

Review Article

Prophylaxis in people with haemophilia

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Summary

A four-decade clinical experience and recent evidence from randomised controlled studies definitively recognised primary prophylaxis, i.e. the regular infusion of factor concentrates started after the first haemarthrosis and/or before the age of two years, as the first-choice treatment in children with severe haemophilia. The available data clearly show that preventing bleeding since an early age enables to avoid or reduce the clinical impact of muscle-skeletal impairment from haemophilic arthropathy and the related consequences in psycho-social development and quality of life of these patients. In this respect, the aim of secondary prophylaxis, defined as regular long-term treatment started

after the age of two years or after two or more joint bleeds, is to avoid (or delay) the progression of arthropathy. The clinical benefits of secondary prophylaxis have been less extensively studied, especially in adolescents and adults; also in the latter better outcomes and quality of life for earlier treatment have been reported. This review summarises evidence from literature and current clinical strategies for prophylactic treatment in patients with severe haemophilia, also focusing on challenges and open issues (optimal regimen and implementation, duration of treatment, long-term adherence and outcomes, cost-benefit ratios) in this setting.

Keywords

Prophylaxis, bleeding, children, haemophilia, quality of life

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Introduction

Milestones in modern treatment of haemophilia are represented by the availability of safe (both plasma-derived and recombinant) products for replacement therapy and the large-scale implementation of prophylaxis in children (1). In patients with haemophilia, prophylaxis is defined as the infusion of factor concentrate replacement treatment before the occurrence and in order to prevent bleeding. This definition also includes short-term treatments in occasion of surgery or other invasive procedures, but is generally referred to a long-term, regular modality of treatment, in which the aim of preventing joint bleeds, the typical and most common bleeding in severe haemophiliacs, is devoted to prevent the long-term harmful effects of bleeds on joint structure and function, leading to the haemophilic arthropathy (2), the main cause of morbidity and factor affecting quality of life in severe haemophiliacs. Prophylaxis has been used for more than 40 years in Northern Europe and more recently in other European countries and in Northern America, becoming the first-choice treatment in severe haemophilia, recommended by the World Health Organization and the World Federation of Haemophilia since 1994 (3, 4).

This review will focus on the present knowledge and clinical implementation of prophylactic treatment in haemophiliacs.

Background and definitions of prophylaxis in haemophilia

Pioneer clinical observations in Sweden that patients with moderate or mild haemophilia, with factor (F)VIII:C or IX:C levels >1%, show a low frequency of joint bleeds and rarely develop severe arthropathy (5, 6), led to define the pathophysiological background of the prophylactic replacement treatment, i.e. to minimise the number of joint bleeds since an early age by converting the severe form of haemophilia to a milder form, in order to prevent or reduce the muscle-skeletal impairment from haemophilic arthropathy. Avoiding a clinically relevant impact of joint deterioration by prophylaxis means to enable normal life and psychosocial development for haemophilic children, including the possibility of physical activities, regular school attendance and, consequently, social and work opportunities. On the whole, severe haemophiliacs on prophylaxis and their families

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experience a greater quality of life than patients who receive on demand treatment (3, 4, 7).

The report of the 25-year Swedish experience in 1992 (3) and numerous following studies clearly described these clinical and social benefits (7–11), showing that the earlier the start of prophylaxis, the better the outcome in patients' joint status. However, heterogeneity in definitions and clinical implementation of prophylaxis has made it difficult to analyse and compare clinical outcomes (12, 13). A revision of definitions of prophylaxis, in order to encompass the different strategies in Europe (start by age of 2, regardless bleeding tendency) and in North America (start after the first bleed), was proposed by a Consensus Conference in 2002 (12) and has been updated more recently (14) (Table 1). Even though the number of joint bleeds resulting in irreversible joint damage is still unknown, the definition of primary prophylaxis is focused on the avoidance of any joint abnormality, in order to warrant the best degree of patients' quality of life. The objective of secondary prophylaxis, whenever started, is to avoid (or delay) the progression of arthropathy. According to some Authors, early or delayed secondary prophylaxis are distinguished and better outcomes and quality of life for earlier start of treatment are reported (15). In some patients a secondary prophylaxis regimen is prescribed for short periods, usually to reduce the frequency of bleeds, in particular in target joints. On the whole, the definitions of prophylaxis reflect a wide spectrum of clinical conditions and objectives of the treatment, from the prevention of severe or life-threatening bleeds to the absence of arthropathy enabling patients to live a substantially normal life, without overprotection (16). In a congenital, chronic disease like haemophilia, for which the definitive cure is still not available, the latter perspective is an important and reliable goal, actually achieved by primary prophylaxis.

