias)	Unclear risk	No details were given regarding allocation concealment.
Blinding (performance bias and detection bias) Clinical Joint Function	Unclear risk	Not assessed.
Blinding (performance bias and detection bias) Bleeding	High risk	An open-label trial.
Blinding (performance bias and detection bias) Radiologic Joint Score	Unclear risk	Not assessed.
Blinding of outcome assessment (detection bias) Bleeding	High risk	An open-label trial, outcome assessors were aware of allocation.
Blinding of outcome assessment (detection bias) Clinical Joint Function	Unclear risk	Not assessed.
Blinding of outcome assessment (detection bias) Radiologic Joint Score	Unclear risk	Not assessed.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Dropouts were balanced between groups (N = 3 in both allocation arms) and reasons for dropout noted.
Selective reporting (reporting bias)	Low risk	While the original protocol could not be located all expected trial results were reported.
Other bias	Low risk	No other potential sources of bias identified.

ABR: annualised bleed rate
HRQoL: health-related quality of life
MRI: magnetic resonance imaging

ITT: intention-to-treat
IU: international units
PK: pharmacokinetic
PwHA : people with haemophilia A
RCT: randomised controlled trial

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

Study	Reason for exclusion
Aledort 1994	Prospective observational study.
Ali 2018	Includes participants with inhibitors.
Andreeva 2015	Unclear if participants were previously treated (conference abstract only).
Antunes 2013	Includes participants with inhibitors.
ASPIRE 2020	Prospective observational study.
Astermark 1999	Retrospective observational study.
Astermark 2019	Intervention includes the anti-Tissue Factor Pathway Inhibitor (TFPI),concizumab, which is not a clotting factor therapy. This could be eligible for the subsequent review on non-clotting factor therapies.
Bertolet 2020	Intervention includes emicizumab, which is not a clotting factor therapy.
Booth 2017	Prospective observational study
Brackmann 1992	Retrospective observational study.
Carlsson 1997	Includes children previously on prophylaxis.
Chakraborty 2018	Includes children on primary prophylaxis.
Chowdary 2013	Intervention includes the anti-Tissue Factor Pathway Inhibitor (TFPI), concizumab, which is not a clotting factor therapy.
Chowdary 2017	Intervention is an investigational RNA interference (RNAi) therapeutic, not a clotting factor therapy.
Chozie 2018	Includes children on primary prophylaxis.
Chuansumrit 1995	Retrospective observational study.
Collins 2010	Prospective observational cross-over study.
Collins 2014	Includes children on primary prophylaxis.
Courter 2001	Prospective observational study.
Curry 2019	Includes people on primary prophylaxis.
Davydkin 2015	Unclear if participants were children or previously treated (conference abstract only).
Dzinaj 1996	Prospective observational study.

Study	Reason for exclusion
Eichler 2018	Intervention includes concizumab, which is not a clotting factor therapy.
ENJOIH 2010	Includes participants with inhibitors.
Escuriola 2019	Pharmacokinetics evaluated.
ESPRIT 2011	Pediatric population on primary prophylaxis.
Feldman 2006	Prospective observational single-arm dose-escalation study.
Fernandez-Bello 2017	Pharmacokinetics evaluated in participants with inhibitors.
Fischer 2005	Retrospective observational study.
HAVEN 1 2017	Includes participants with inhibitors.
Hazendonk 2015	Pharmacokinetic parameters evaluated.
INHIBIT 2014	Children on primary prophylaxis.
Kavakli 1997	Prospective observational study.
Khayat 2016	Children on primary prophylaxis.
Kids B-LONG 2017	Prospective observational study in children.
Konkle 2016	Retrospective observational study.
Kreuz 1998	Prospective observational study.
LEOPOLD I 2015	Participants on primary prophylaxis
Liesner 1996	Retrospective observational study.
Lofqvist 1997	Retrospective observational study.
Ma 2015	Retrospective observational study.
Manco-Johnson 1994	Prospective observational study.
Manco-Johnson 2007	Children on primary prophylaxis.
NCT03315455	Intervention includes emicizumab, which is not a clotting factor therapy.
NCT04303559	Intervention includes emicizumab, which is not a clotting factor therapy.
Nemes 2007	Prospective observational single-arm study.
Nilsson 1970	Retrospective observational study with historical control.
Nilsson 1976	Prospective observational study with historical control.
Nilsson 1992	Retrospective observational study.
PERSEPT 1 2017	Includes participants with inhibitors.

