PharmacoEconomics (2018) 36:263–284
https://doi.org/10.1007/s40273-017-0588-z

REVIEW ARTICLE

Modern Treatments of Haemophilia: Review of Cost-Effectiveness Analyses and Future Directions

Paolo A. Cortesi[1] · Lucia S. D'Angiolella[1] · Alessandra Lafranconi[1] · Mariangela Micale[1] · Giancarlo Cesana[1] · Lorenzo G. Mantovani[1]

Published online: 23 November 2017

Abstract

Background Cost is currently one of the most important aspects in haemophilia care. Factor concentrates absorb more than 90% of healthcare direct costs of haemophilia care, and the debate regarding the high cost of haemophilia treatments and their different use across different countries is increasing.

Objective The objective of this study was to review cost-effectiveness analyses conducted on treatment options in haemophilia, focusing on their results and their strengths and limitations; to highlight the possible issues associated with economic evaluations of new treatment options.

Methods Electronic searches in PubMed and EMBASE were performed to retrieve papers published between November 2015 and September 2017 to update the previous review of economic evaluations of haemophilia treatments by Drummond et al. Reference lists of included articles and reviews were examined for relevant studies, which were assessed for their quality and their empirical results.

Results Twenty-six relevant economic analyses were identified; 15 (57.7%) were conducted in patients with haemophilia with inhibitors while 11 (42.3%) involved patients without inhibitors. There were methodological variations among the included studies, and differences in the treatment schemes make a comparative assessment of interventions for patients with haemophilia difficult. Only immune tolerance induction showed consistent results in its cost-saving profile compared with the treatment with bypassing agents.

Conclusions Economic evaluations of haemophilia treatments are increasing, but the identification of general cost-effectiveness trends is still difficult in these studies. We are now facing a new era in haemophilia management with a soaring need for high-quality economic evaluations, performed through proactive collaboration between clinical experts, budget holders and health economists.

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s40273-017-0588-z) contains supplementary material, which is available to authorized users.

✉ Lorenzo G. Mantovani
lorenzo.mantovani@unimib.it

[1] Research Centre on Public Health (CESP), University of Milan-Bicocca, Via G. Pergolesi 33, Monza 20900, Italy

Key points

Economic evaluations in haemophilia are increasing in number and quality, providing information on the cost effectiveness of different treatment options in patients with and without inhibitors. However, the variability in the methods used and the differences in the treatments under assessment often make the identification of general trends difficult.

Only immune tolerance induction showed consistent results in its cost-saving profile compared with the treatment with bypassing agents. While prophylaxis with recombinant Factor VIII seems a cost-effective option, compared with on demand, this observation depends on several factual variables, including (1) annual background bleeding rate, (2) relative efficacy, (3) dosing regimens and (4) the price of recombinant Factor VIII.

The introduction of new treatments is changing haemophilia management and making new economic assessments based on solid evidence and methods mandatory. In light of the evolution of the haemophilia health economic literature, future analyses based on short-term time spans and intermediate outcomes will neither match current scientific standards nor fulfil the requirements of policy-making bodies.

1 Introduction

Haemophilia is a rare congenital bleeding disorder characterised by gene abnormalities leading to defective or missing clotting Factor VIII (FVIII), called haemophilia A (HA), and Factor IX (FIX), called haemophilia B (HB), with a variable impact both from clinical and quality-of-life points of view [1–3]. The prevalence of HA is approximately five times that of HB [4], with a worldwide frequency estimated at one per 5000–7000 male births [5].

Patients affected by severe HA or HB present with repeated, spontaneous and post-traumatic bleeding episodes that seriously interfere with their everyday lives. In particular, recurrent haemarthrosis (bleeding into the joint cavities) leads to serious deterioration of joint structures, with a consequent reduction in function and atrophy of the associated skeletal muscles [6]. In the last decade, there has been a continuous improvement in the treatment of patients with haemophilia, thanks to the availability of recombinant concentrates characterised by high efficacy and safety, and to the widespread adoption of prophylaxis as the replacement therapy regimen [7]. Indeed, patients with haemophilia can be treated on demand (OD) (i.e. following a bleed), or prophylactically to prevent bleeding and the consequent deleterious effects on joint status in the first instance. Increasing evidence supports the clinical and quality-of-life benefits over OD treatment of the adoption of prophylaxis, started before the age of 3 years, prior to two joint bleeds ('primary prophylaxis'), but also after the onset of serial bleeding or established joint damage ('secondary prophylaxis' or 'tertiary prophylaxis', respectively) [8]. Starting prophylaxis early in life and after very few joint bleeds is associated with better joint outcomes [9].