Primary prophylaxis and early secondary prophylaxis in children

Despite a four-decade clinical experience and the large-scale implementation of prophylaxis, in particular in some European countries, data supporting the benefits of prophylaxis in haemophiliacs come mostly from retrospective or non-controlled studies. These studies evaluated the effects of different regimens of treatment on frequency of bleeding, in particular joint bleeds, and on long-term clinical outcome in terms of arthropathy, assessed by clinical and radiological scores (17, 18). In some studies other medical and social implications on patients' quality of life were also investigated, reporting the number of visits and hospitalisations and of work/school days lost. Some relevant studies, from which the current definitions and clinical choices of primary prophylaxis in children have been drawn, are summarised in Table 2.

The different cohorts of patients described in the Malmö experience reflect the evolution in clinical implementation of prophylaxis (3): the oldest patients (24–32 years at study evaluation) started at a median age of seven years (range 3–13) a regimen with lower factor doses and frequency of infusion (10–20 IU/kg every 3–5 days) and experienced a median number of 5 (1.6–16) joint bleeds per year and radiological scores ranging from 0 to

Table 1: Definitions of replacement treatment regimens in haemophilia (12, 14).

Regimen	Definition
Primary prophylaxis A (by first bleed)	Long-term continuous* treatment started: after the first joint bleed and before the age of 2 years
B (by age)	before the age of 2 years, in the absence of clinically evident joint bleeds
Secondary prophylaxis A	Long-term continuous* treatment not fulfilling the criteria for primary prophylaxis, i.e. started after two or more joint bleeds or at an age >2 years
Secondary prophylaxis B (short-term prophylaxis)	Intermittent regular (short-term) treatment, generally started because of frequent bleeds.
On demand therapy	Treatment given when bleeding occurs.

* at least 46 weeks/year, with the aim of treating 52 weeks/year up to adulthood.

41. Patients aged 13–17 years, starting prophylaxis at a median age of 2.6 years (range 1–4.5) showed a similar frequency of joint bleeds (0.1–16 per year) and progression of orthopaedic and radiological scores, despite more intensive regimens of treatment. Only younger children (3–12 years), receiving higher doses (25–40 IU/kg thrice weekly) earlier in life (median age at start of prophylaxis 1.2 years, range 0.5–2), did not show any bleeding episode at all and any signs of arthropathy at orthopaedic and radiological evaluations (3). Other studies in the following years confirmed that sign of arthropathy were not detectable in children starting prophylaxis before two years of age or after no more than one joint bleed (8) and that, irrespective of regimens, starting prophylaxis at an age of about four years was associated with a significant reduction in the frequency of joint bleeds (a major predictor of clinical outcome in the prospective multi-national 6-year Orthopaedic Outcome Study [7]), but did not prevent the development of arthropathy in most patients (9–11). Thus, primary prophylaxis was associated with better clinical outcomes than early secondary prophylaxis. Along this line, a later Swedish study reported that age at start of prophylaxis was an independent predictor for development of arthropathy (19), more important than the frequency of infusions; therefore, as no significant difference in the joint outcome was found between children starting high-dose prophylaxis (i.e. 25–40 IU/kg 2–3 times weekly) before the age of three and those starting between three and five years of age, the authors concluded that an individualization of prophylaxis regimen may be operated on the basis of the patient's bleeding pattern. It is likely that the number of joint bleeds until start of prophylaxis has a higher predictive value than the age at start of prophylaxis itself, as was also shown in the Dutch experience with lower dose regimens (15–25 IU/kg 1–2 times weekly), tailored to the patients' bleeding tendency (9, 20). Patients starting prophylaxis before the age of four showed more favorable long-term clinical outcome (no arthropathy in 50% of patients vs. 21% in those starting between 3 and 7 years), with an estimated 8% higher Pettersson score per year of postponed prophylaxis from birth, and the best results (70% of patients with score 0) were found in patients starting prophylaxis with a history of less than three bleeds (20).