Study	Reason for exclusion
Petrini 1991	Retrospective observational study.
Pettersson 1981	Retrospective observational study with historical control.
PRO-FEIBA 2010	Includes participants with inhibitors.
PROTECT VIII 2017	Includes participants on primary prophylaxis.
Ragni 2017	Pilot feasibility study with cross-over design.
Ramsay 1973	Prospective observational study.
Royal 2002	Retrospective observational study with parallel groups.
Santagostino 2016	Prospective observational single-arm study.
Schimpf 1977	Prospective observational cross-over study.
Schobess 2008	Prospective observational study.
Shah 2019	Pharmacokinetic parameters evaluated.
Shapiro 2018	Intervention includes concizumab, which is not a clotting factor therapy.
Smith 1996	Retrospective observational switch study.
Smith 2018	Includes children on primary prophylaxis
Solms 2020	Pharmacokinetic parameters evaluated.
Song 2012	Ad-hoc analysis of a randomized controlled trial. Protocol or full study with results not found on trial registries. Also, the comparison focused on the degree of availability of factor concentrates per country i.e. low versus high IU/capita countries.
Szucs 1996	Prospective observational study.
Tagliaferri 2008	Retrospective observational switch study.
Van den Berg 2001	Retrospective observational single-arm study.
Verma 2016	Includes children on primary prophylaxis
Windyga 2014	No randomization in the comparison arm assessing outcome of interest (hemostatic efficacy).
Wu 2011	Prospective observation with historical control.
Young 2015	Prospective observational study in children.
Young 2017	Prospective dose and dose-interval comparison study (conference abstract only).

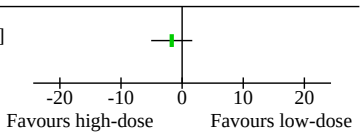
DATA AND ANALYSES

Comparison 1. Comparison between two prophylaxis regimens

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 Joint bleeds per year	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
1.2 Joint bleeds per year (2)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
1.3 Spontaneous joint bleeds	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
1.4 Joint bleeds per year (3)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
1.5 Total bleeds per year	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
1.6 Overall bleeding frequency (bleeds per 100 days)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
1.7 Annualised bleeding rates	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
1.8 Total bleeding frequency (HB)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
1.9 Overall bleeding frequency	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
1.10 Total bleeds per year (2)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
1.11 Total treatment emergent adverse event	1		Risk Ratio (IV, Fixed, 95% CI)	Totals not selected
1.12 Rate of adverse events	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected

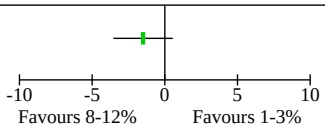
Analysis 1.1. Comparison 1: Comparison between two prophylaxis regimens, Outcome 1: Joint bleeds per year

Study or Subgroup	High-dose Mean	SD	Total	Low-dose Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
LEOPOLD II 2015	3.5	6.2	31	5.2	6.9	28	-1.70 [-5.06 , 1.66]