The major complication in the treatment of patients with haemophilia is the development of inhibitory antibodies to FVIII or FIX, which occurs in approximately 30% of patients with HA and in approximately 3% of patients with HB [10, 11]. These antibodies reduce therapy effectiveness even to zero, neutralising the clotting activity and requiring the use of immune tolerance induction (ITI) treatment, a bypassing agent in prophylaxis or an OD regimen [12]. Immune tolerance induction therapy consists of providing a factor concentrate (FVIII for HA and FIX for HB) regularly at a high dose until the body is trained to recognise the treatment product without reacting to it [13]. When ITI is successful, the inhibitors disappear and the patient's response to factor concentrates (FVIII or FIX) returns to normal. When ITI fails, the persistence of inhibitors at a high titre precludes the standard replacement treatment with FVIII/FIX concentrates and requires the use of bypassing agents in prophylaxis or an OD regimen, making patient management challenging. Indeed, the efficacy of bypassing agents, i.e. activated prothrombin complex concentrates (aPCC) and recombinant activated FVII (rFVIIa), needed to overcome the haemostatic interference of the inhibitor, is not comparable to that of factor concentrates [13]. Further, the treatments for patients with haemophilia with inhibitors are more expensive than the treatment for patients without inhibitors [13–15].

Currently, cost is one of the most important aspects in haemophilia care. Numerous studies have analysed the healthcare direct costs of patients with haemophilia [13, 15–22]. The costs of factor concentrates amount to 90% of the total healthcare direct costs of haemophilia care [23]. The scientific and political debate regarding the high cost of haemophilia treatment, its effects and the different use across different countries is increasing [24, 25]. A recent review [26] assessed the quality of reporting in more recent economic evaluations in haemophilia; focusing on the common methodological deficiencies and proposing standards for conducting and reporting future economic evaluations. However, there are still unresolved important

questions on the economic evaluations of haemophilia treatments, such as:

1. Is it cost effective to provide recombinant factor prophylaxis for severe HA or HB without an inhibitor, or is OD therapy a more cost-effective option?
2. Is the provision of prophylactic therapy for adults with severe HA or HB cost effective?
3. Is ITI for patients with inhibitors cost effective?
4. Is prophylaxis for patients with inhibitors cost effective?
5. Will new recombinant factor products (which have an extended half-life) or non-factor replacement strategies (e.g. a recombinant, humanised, bispecific monoclonal antibody that bridges activated FIX and Factor X to restore the function of missing activated FVIII) offer good value compared with existing recombinant products?

In light of such crucial questions, we examined cost-effectiveness analyses conducted on treatment options in haemophilia, focusing on their results and their strengths and limitations. In the discussion, we identify some possible issues associated with the economic evaluations of new treatment options for patients with haemophilia, considering such new treatments are now coming onto the market [24, 25].

2 Methods

A systematic literature review was performed to collect and critically review the health economic evidence on the different treatments of patients affected by haemophilia. Our study updates a previous review of economic evaluations of haemophilic treatments options by Drummond et al. covering the years from 2008 until 2015 [26]. While the review by Drummond and colleagues focussed on methodological issues related to reporting economic evaluations in haemophilia, our review focuses on the assessment of empirical results. Studies published earlier than 2008 were not included given the focus of our review on modern treatments, and the lack of consensus on standardised reporting prior to that year [27]. To update Drummond et al.'s review, original studies and analyses published between November 2015 and September 2017 were searched for in PubMed and EMBASE, using "cost effectiveness" OR "economic evaluation" OR "cost analysis" OR "cost utility" OR "cost–benefit" OR "economic analysis" OR "pharmaco economic" OR "economic near model" OR "decision model" OR "economic study" OR "cost-effectiveness" OR "cost-analysis" OR "cost-utility" OR "cost–benefit" OR "pharmaco-economic" OR "decision-model" OR "economic-study" OR "cost" AND "haemophilia" OR "haemophilia" OR "factor VIII deficiency" OR "factor 8 deficiency" as keyword research terms.