Table 2: Relevant clinical studies of primary / early secondary prophylaxis in children with haemophilia.

Author, year [ref.] Design	Patients	Median age at start of prophylaxis, years; (range)	Main results
Nilsson, 1992 [3] Retrospective cohort	35 (30 HA, 5 HB)* 3 cohorts, age at study evaluation 3–6, 7–12 and 13–17 yrs	1.1 (1–1.5), n=6 1.2 (0.5–2), n=9 2.6 (1–4.5), n=20	The two younger cohorts, starting prophylaxis before the age of 2, minimized joint bleeds (median 0.1/yr) and maintained OJS and PS 0, with higher FVIII/IX consumption compared to patients who started prophylaxis later, experiencing higher frequency of joint bleeds (median 3/year) and worse joint status (median OJS and PS 1.2 and 4.8, respectively).
Aledort, 1994 [7] Prospective, observational	48 HA**	n.a.	At 6-year follow-up absence of progression of OJS and PS was correlated to significantly lower frequency of joint bleeds (mean, 1.8 vs. 11.2, p=0.0001) and higher use of prophylaxis longer than 45 weeks/year (9 vs. 0, p=0.002).
Kreuz, 1998 [8] Retrospective cohort	14 (11 HA, 3 HB)* 2 groups, median age at study evaluation 12 and 9.	1.75 (1–2.5), n=8 4.25 (3.1–5.5), n=6	At study entry median OJS and PS 0 in both groups; at 4-year follow-up similar frequency of joint bleeds (0.14 vs. 0.22/year) but better joint outcome (median PS 0 vs. 4) in the first group, starting prophylaxis earlier and with history of ≤1 joint bleed.
van den Berg, 2001 [9] Retrospective cohort	22 HA	4.0 ± 0.5	At mean age of 14.7 years, patients, starting prophylaxis after 2–5 joint bleeds and a 2.3 years mean from the first bleed, had mean 3.2 joint bleeds/year and mean PS 2.3.
Panicker, 2002 [10] Retrospective cohort	20 (17 HA, 3 HB)	4.5	Reduction of mean frequency of major bleeds from 15.4 to 1.9/year at median age of 11.4 years, with significant reduction of target joints and of number of visits and hospitalisations.
Yee, 2002 [11] Retrospective cohort	29 (24 HA, 5 HB)	4.0 (2–12.7)	At median follow-up of 4.1 yrs (0.3–11.5), reduction of median joint bleeds from 3.5 to 0.5/year; 20 children (70%) maintained OJS 0, in the other 9 median OJS 1.5.
Manco-Johnson, 2007 [30] Prospective, randomised	65 HA (57 evaluable) ^o	1.6 (≤ 2.5)	At median follow-up of 49 months, higher rate of preserved joint structure at MRI evaluation (93% vs. 55%, p=0.002) and lower median total and joint bleeds (1.15 and 0.2 vs. 17.1 and 4.35, p<0.001) in children on prophylaxis vs. intensive on-demand therapy.
Gringeri, 2008 [34] Prospective, randomised	40 HA	2.0 (≤ 7)	At 10-years follow-up, lower median frequency of joint bleeds (0.2 vs. 0.52 per month) and rate of absence of radiological signs of arthropathy (29% vs. 74%, median PS 5 vs. 8) in children on prophylaxis vs. on-demand therapy.

Abbreviations: n.a.: not available; HA: haemophilia A; HB: haemophilia B; OJS: orthopaedic joint score; PS: Pettersson score; MRI: magnetic resonance imaging. *only patients considered on primary or early secondary prophylaxis from the whole study population (60 patients, 52 HA, 8 HB, in the Swedish study, 21 patients, 18 HA, 3 HB in the German study) are mentioned. **the subgroup of children with orthopaedic and Pettersson scores 0 at study entry is considered. ^o for the primary end-point (preservation of joint structure at MRI and/or radiography).