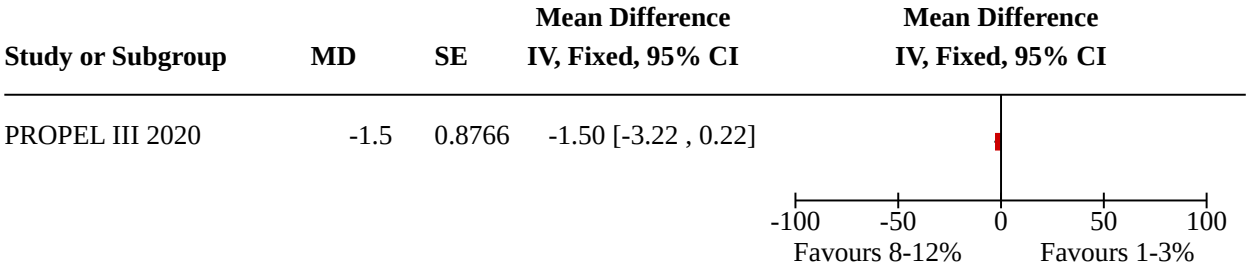


Analysis 1.2. Comparison 1: Comparison between two prophylaxis regimens, Outcome 2: Joint bleeds per year (2)

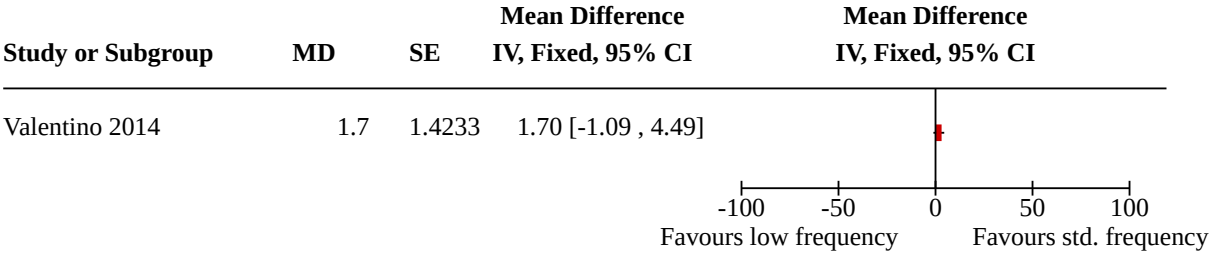
Study or Subgroup	Targeting trough of 8-12% Mean	SD	Total	Targeting trough of 1-3% Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
PROPEL III 2020	1.1	2.6	53	2.6	7.4	57	-1.50 [-3.54 , 0.54]



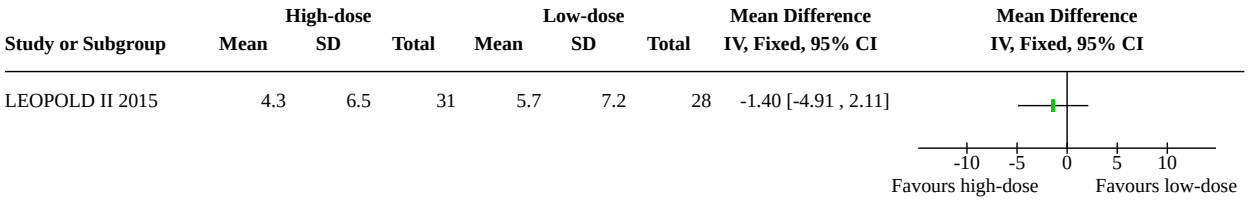
Analysis 1.3. Comparison 1: Comparison between two prophylaxis regimens, Outcome 3: Spontaneous joint bleeds



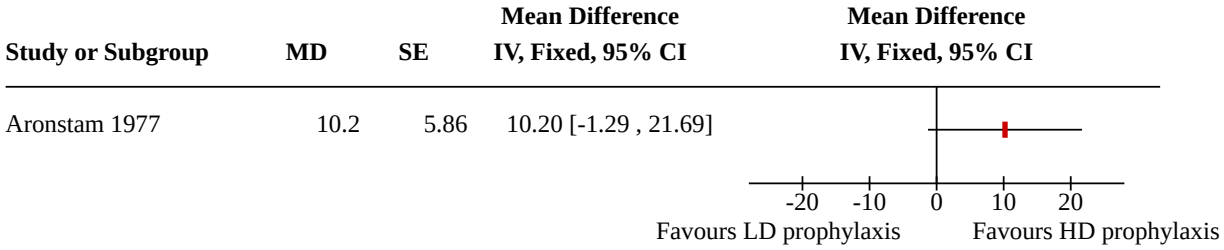
Analysis 1.4. Comparison 1: Comparison between two prophylaxis regimens, Outcome 4: Joint bleeds per year (3)