To maximise retrieval of all pertinent papers, we applied medical subject headings ('MeSH' terms), or keyword searches when at all appropriate, and for the sake of completeness, we reviewed the reference lists of all relevant studies and reviews on the topic to identify additional studies of interest. Two members of the review team (AL, MM) examined the studies in a three-step process: (1) we selected the articles based on the title and abstract, (2) we retrieved and reviewed the potentially relevant articles selected based on the abstract in step 1, and (3) we analysed articles that met the inclusion criteria and included them in the review. Disagreement between the two reviewers was resolved by consensus of a third party (PAC).

To be included in the review, an article had to summarise findings in English, and compare treatments in patients with haemophilia, reporting information on costs and effects (e.g. cost-effectiveness study, and cost-utility study). Papers reporting information on treatment costs only (e.g. cost-of-illness study) and articles that did not assess treatment options but focused on other aspects of haemophilia management, such as diagnostic tests or surgical operations, and differences in access to healthcare services were excluded. The quality of identified studies was assessed by two reviewers (PAC and LSD) using the Consolidated Health Economic Evaluation Reporting Guidelines checklist [28]. Further, for each included study, we extracted the following data using a standardised form: aim, design, time horizon, perspective, subject characteristics, treatments, clinical parameters, results including costs, outcomes, incremental cost-effectiveness ratios (ICERs) and authors' conclusions.

3 Results

The literature search identified 136 records from bibliographic database searches and supplementary searching (e.g. reference/citation checking and additional references). After title and abstract screening, 35 records were considered to be potentially relevant and, after full-text screening, 26 studies were considered eligible for inclusion (Fig. 1). Tables 1, 2, 3 summarise these studies.

The majority of economic evaluations reported information on many items required by the Consolidated Health Economic Evaluation Reporting Guidelines checklist (see Table 1 of the Electronic Supplementary Material). The quality of the studies seems to have improved in the last few years, and this improvement is more evident if we compare the quality of the studies retrieved in our review