Until recently, evidence from randomised controlled studies providing a direct comparison of prophylaxis to on-demand treatment was lacking, probably because of the relative rarity of the disease and the difficulty to perform such trials, especially in countries in which consolidated experience on prophylaxis raised ethical considerations on possible randomisation of children to on-demand treatment. As a consequence, in 2005 a Cochrane review (21) was able to identify only four small randomised cross-over trials (3 of them carried out in the 1970s, 3 in haemophilia A and 1 in haemophilia B), comparing a prophylaxis regimen with placebo (22) or two different prophylactic regimens (23–25). On the whole these studies involved only 44 patients and the heterogeneity of study designs, interventions and patients' characteristics hampered a meta-analysis. The authors concluded that evidence supporting clinical benefits of prophylaxis over on-demand treatment were insufficient and remarked the need for well designed randomised controlled trials (RCTs) addressing this issue. These conclusions seemed to confirm perplexities to the implementation of prophylaxis in children in countries requiring rigorous evidence-based data for the acceptance of health-care approaches and reimbursements.

On the other hand, many authors criticised the rigid emphasis on RCTs (26–29), considered unjustified and substantially infeasible in a chronic disease like haemophilia, with a life-time perspective, in order to assess the long-term impact of a treatment, in terms of outcomes and cost-effectiveness ratio (in the case of prophylaxis, joint outcome, disability, labor force participation, health-care costs for hospitalisations, physiotherapy, orthopaedic procedures and the overall patients' quality of life) (29). Moreover, the Cochrane review seemed rather untimely: in the conclusions the Authors also stated that two RCTs were ongoing (21), and preliminary results of one of them were available. Indeed, the first RCT on prophylaxis versus on-demand treatment, the Joint Outcome Study (JOS), was published in August 2007 (30). This study enrolled 65 severe (FVIII:C ≤ 2%) children from 15 US Centres aged 6–30 months, with a history of two or fewer bleeds in any single index joint (elbow, knee, ankle). Thirty-two children were randomised to prophylaxis (25 IU/kg every other day), whereas 33 patients were assigned to receive an intensive on-demand treatment (40 IU/kg at bleeding onset, then 20 IU/kg at 24 and 72 hours and every other day thereafter up to 4 weeks, until resolution of pain and limitation of mobility). The

primary end-point of the JOS was focused on the prevention of joint deterioration, assessed at the age of six years by radiography and/or by the most advanced approach for evaluating the joint structure, the magnetic resonance imaging (MRI) (31). After a median 49 months follow-up, the expected lower median annual number of total and joint bleeds in children on prophylaxis compared to those on episodic treatment was associated with an about six-fold reduction (85%) of risk of joint damage (30) (Table 2). Interestingly, only the MRI assessment enabled to show a significant difference in the joint outcome, more than half of joint abnormalities being not detectable by the traditional radiological evaluation. Although the standardisation of interpretation and scoring of findings is still debated (32), the JOS confirmed the MRI as the preferable imaging technique in haemophilic children, able to reveal early signs of joint deterioration also in the absence of overt history of haemarthroses and of abnormalities at physical examination (30). These findings suggest a role for microhaemorrhages, not associated with clinical signs of joint bleeds, in the development of early joint damage, as also previously hypothesised to explain discrepancies between radiological and clinical data in the Orthopaedic Outcome Study (7). However, the weak relationship between the number of clinical joint bleeds and MRI findings is confirmed by the absence of abnormalities in some joints with a history of more than 10 haemarthroses (30). These quite surprising data highlight the need for further studies on the determinants of joint deterioration and on interpretation of MRI outcome in haemophilic children (2, 32). The JOS showed for the first time in a real RCT the well recognised clinical benefits of primary prophylaxis and confirmed that prophylaxis can be started on the basis of the occurrence of the first joint bleeds rather than at a specific age. Moreover, data on FVIII concentrate utilisation provide evidence for a tendency to increase of FVIII consumption with age in the episodic therapy group, supporting further improvements of cost-benefit ratio of prophylaxis in long-term evaluations (30).

The results of the other randomised trial carried out in Italy, the ESPRIT (Evaluation Study on Prophylaxis: a Randomized Italian Trial) (33), have been recently published in abstract form (34). Forty patients aged <7 years (median 2 years) with negative clinical and radiological scores at study entry were randomised to 25 IU/kg three times a week, with dose adjustments to maintain trough FVIII levels >1%, or on-demand treatment (≥ 25 IU/kg per day until complete healing). Significantly lower bleeding frequency and Petterson scores have been reported in children on prophylaxis than in those on-demand after a 10-year follow-up (34) (Table 2).