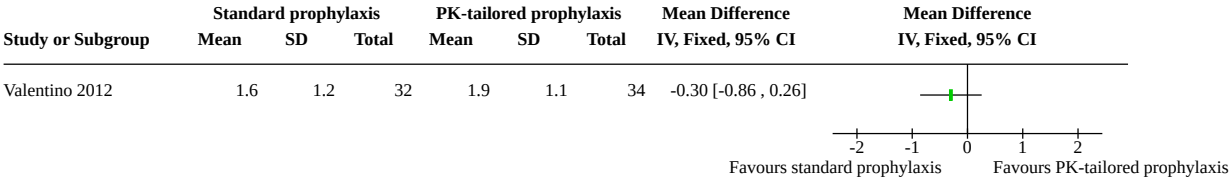
Analysis 1.5. Comparison 1: Comparison between two prophylaxis regimens, Outcome 5: Total bleeds per year



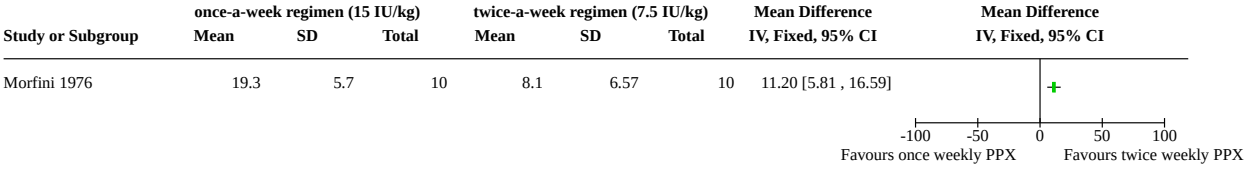
Analysis 1.6. Comparison 1: Comparison between two prophylaxis regimens, Outcome 6: Overall bleeding frequency (bleeds per 100 days)



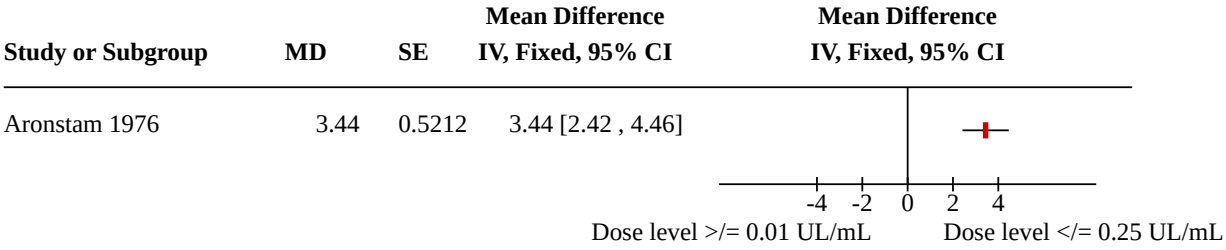
Analysis 1.7. Comparison 1: Comparison between two prophylaxis regimens, Outcome 7: Annualised bleeding rates