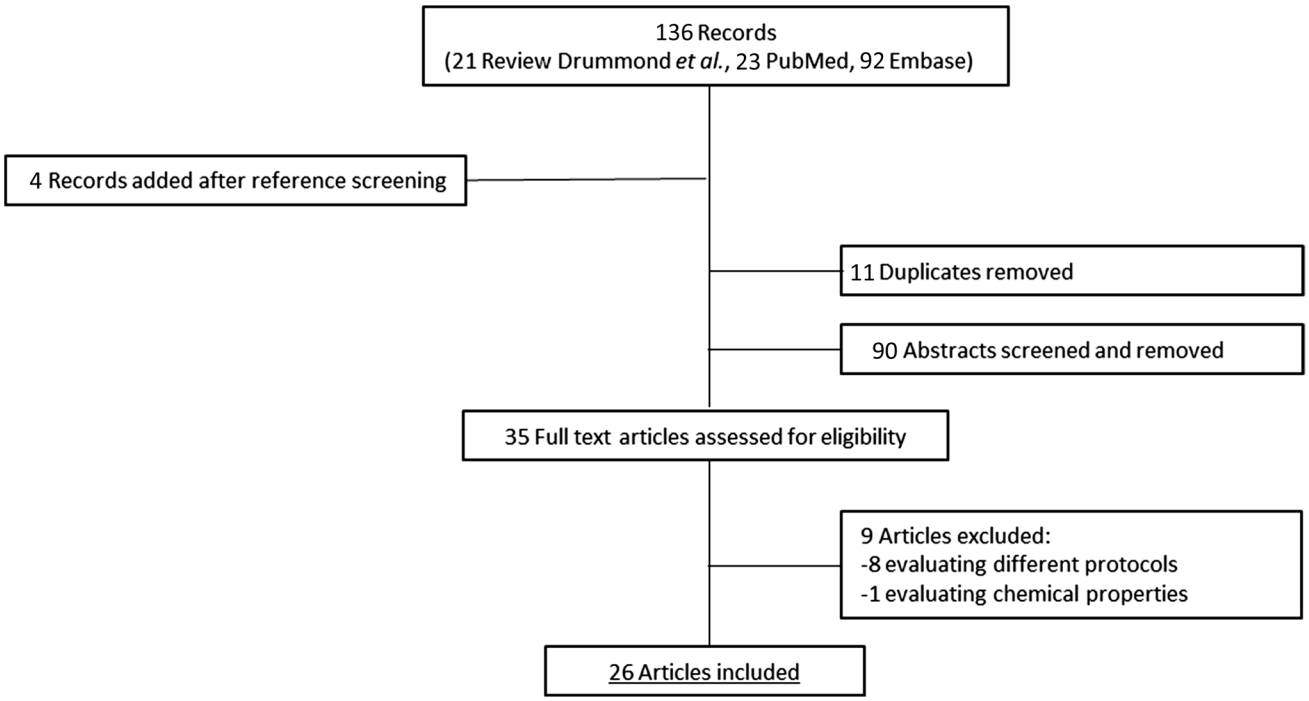

Fig. 1 Flowchart of the selection process

with the quality of the studies published between 1996 and 2008 and assessed by Miners [29].

Within the included studies, 14 were cost-effectiveness analyses, seven were cost-utility analyses, while nine reported information on the cost and effectiveness of treatments, making it possible to estimate their cost effectiveness. Most studies were conducted in Europe ($n = 13$, 50.0%) and in North American countries ($n = 5$, 19.2%) or in both continents ($n = 3$, 11.5%), followed by Asia ($n = 4$, 15.4%) and Latin America countries ($n = 1$, 3.8%). The majority of studies used the third-party payer's perspective for measuring costs, while three studies applied a societal perspective, although cost inputs were not always consistent with the perspective taken. Nine studies included drug costs only, while 15 studies included drug costs, direct medical costs (e.g. hospitalisation, visits/examinations/check-ups, tests, rehabilitation and management of bleeding) and non-medical costs (e.g. travelling costs). Only two studies measured indirect costs (e.g. productivity losses and parents' lost workdays).

The articles retrieved were divided based on the target population: (1) patients without inhibitors and (2) patients with inhibitors. Eleven (42.3%) of the included studies assessed treatments for patients with haemophilia without inhibitors [1, 21, 30–38], while 15 (57.7%) studies assessed treatments for patients with inhibitors [13, 14, 39–51]. The details of the studies included in each group and the treatments assessed are reported below.

3.1 Patients Without Inhibitors

On-demand treatments were compared with one or more prophylaxis regimens in nine of 11 studies conducted in patients without inhibitors; while only two studies compared different prophylaxis regimens without including ON treatment (Table 1).

3.1.1 Comparisons of Prophylaxis vs. On-Demand Treatment in Haemophilia A and B

All studies except one included only direct costs using the insurance or National Health Service point of view. These studies used different outcomes to assess the cost effectiveness of prophylaxis vs. OD treatment: five studies used quality-adjusted life-years (QALYs), four studies used number of bleedings avoided, and one study used both QALYs and number of bleedings avoided (Table 1). The majority of the studies assessed the cost effectiveness using a Markov model, while three studies used direct evidence from either a clinical trial or a retrospective cohort study.

Only one study reported prophylaxis as a cost-saving treatment compared with OD treatment, using the UK National Health Service point of view [34]. In the same multi-country study, primary prophylaxis was more effective and costly compared with OD treatment when the analysis was conducted using the US or Swedish third-party payer's perspective, with an ICER of US$68,108 and SEK484,888 per QALY gained, respectively [34]. The