Open issues and challenges in primary prophylaxis

In the general lack of high-level of evidence data supporting clinical choices for the optimal prophylaxis regimen, convincing findings from observational studies show that the early start of prophylaxis may be individualised on the basis of the bleeding pattern (7–9, 19, 20). These data led to tailor the dose and/or the frequency of prophylactic infusions, in order to improve the adherence of families to such a highly demanding treatment, whose

perceived need and knowledge of benefits are often poor when prophylaxis is started (35). The problem of frequent venous access remains a crucial issue for the early implementation of prophylaxis (36). Reaching full-dose (with higher frequency of infusions) regimens later in life, when children may have good peripheral vein accesses, could reduce the need for central venous access devices. The latter may warrant a stable and long-lasting venous access, making feasible home-treatment and prophylaxis, but their complications (infections, thrombosis) are a major problem in the management of haemophilia in the first years of life (37–40), leading to the search for newer, and possibly safer, approaches, like arteriovenous fistula (41). Step-up regimens have been shown to facilitate the implementation of prophylaxis and to avoid, at least in part, problems with venous access. Moreover, such approaches may consider the reported variability of bleeding phenotype among children with severe haemophilia (approximately 10% of severe patients are mild bleeders and the age of first joint bleed is notably different) (42). According to the Swedish approach, prophylaxis is started between one and two years of age or after the first joint bleed, with a single 500 IU infusion weekly at the Haemophilia Centre. Frequency of infusions is escalated to two and then three weekly, based on the availability of adequate peripheral veins (in parallel parents' training for home treatment is carried out) or, more rarely, on the bleeding frequency. In this approach, home treatment with 500 IU every other day was achieved in 6–18 months and no clinical influence of maintaining a trough level of >1% was shown (43). Another tailored dose approach has been proposed in Canada, where children generally receive 50 IU/kg once weekly starting between one and two years of age and the bleeding frequency is evaluated by clinical follow-up every three months. Patients experiencing three bleeds in the same joint or four total bleeds over a 3-mo period increase prophylaxis dose by infusing 30 IU/kg twice weekly and then by a regimen of 25 IU/kg every other day. According to the recently published experience, 40% of children maintained the once weekly infusion and 16% reached the full-dose prophylaxis regimen over a median 4.1-year follow-up (44). The development of target joints in 22.5% of these children raised some perplexities (44); however, both the Swedish and the Canadian approaches enabled a remarkable reduction of the need for central venous accesses (24% and 40%, respectively) (43, 44), compared to the highest frequency reported in the JOS (91%) (30). The perspective of new factor concentrates with longer half-life (45) is encouraging for planning regimens with less frequent infusions, allowing better acceptance and adherence of patients and, probably, lower consumption of replacement factors.

The issue of the availability and, in particular, of costs of clotting factor concentrates remains the main barrier to the diffusion of prophylaxis, being prohibitive particularly for developing countries (35, 36). However, on-demand treatment is still the predominant replacement approach also in many developed countries. According to recent data, only 19% of children receive primary prophylaxis in the United States and a large variability is reported also in European countries, with highest figures in Sweden (73%) (46). The comparison of different dose regimens for prophylaxis showed that the intermediate-dose used in the Netherlands requires a median annual amount of factor concen-

Table 3: Prophylaxis regimens in children with haemophilia.

High-dose regimens (Sweden, Germany, UK, Italy, North America) [3, 8, 10, 11, 19, 30, 33, 34, 43, 44, 54–58]
Haemophilia A: 25–40 IU/Kg 3 times weekly or every other day
Haemophilia B: 25–40 IU/Kg 2 times weekly
Intermediate-dose regimens (the Netherlands) [9, 20, 47, 48, 60, 61]
Haemophilia A 15–25 IU/Kg 2–3 times weekly
Haemophilia B 30–50 IU/Kg 1–2 times weekly

trates approximately half of that used in Sweden with the high-dose regimen (Table 3). When long-term outcomes are considered, frequency of joint bleeds, orthopaedic and radiological scores were significantly lower in Swedish than in Dutch patients (47). The latter, however, achieved a more favorable orthopaedic outcome than French patients treated on-demand, with almost comparable clotting factor consumption (48). In the lack of prospective and controlled data, the individualisation of regimens may help to tailor more cost-effective treatments (24, 35, 43). In this respect, the evaluation of outcomes in haemophilia requires longer follow-up and should not be confined to direct costs of concentrates, taking into account all the additional health resources related to the management of haemophilia and its orthopaedic complications (49, 50). Moreover, newer outcome measures useful in determining the overall benefits to patients should be added to the clinical outcomes, including Health Related Quality of Life, for which specific validated instruments have been now developed (51).