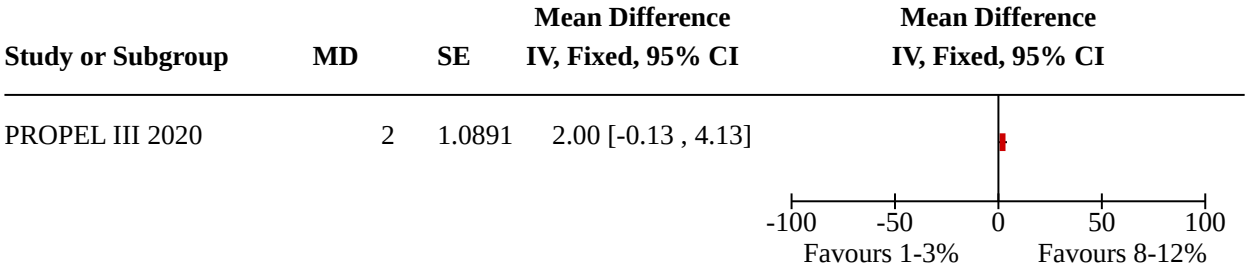
Analysis 1.8. Comparison 1: Comparison between two prophylaxis regimens, Outcome 8: Total bleeding frequency (HB)



Analysis 1.9. Comparison 1: Comparison between two prophylaxis regimens, Outcome 9: Overall bleeding frequency

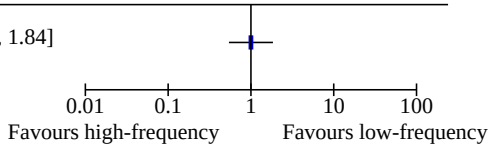


Analysis 1.10. Comparison 1: Comparison between two prophylaxis regimens, Outcome 10: Total bleeds per year (2)



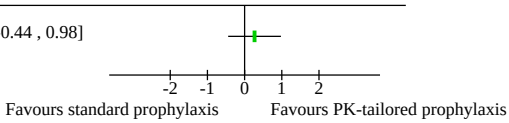
Analysis 1.11. Comparison 1: Comparison between two prophylaxis regimens, Outcome 11: Total treatment emergent adverse event

Study or Subgroup	High-frequency Events	High-frequency Total	Low-frequency Events	Low-frequency Total	Risk Ratio IV, Fixed, 95% CI
Valentino 2014	14	44	14	44	1.00 [0.54 , 1.84]



Analysis 1.12. Comparison 1: Comparison between two prophylaxis regimens, Outcome 12: Rate of adverse events

Study or Subgroup	Standard prophylaxis Mean	SD	Total	PK-tailored prophylaxis Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
Valentino 2012	0.356	2.012	32	0.089	0.383	34	0.27 [-0.44 , 0.98]

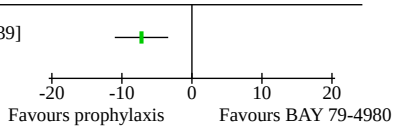


Comparison 2. Standard prophylaxis versus investigational drug

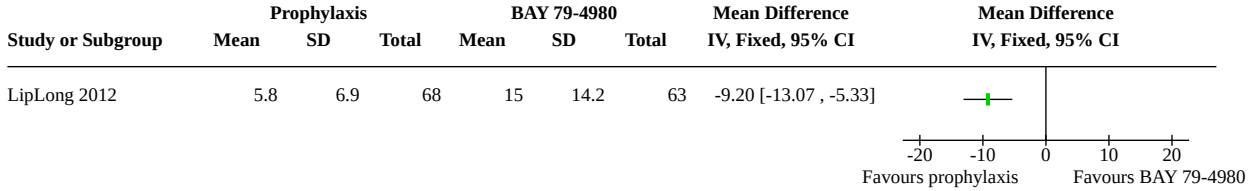
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.1 Annualised joint bleeding rate	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
2.2 Annualised total bleeding rate	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected

Analysis 2.1. Comparison 2: Standard prophylaxis versus investigational drug, Outcome 1: Annualised joint bleeding rate

Study or Subgroup	Prophylaxis Mean	SD	Total	BAY 79-4980 Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
LipLong 2012	5	6.3	68	12.2	14.2	63	-7.20 [-11.01 , -3.39]