Table 1 Studies on patients without inhibitors

Reference and funding sources	Study design and time horizon	Country	Population	Treatment option	Perspective and year of cost	Clinical parameters in the analytical model-based study (bleeding)	Costs (description)
Risebrough et al. [30]; funded in part by Bayer, Inc. Canada	Markovmodel; time horizon:5 years	Canada	Boys < 1 year of age with severe haemophilia A; PUPs (treatment starts at 1 year of age)	1. PP 2. EscDose P 3. OD (using rFVII)	Societal, 2003	Annual bleeds OD: 25.9 Relative risk reduction of bleeding SP: 94.1% EscDose P Step 1: 63.4% Step 2: 89.2% Step 3: 94.1%	Direct and indirect costs (drugs, visits and tests, complications, hospitalisation, home programmes and parents' lost workdays)
Miners [31]; funded by Baxter Healthcare	Markov model; time horizon: lifetime (70 years)	UK	Patients with severe haemophilia A at birth	1. PP 2. OD (using rFVIII)	UK National Health Service, 2007	Annual bleeds OD age < 18 years: 15.8 OD age > 18 years: 31.8 PP: NR	Direct costs (drugs, visits and tests, major surgery, hospitalisation)
Daliri et al. [32]; funded by the Health Ministry of Iran	Retrospective chart review of 25 patients; time horizon:6 months	Iran	Boys (0–9 years of age) with severe haemophilia A	1. OD 2. PP (using rFVIII)	Third-party payer, 2008	NA	Direct costs (clotting factor used/patient, in 6 months)
Colombo et al. [33]; funded by Pfizer Italia Srl	Markov model; time horizon:70 years	Italy	Patients with severe haemophilia A	1. "hybrid" (primary PP followed by OD in adults) 2. OD 3. PP 4. SP (OD used in 0–2 years of age followed by prophylaxis) [using rFVIII]	Italian National Health System, 2010	Annual bleeding rate Adolescent "hybrid": 2.5–33.7 OD: 33.7 PP:2.5 SP: 33.7–2.5 Adults "hybrid": 5.4–36.9 OD: 36.9 PP: 5.4 SP: 36.9–5.4	Direct costs (drug, visits, tests, major surgery and hospitalisation)

Table 1 continued

Reference and funding sources	Study design and time horizon	Country	Population	Treatment option	Perspective and year of cost	Clinical parameters in the analytical model-based study (bleeding)	Costs (description)
Farrugia et al. [34]; funding NR	Markov model; time horizon: lifetime	USA, UK, Sweden	Patients with severe haemophilia A with prophylactic treatment initiated in the first year of life and OD treatment initiated at the earliest haemorrhage	1. PP 2. Daily Pro dosing 3. OD (using rFVII)	Single provider (UK NHS), third-party provider (USA) and Sweden, NR	Annual bleeding rate OD: 36 PP: 3	Direct costs (drug, surgery and costs associated with bleeding episodes)
Castro Jaramillo et al. [35]; funded in part by Departamento Administrativo de Ciencia, Tecnologia e Innovación	Markov model; time horizon: lifetime	Colombia	Patients untreated with severe haemophilia A (2 years of age)	1. PP 2. OD (using rFVIII or pdFVIII)	Colombian health system, 2013	Annual bleeding rate OD: 17 PP: 3	Direct costs (drug, visits, procedures and imaging)
Gringeri et al. (the ESPRIT Study) [1]; funded by Baxter Italy	Randomised control study; time horizon: 10 years	Italy	Children with severe haemophilia A, aged 1–7 years, with negative clinical-radiologic joint score at entry and at least one bleed during the previous 6 months	1. PP 2. OD (using rFVIII)	Italian National Health Service, 2010	NA	Direct costs [drug (rFVIII)]
Polack et al. 2015 [21]; funding NR	Clinical observational trial; time horizon:1 year	France	Patients with severe and moderate haemophilia B and without inhibitors (mean age 28.1 ± 18.1 years)	1. OD 2. PP (with rFIX and pdFIX)	French National Health Insurance System, 2011	NA	Direct costs (therapy, hospitalisations, tests and exams, visits, surgery, rehabilitation, transportation)
Coppola et al. [36]; funded by Bayer SpA	Markov model; time horizon: lifetime	Italy	Patients with severe haemophilia A	1. LP 2. OD	Italian National Health Service, 2016	Relative risk of joint bleeds LP vs. OD: 7.85 Relative risk of other bleeds LP vs. OD: 7.67	Direct costs (drug, bleeds management, hospitalisations and ambulatory)
Iannazzo et al. [37]; funded by Baxalta Innovation GmbH	Microsimulation model; time horizon:1 year	Italy	Patients with severe haemophilia A	1. SP 2. PK-driven P	Italian National Health Service, 2016	Annual bleeding rate 18.3 (when FVIII level $< 1\%$)	Direct costs (drug)