Recent data suggest new potential benefits of early start of prophylaxis in severe haemophilic children. A protective effect against the development of inhibitors has been shown in a case-control Italian study (52), reporting a 70% reduction of inhibitor risk in children starting prophylaxis at a median age of 35 months. Similar findings were shown in the larger multinational CANAL study, in which early regular prophylaxis (started at a median age of 20 months) was an independent negative predictor associated with a 60% lower risk of inhibitor development than on-demand treatment (53). This additional benefit could further help to overcome barriers to the acceptance and the diffusion of primary prophylaxis that, irrespective of evidence-based medicine, has undeniably transformed the lives of children with severe haemophilia and their families over the last four decades.

Secondary prophylaxis in children

A number of studies are available in the literature on secondary prophylaxis started in children of school age or even in adolescence (3, 7, 54–57). In most cases secondary prophylaxis was initiated because of a high bleeding frequency when patients were treated on-demand or after the development of target joints. The clinical impact of a delayed start of prophylaxis may be drawn from the outcome reported for the oldest cohorts of the classic report of 25-year Swedish experience (3). As previously mentioned, these patients, who started prophylaxis between three and 13 years of age (median 7 years) experienced higher

number of joint bleeds and of work-school days lost, together with greater orthopedic and radiological scores, than patients from the younger cohorts starting prophylaxis earlier (3). Similarly, better results after a 12-year follow-up were reported in German patients aged 9–12 years at the study start than those aged 13–16 years (54). Interestingly, in this German experience long-term prophylaxis was associated with physiotherapy and self-trained physical activity. Patients' orthopaedic scores showed a substantial improvement compared to poor modifications of radiological abnormalities, thus highlighting the importance of preserving muscle function by physical exercise in clinical joint outcome (54). On the other hand, children may practice a wider range of physical activities and better tolerate muscle strengthening exercises thanks to prophylaxis, with significant clinical improvement also in patients with target joints (55). On the whole, these studies show that even delayed prophylaxis is able to reduce the frequency of bleeding, to improve physical functioning and quality of life of children and to delay the progression of arthropathy (15, 59). In this respect, a milestone is represented by the Orthopedic Outcome Study (7). In this six-year prospective multinational study involving 477 patients with a mean age of about 12 years, prophylaxis was associated with a significant slower progression of arthropathy, being the annual variation of orthopaedic and radiological scores about one third and half than that reported in patients treated on-demand, respectively (7). Moreover this study provided data on the reduction of health-related direct and indirect costs in patients on prophylaxis, showing a significant reduction of number of hospitalisations and of school absenteeism and the consequent favorable impact of prophylaxis on psycho-social development of haemophilic boys of school age.

Prophylaxis in adolescents and adults

The indications of prophylaxis in adolescent and adult severe haemophiliacs are related to two different clinical settings, both controversial. The first issue concerns the duration of a primary or secondary prophylactic regimen started during childhood. It was thought that prophylaxis should be continued until the complete development of muscle-skeletal apparatus, being joint bleeds less frequent after the epiphyses fuse and growth stops (59). It is notable that patients who started prophylaxis in early childhood may enter the adolescence or the adulthood with healthy or highly preserved joints. This condition is associated with low susceptibility to joint bleeding and could be maintained by prophylaxis. Although the peak frequency of haemophilic bleeding and of risk of development of target joints are during childhood and adolescence, shifting to on-demand treatment in adult age may produce an increased bleeding rate and consequently joint damage. However, few studies addressed the issues of the comparison between patients discontinuing or not prophylaxis in the adulthood with respect to the risk of bleeding and of progression of joint damage, and consequently, of the identification of candidates for continuous prophylaxis (59). A Dutch study reported that among 49 patients with a median age of 23 years who started prophylaxis at a median age of 5.5 years, full long-term compliance to prophylaxis was shown only in about 30% of patients, whereas the remaining had voluntarily

Table 4: Studies on secondary prophylaxis in adolescent and adult haemophiliacs.