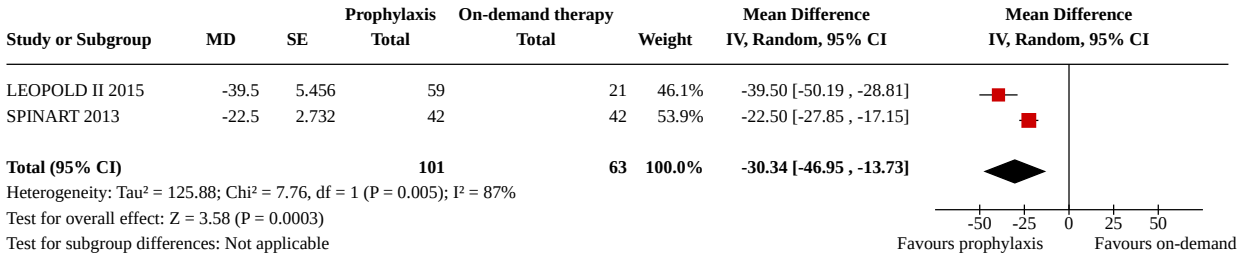
Analysis 2.2. Comparison 2: Standard prophylaxis versus investigational drug, Outcome 2: Annualised total bleeding rate



Comparison 3. Prophylaxis versus on-demand

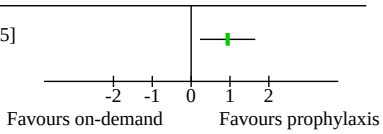
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.1 Mean total joint bleeds per year	2	164	Mean Difference (IV, Random, 95% CI)	-30.34 [-46.95, -13.73]
3.2 Mean change in joint health scores (CAJAS)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
3.3 Mean total bleeds per year	2	164	Mean Difference (IV, Random, 95% CI)	-40.24 [-64.04, -16.44]
3.4 Pain scores	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
3.5 Radiologic measurements of joint damage (deterioration shown in eMRI)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
3.6 Participants with adverse events	2	131	Risk Ratio (IV, Fixed, 95% CI)	1.71 [1.24, 2.37]

Analysis 3.1. Comparison 3: Prophylaxis versus on-demand, Outcome 1: Mean total joint bleeds per year



Analysis 3.2. Comparison 3: Prophylaxis versus on-demand, Outcome 2: Mean change in joint health scores (CAJAS)

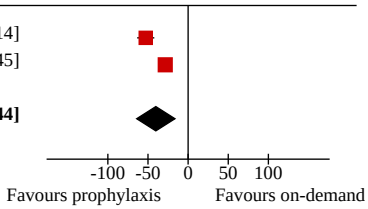
Study or Subgroup	On-demand Mean	SD	Total	Prophylaxis Mean	SD	Total	Mean Difference IV, Fixed, 95% CI	Mean Difference IV, Fixed, 95% CI
SPINART 2013	0.63	1.76	42	-0.31	1.56	42	0.94 [0.23 , 1.65]	



Analysis 3.3. Comparison 3: Prophylaxis versus on-demand, Outcome 3: Mean total bleeds per year

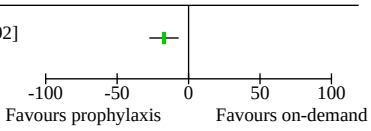
Study or Subgroup	MD	SE	Prophylaxis Total	On-demand Total	Weight	Mean Difference IV, Random, 95% CI	Mean Difference IV, Random, 95% CI
LEOPOLD II 2015	-52.8	5.44	59	21	48.3%	-52.80 [-63.46 , -42.14]	
SPINART 2013	-28.5	3.088	42	42	51.7%	-28.50 [-34.55 , -22.45]	
Total (95% CI)			**101**	**63**	**100.0%**	**-40.24 [-64.04 , -16.44]**	

Heterogeneity: Tau² = 275.68; Chi² = 15.09, df = 1 (P = 0.0001); I² = 93%
Test for overall effect: Z = 3.31 (P = 0.0009)
Test for subgroup differences: Not applicable



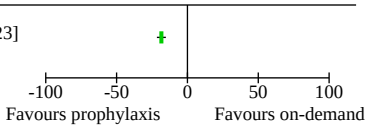
Analysis 3.4. Comparison 3: Prophylaxis versus on-demand, Outcome 4: Pain scores