Table 1 continued

Reference and funding sources	Study design and time horizon	Country	Population	Treatment option	Perspective and year of cost	Clinical parameters in the analytical model-based study (bleeding)	Costs (description)
Pasca et al. [38]; funding NR	Observational retrospective study; time horizon: 6 months	Italy	Paediatric patients aged < 12 years with severe haemophilia A and already receiving prophylaxis treatment with Advate® ($n = 6$)	1. PK-driven P vs. 2. SP	Regional Health Service (Veneto), 2017	NA	*Direct costs (drug for prophylaxis and further treatments owing to bleeding, instrumental and standard laboratory examinations, visits)* *The authors incorrectly reported the inclusion of indirect costs*

Reference and funding sources	Costs (quantification)	Type of analysis	Outcomes (description)	Outcome (quantification)	Treatment comparison	ICER (ratio)
Risebrough et al. [30]; funded in part by Bayer, Inc. Canada	5 year total cost per patient OD: 277,209 CAD EscDose P: 443,185 CAD PP: 569,835 CAD	CEA	Joint bleeding events	OD: 69.1 joint bleeding EscDose P: 17.3 joint bleeding PP: 4.1 joint bleeding	EscDose P vs. OD	Can$3192 per joint bleeding avoided
					PP vs. EscDose P	Can$9046 per joint bleeding avoided
		CEA	Target joints (% 1 TJ at age 6 years)	OD: 64.8% of patients with 1 TJ	EscDose P vs. OD	Can$244,082 per TJ avoided
				EscDose: 43.8% of patients with 1 TJ	PP vs. EscDose P	Can$61,857 per TJ avoided
				PP: 11.6% of patients with 1 TJ		
		CUA	QALYs	OD: 4.17 QALYs EscDose: 4.47 QALYs	EscDose P vs. OD	Can$542,938per QALY
				PP: 4.48 QALYs	PP vs. EscDose P	Can$1,000,000 per QALY gained
Miners [31]; funded by Baxter Healthcare	70-year total cost per patient OD: £644,000 PP: £858,000	CUA	QALYs	OD: 13.95 QALYs PP: 19.58 QALYs	PP vs. OD	£38,000 per QALY gained
Daliri et al. [32]; funded by the Health Ministry of Iran	6 months cost per patient OD: €3571.42 PP: €6747.45	CEA	Bleeding event	OD: 16.42 bleeds PP: 1.54 bleeds	OD vs. PP	€213,45 per avoided bleed

Table 1 continued

Reference and funding sources	Costs (quantification)	Type of analysis	Outcomes (description)	Outcome (quantification)	Treatment comparison	ICER (ratio)
Colombo et al. [33]; funded by Pfizer Italia Srl	Total cost per 100 patients followed up to 70 years OD: €87,426,642 Hybrid: €129,600,063 PP: €166,168,643 SP: €164,440,652	CUA	QALYs	OD: 4137 QALY per 100 patients Hybrid: 4491 QALYs per 100 patients PP: 6094 QALYs per 100 patients SP: 6051 QALYs per 100 patients	"Hybrid" vs. OD PP vs. OD SP vs. OD	€119,134 per QALY €40,236 per QALY €40,229 per QALY
Farrugia et al. [34]; funding NR	Lifetime total cost per patient USA OD: US$4,140,275 PP: $4,563,274 UK OD: £1,784,095 PP: £1,503,229 Sweden OD: SEK22,101,124 PP: SEK27,432,176 Daily PP dosing: SEK11,559,131	CUA (in US setting)	QALYs	USA OD: 19.42 QALYs PP: 25.48 QALYs	PP vs. OD	US$68,109 per QALY gained
		CUA (in UK setting)	QALYs	UK OD: 27.16 QALYs PP: 36.85 QALYs	PP vs. OD	PP is cost saving
		CUA (in Sweden setting)	QALYs	Sweden OD: 17.87 QALYs PP: 28.87 QALYs	PP vs. OD	SEK484,888 per QALY gained
			QALYs	Sweden OD: 17.87 QALYs Daily Pro dosing: 28.87 QALYs	Daily Pro dosing vs. OD	Daily Pro dosing is cost saving
Castro Jaramillo et al. [35]; funded in part by Departamento Administrativo de Ciencia, Tecnologia e Innovación	Lifetime total cost per patient pdFVIII OD: US$1,690,993 pdFVIII PP: US$1,944,996 rFVIII OD: US$2,695,812 rFVIII PP: US$3,117,282	CUA (using pdFVIII)	QALYs	OD: 27.71 QALYs PP: 32.33 QALYs	PP vs. OD	US$54,995 per QALY gained
		CUA (using rFVIII)	QALYs	OD: 27.71 QALYs PP: 32.33	PP vs. OD	US$91,147 per QALY gained
Gringeri et al. (the ESPRIT Study) [1]; funded by Baxter Italy	OD: €35,829 per year PP: €79,668 per year	CEA	Mean annual bleeding per patient	OD: 1.08 bleeds per month PP: 0.52 bleeds per month	PP vs. OD	€7537 per bleeding event avoided[a]