Author, year [ref.]	Publication	Patients	Median age (range)	Results
Miners, 1998 [62]	Full paper	19 HA, 5 HB, 1 VWD	30 (4–63)	SPT reduced the bleeding frequency (from a median of 37 bleeds per year with ODT to a median of 13 bleeds per year with SPT) but required increased (350%) clotting factor use.
Loverin, 2000 [63]	Abstract	4 HA	-	A 89% reduction of joint bleeds, a better joint status and lower annual factor usage was observed during SPT
Saba, 2000 [64]	Abstract	6 HA, 1 HB	37 (29–49)	SPT reduces the number of joint bleeds per month (from 4.16 with ODT to 0.48 with SPT) but increases costs.
Fischer, 2005 [65]	Abstract	61 SH	26 (19–43)	Long-term secondary prophylaxis prevented joint bleed but did not stop the progression of hemophilic arthropathy.
Coppola, 2005 [66]	Abstract	19 SHA	29 (17–46)	A greater than 70% reduction of bleeding episodes, with about 30% increase of FVIII consumption and costs, was found during SPT.
Tagliaferri, 2006 [67]	Letter	17 HA, 3 HB	27 (12–74)	SPT reduced the number of joint bleeds (from 26.1 per year with ODT to 3.4 per year with SPT) and improved orthopaedic scores and well-being, with 31% increase of costs.
Tagliaferri, 2008 [68]	Full paper	76 HA, 8 HB	28 (13–76)	SPT significantly reduced the number of joint bleeds and slowed deterioration of orthopaedic and radiological scores, with an increase of costs, especially in adolescents.

Abbreviations: HA, haemophilia A; HB, haemophilia B, VWD, von Willebrand disease; SH, severe haemophilia; ODT, on demand therapy; SPT, secondary prophylaxis treatment.

discontinued treatment during late adolescence (60). Among the latter, the majority (23/34) restarted prophylaxis because of increased bleeding frequency whereas 11 definitively switched to on-demand treatment. Interestingly, these 11 patients had later age of start of prophylaxis and lower dose regimen and number of breakthrough bleeds while on prophylaxis, suggesting a milder bleeding phenotype, which also enabled patients to stop prophylaxis of their own initiative (60). It is likely that these clinical indicators may help to identify patients possibly candidates to safely stop prophylaxis. However, an increase of bleeding tendency in patients stopping prophylaxis was also documented in a following study involving patients from the Netherlands and Denmark (61). These data remark the need for adequate training for self-management of treatment and for promoting compliance to prophylaxis in adolescence, the transition age towards the independence, in which major psychological changes may induce the denial of chronic diseases and reduce adherence to treatment (36). On the whole, the clinical indicators above mentioned (60, 61), the patients' bleeding pattern when shifted to on-demand treatment, together with consideration of their lifestyle and physical activities, should be taken into account for treatment choices able to maintain low bleeding triggers for joint damage and to preserve the positive joint outcome of prophylaxis in these generations of patients during adolescence and adulthood.

The other controversial issue concerns the possible benefits of a secondary prophylaxis regimen started later in life, in adolescent or adult individuals who usually already show established arthropathy. Only few publications are available on secondary prophylaxis started in young-adult haemophiliacs (62–68). These reports are all retrospective and often involve small study populations (Table 4). On the whole, these studies report a significant reduction of total and/or joint bleeds in patients on secondary prophylaxis (62–68), associated with a widely