Study or Subgroup	Prophylaxis Mean	SD	Total	On-demand Mean	SD	Total	Mean Difference IV, Fixed, 95% CI	Mean Difference IV, Fixed, 95% CI
SPINART 2013	-17.2	22.9	42	0	25.1	42	-17.20 [-27.48 , -6.92]	



Analysis 3.5. Comparison 3: Prophylaxis versus on-demand, Outcome 5: Radiologic measurements of joint damage (deterioration shown in eMRI)

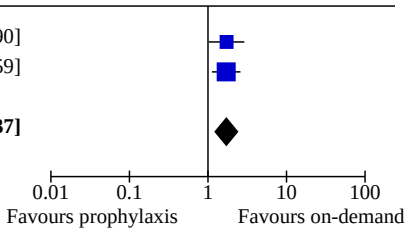
Study or Subgroup	Prophylaxis Mean	SD	Total	On-demand Mean	SD	Total	Mean Difference IV, Fixed, 95% CI	Mean Difference IV, Fixed, 95% CI
SPINART 2013	0.75	1.59	41	19.14	9.81	38	-18.39 [-21.55 , -15.23]	



Analysis 3.6. Comparison 3: Prophylaxis versus on-demand, Outcome 6: Participants with adverse events

Study or Subgroup	Prophylaxis Events	Prophylaxis Total	On-demand Events	On-demand Total	Weight	Risk Ratio IV, Fixed, 95% CI
A-LONG 2014	18	24	10	23	39.4%	1.73 [1.03 , 2.90]
SPINART 2013	29	42	17	42	60.6%	1.71 [1.12 , 2.59]
Total (95% CI)		**66**		**65**	**100.0%**	**1.71 [1.24 , 2.37]**
Total events:	47		27			

Heterogeneity: Chi² = 0.00, df = 1 (P = 0.97); I² = 0%
Test for overall effect: Z = 3.23 (P = 0.001)
Test for subgroup differences: Not applicable



APPENDICES

Appendix 1. Search strategies

Search engine or registry	Search terms
Medline OVID (2010 - June 2016)	1 exp Hemophilia/
	2 Haemophilia.mp.
	3 hemophilia.mp. or exp Hemophilia/
	4 Inherit:.mp.
	5 Heredit:.mp.
	6 Congenital.mp.
	7 4 or 5 or 6
	8 1 or 2 or 3
	9 7 and 8
	10 factor concentrat:.mp.
	11 Factor Product:.mp.
	12 recombinant factor:.mp.
	13 plasma$ factor$.mp.
	14 clot$ factor$.mp.
	15 Factor$ VIII.mp.
	16 Factor eight.mp.
	17 FVIII.mp.
	18 FIX.mp.
	19 Factor nine.mp.
	20 Factor$ IX.mp.

(Continued)

	21 cryoprecipitat$.mp. 22 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 23 Prophyla:.mp. 24 prevent:.mp. 25 23 or 24 26 Secondar:.mp. 27 Adult.mp. 28 26 or 27 29 25 and 28 30 9 and 22 and 29
ISRCTN www.isrctn.com/	[Basic Search] (haemophilia OR hemophilia) AND (prophylactic OR prophylaxis)
Clinicaltrials.gov ClinicalTrials.gov	[Advanced Search] Condition or disease: haemophilia OR haemophilia Other terms: prophylactic OR prophylaxis Study type: Interventional Studies (Clinical Trials)
WHO ICTRP	[Advanced Search] Condition: haemophilia OR haemophilia AND Intervention: prophylactic OR prophylaxis Recruitment status is: All