Table 1 continued

Reference and funding sources	Costs (quantification)	Type of analysis	Outcomes (description)	Outcome (quantification)	Treatment comparison	ICER (ratio)
Polack et al. 2015 [21]; funding NR	OD = €69,425 ± 80,398 PP = €135,435 ± €71,126 (1 year)	CEA	Mean annual number of haemorrhages	OD = 4.73 ± 7.88 PP = 1.81 ± 3.06	OD vs. PP	€22,605 per haemorrhage event prevented
Coppola et al. [36]; funded by Bayer SpA	Lifetime total cost per patient LP €1,682,380 OD: €1,452,686	CEA	QALY	LP: 20.10 QALYs OD: 15.84 QALYs	LP vs. OD	€5,3978 per QALY gained
Iannazzo et al. [37]; funded by Baxalta Innovation GmbH	One-year total cost per patient SP: €265,859 PK-driven P: €260,662 (annual)	CEA	AJBR	SP: 1.012 PP: 0.845	SP vs. PK-driven P	PK-driven P is cost saving
Pasca et al. [38]; funding NR	One-year total cost per all patients SP: €513,525 PK-driven P: €458,727	Economic evaluation	Number of bleedings, during standard and PK driven	SP: 7 in 6 patients PK-driven P: 2 in 6 patients	PK-driven P vs. SP	PK-driven P is cost saving

AJBR annual joint bleed rate, *CEA* cost-effective analysis, *CUA* cost-utility analysis, *EscDose P* escalating-dose prophylaxis, *FVIII* Factor VIII, *ICER* incremental cost-effectiveness ratio, *LP* late prophylaxis, *NA* not applicable, *NGO* non-governmental organisation, *NHS* National Health Service, *NR* not reported, *OD* on-demand, *OOP* out-of-pocket, *PdFIX* plasma-derived Factor IX, *PK-driven P* pharmacokinetic-driven prophylaxis, *PP* primary prophylaxis, *PUPs* previously untreated patients, *QALYs* quality-adjusted life-years, *rFIX* human recombinant factor IX, *rFVII* human recombinant Factor VII, *RFVIII* human recombinant Factor VIII, *SP* standard prophylaxis, *TJ* target joint

[a]The ICER was estimated using the total cost and bleeds reported by the patients in the two treatment options during the follow-up period and not using the mean cost and bleed per patient

Table 2 Studies on patients with inhibitors [excluded immune tolerance induction (ITI)]