variable increase of concentrate consumption and costs (from 30–40% [66–68] to 350% [62]). The largest survey in this setting was recently carried out among the members of the Italian Association of Hemophilia Centers (AICE) on 84 severe haemophiliacs switched from on-demand treatment to prophylaxis in adolescence (n=30) or adulthood (n=54) (68). After a median follow-up of about five years, this change in modality of treatment significantly reduced the mean number of total and joint bleeds (35.8 vs. 4.2 and 32.4 vs. 3.3, respectively) and the work/school days lost (34.6 vs. 3.0). Furthermore, a statistically significant reduction in the orthopaedic score between on-demand and prophylaxis regimens was observed in the adolescent group, but not in the whole study population. Finally, adolescent/adult haemophiliacs received significantly more (about 39%) factor concentrate, with consequently higher costs, during secondary prophylaxis than during on-demand treatment. In a subgroup of patients data on health-related quality of life assessment, although obtained by non-validated specific instruments, were also available. Notable improvements of patients' satisfaction for treatment, pain/discomfort and mobility, with concurrent reductions of haemophilia-related physical restrictions and psychological impact were shown. On the basis of these results, the significantly higher costs of secondary prophylaxis appeared to be well balanced by the clinical improvement and the greater well-being in this cohort of severe hemophiliacs (68). The reduction of pain and of need for analgesics reported in this and previous studies (54, 63, 64, 68), possibly reflecting the reduction on secondary prophylaxis of chronic inflammatory symptoms triggered by subclinical joint bleeds, is particularly relevant for quality of life of adult patients. A prospective observational study is now ongoing in Italy and the preliminary two-year results confirm the clinical benefits of secondary prophylaxis (69), well beyond the expected reduction of the number of bleeding episodes.

Whether secondary prophylaxis may slow the progression of haemophilic arthropathy in patients with established joint damage is still debated. However, these benefits are likely to be more limited than in earlier prophylaxis, as shown in a Dutch study concluding that long-term secondary prophylaxis was able to reduce but did not stop the progression of joint deterioration (65). In view of this and of the limited resources for haemophilia treatment, the general introduction of secondary prophylaxis in adult patients rises perplexities and the selection of candidate patients on a case-by-case basis is suggested (15, 59). However, in the frame of a general tendency towards more intensive treatment both for prophylaxis or for on demand approaches, the large variations in the use of factor replacement in different countries reveal an overlap between concentrate consumption used on demand in some countries (for example, in France or in Denmark) and more conservative prophylactic regimens (Dutch approach) (47, 48, 59, 61). The reported tendency to the reduction of concentrate requirement for prophylaxis with age and the increased consumption with progression of arthropathy in patients treated on-demand, resulting in substantially comparable concentrate use when long-term follow up are considered (70, 71), should also be taken into account. Moreover the cost-benefit ratio of prophylaxis in adult patients is more clearly affected by the indirect health-related costs, including hospitalisations, visits at haemophilia centres, physiotherapy cycles, orthopedic consultancies and surgical procedures (49, 50, 68), and benefits may be even more evident in studies with long-term follow-up (71).

Optimal regimens and duration of secondary prophylaxis in adolescent and adult patients are even more uncertain than in children. It is likely that tailoring regimens of treatment on the basis of patients' bleeding pattern and lifestyle may improve the overall cost-benefit ratio of prophylaxis in this setting. Only large, prospective, long-term, possibly randomised, studies will help to definitively assess the clinical impact of this strategy in adolescent and adult haemophiliacs.

Conclusions

While primary prophylaxis has been definitively proven as the gold standard for preserving joint function in severe haemophiliacs, the literature data also support the effectiveness of early secondary prophylaxis in children. Furthermore, recent evidence suggests the potential role of delayed secondary prophylaxis in increasing joint protection as compared to on-demand therapy, even in adulthood. The excellent results in patients without inhibitors are leading to experience prophylaxis approaches with both bypassing agents (recombinant activated FVII and activated prothrombin complex concentrates) also in children with an inhibitor, as these patients are at high risk to develop severe musculoskeletal impairment (36, 72). However, larger and more rigorous studies are needed to confirm the encouraging findings recently reviewed (72) and the hope that extrapolations from patients without inhibitors are applicable to those with inhibitors.

Despite the lack of controlled studies, it is unquestionable that prophylaxis reduces the number of joint bleeds and, in parallel, the patients' physical and psychological restrictions at any age. In this respect, the improvement of quality of life appears to counterbalance the undoubtedly higher costs of secondary prophylaxis, also in adolescent and adult patients. Moreover, some indirect benefits of prophylaxis are very difficult to be quantified (for example, social benefits arising from regular school and work activities), even in the complex cost-efficacy and cost-utility models recently developed also in the pharmacoeconomics of haemophilia (50, 73, 74). For the same reasons, with the obvious limitations related to the general resources of the health-care systems and to the specific conditions of each patient and his family, the recent recommendation from the Medical and Scientific Advisory Council of the US National Hemophilia Foundation (MASAC), extending the concept of prophylaxis as the standard of care for severe haemophiliacs of all ages, seem justified (75).

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