WHAT'S NEW

Date	Event	Description
12 August 2021	New citation required and conclusions have changed	This review of previously treated individuals is one of two set to replace the original 2011 published review - *Clotting factor concentrates given to prevent bleeding and bleeding-related complications in people with hemophilia A or B* (Iorio 2011). The original review is currently still available on the Cochrane Library, but when this is next updated (currently in production), will only include previously untreated individuals. The conclusions of this new review have changed from the original review. Previously we identified evidence that the use of these concentrates was effective in decreasing the frequency of joint bleeds and in partially preventing or slowing down the development of arthropathy. Currently, in relation to people previously treated with clotting factor concentrates, we have found evidence that the use of these concentrates may be effective in

Date	Event	Description
		decreasing the frequency of total bleeds and joint bleeds and improve joint function, pain and quality of life, even though this does not translate into a detectable improvement of articular damage when assessed by radiologic assessment.
12 August 2021	New search has been performed	The review 'Clotting factor concentrates given to prevent bleeding and bleeding-related complications in people with haemophilia A or B' has been split into two reviews, of which this is the first to be published. The second review is in production: Clotting factor concentrates for preventing bleeding and bleeding-related complications in previously untreated individuals with haemophilia A or B. The previous review (which included both people previously and not previously treated for bleeding and related complications) included six studies, of which three were regarded as not eligible for this review (Carlsson 1997; ESPRIT 2011; Manco-Johnson 2007). 10 trials (32 references) are included in this review (A-LONG 2014; Aronstam 1976; Aronstam 1977; LEOPOLD II 2015; LipLong 2012; Morfini 1976; PROPEL III 2020; SPINART 2013; Valentino 2012; Valentino 2014). The number of participants included in the review has increased from 142 to 608.

HISTORY

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

Date	Event	Description
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

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

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

Ashma Krishan performed and interpreted initial analyses.

Peter Collins reviewed and commented on the final draft version.

Megan Lowe conducted risk of bias assessment and data extraction.

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

DECLARATIONS OF INTEREST

Omotola Olasupo: has no conflict of interest.

Megan Lowe: has no conflict of interest.

Peter Collins has acted as a paid consultant, received lecture fees and support to attend meetings from Novo Nordisk, Bayer, Baxter, CSL Behring. Grant support has been received from CSL Behring.

Ashma Krishan: none known.

Alfonso Iorio does not perceive any relevant conflict of interest, while his institution receives grants from pharmaceutical companies, he does not benefit from these, nor does he have control over the use of the funds.

Davide Matino reports research grants paid directly to the Institution from Bayer, Pfizer, Novo Nordisk, Sanofi, Spark, Octapharma; personal fees outside the submitted work from Sanofi, Sobi, Novo Nordisk, Bayer, Pfizer, Octapharma for participation in advisory boards, lectures and preparation of educational material.

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Internal sources

- Alberta Research Centre for Child Health Evidence, Canada

  This support was received for the original version of this review (now withdrawn).

External sources

- Association of Hemophilia Clinic Directors of Canada, Canada

  This support was received for the original version of this review (now withdrawn).
- National Institute for Health Research, UK

  This systematic review was supported by the National Institute for Health Research, via Cochrane Infrastructure funding to the Cochrane Cystic Fibrosis and Genetic Disorders Group.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

This review is one of two set to replace the original review - *Clotting factor concentrates given to prevent bleeding and bleeding-related complications in people with hemophilia A or B* (Iorio 2011) - which has now been withdrawn from the Cochrane Library. This new review focuses on people previously treated with clotting factor concentrates.

NOTES

This review of previously treated individuals is one of two set to replace the original 2011 published review - *Clotting factor concentrates given to prevent bleeding and bleeding-related complications in people with hemophilia A or B* (Iorio 2011). The original review is currently still available on the Cochrane Library, but when this is next updated (currently in production), will only include previously untreated individuals.

INDEX TERMS

Medical Subject Headings (MeSH)

Blood Coagulation Factors [*therapeutic use]; Factor VIII [*therapeutic use]; Hemarthrosis [*prevention & control]; Hemophilia A [*complications]; Hemophilia B [*complications]; *Pharmaceutical Preparations

MeSH check words

Humans