Reference and funding sources	Study design and time horizon	Country	Population	Treatment option	Perspective and year of cost	Clinical parameters in the analytical model-based study (bleeding)	Costs (description)
Steen Carlsson et al. [39]; funded by Baxter Bioscience	Economic evaluation based on individual patient data from a clinical study (FENOC); time horizon: time to resolve a bleed	USA, Sweden and Turkey	Patients with severe haemophilia A with inhibitors	1. OD aPCC 2. OD rFVIIa	Third-party payer; 2005 (USA and Turkey) and 2006 (Sweden)	NA	Only drug costs
You et al. [40]; funded by Novo Nordisk Korea	Decision tree (for costs) and observational analysis (for outcomes); time horizon: time to resolve a bleed	Korea	Patients with haemophilia A with inhibitors	1. OD aPCC 2. OD rFVIIa for treating mild-to-moderate bleeds	Korean reimbursement authorities; 2005	NA	Direct costs (drugs, hospitalisations and transportation)
Hay and Zhou [41]; funded by Baxter International Inc.	Decision tree; time horizon: time to resolve a bleed	USA	Patients with haemophilia A with inhibitors	1. OD aPCC 2. OD rFVIIa for treating mild-to-moderate bleeds (home treatment)	US third-party payer; 2009	NA	Direct cost (drugs, hospitalisation and physician fees)
Salaj et al. [42]; funded by Novo Nordisk A/S	Retrospective analysis of data collected from two haemophilia A registries; time horizon: time to resolve a bleed	Czech Republic	Patients with haemophilia A with inhibitors	1. OD aPCC 2. OD rFVIIa for treating mild-to-moderate bleeds (home treatment)	Healthcare payer; 2009	NA	Direct cost
Jimenez-Yuste et al. [43]; funded by Novo Nordisk Pharma sA	Decision analytic model; time horizon: time to resolve a bleed	Spain	Patients with severe haemophilia A with inhibitors	1. OD aPCC 2. OD rFVIIa for treating mild-to-moderate bleeds (home treatment)	Spanish National Healthcare System; 2011	NA	Direct costs (drug and hospitalisation)
Villarrubia et al. [44]; funded by Baxter	Microsoft Excel 2010-based model; time horizon: 1 year	Spain	Patients with severe haemophilia A with inhibitors	1. PP with aPCC 2. OD with rFVIIa	Spanish National Health System; 2013	Number of annual bleedings OD: 25.23 PP: 8	Direct costs (drug, cost related to bleeding episodes and cost of surgery)
Golestani et al. [45]; funded by Aryogen Biopharmaceutical Company	Decision-analytic model; time horizon: time to resolve a bleeding	Iran	Patients with haemophilia A with inhibitors	1. OD rFVIIa 2. aPCC	Iranian Healthcare System; 2014	NA	Direct medical and non-medical cost (drug costs, out-patients, imaging, in-patients, hospitalisation, nursing, adaptation, travelling costs)
Mehta et al. [46]; funded by Baxalta US	Budget impact model; time horizon: 1 year	USA	Patients with haemophilia with inhibitors	1. aPCC prophylaxis, 2. rFVIIa prophylaxis 3. rFVIIa OD	US payer; 2014	Number of annual bleedings PP aPCC: 7.9 PP rFVIIa: 15.8 OD rFVIIa: 28.7	Direct costs (drug)

Table 2 continued

Reference and funding sources	Study design and time horizon	Country	Population	Treatment option	Perspective and year of cost	Clinical parameters in the analytical model-based study (bleeding)	Costs (description)
Leissinger et al. [14]; funded by Baxter Bioscience	Prospective, randomised, crossover study; time horizon: 15 months	Europe and USA	Patients with severe haemophilia A with inhibitors (who used bypassing agents)	1. aPCC OD (85 U/kg for bleeding) 2. aPCC SP (85 U/kg infused on 3 non-consecutive days/week)	Payer perspective; NR	NA	Direct costs (drug)

Reference and funding sources	Costs (quantification)	Type of analysis	Outcomes (description)	Outcome (quantification)	Treatment comparison	ICER (ratio)
Steen Carlsson et al. [39]; funded by Baxter Bioscience	NR	CEA	Bleeding stopped Pain reduction	NR NR	OD aPCC vs. rFVIIa OD aPCC vs. rFVIIa	aPCC is cost saving aPCC is cost saving in the first hours, then rFVIIa is more effective (and more costly)
You et al. [40]; funded by Novo Nordisk Korea	Cost per bleeding rFVIIa: KRW12,460,000 (US$12,311) aPCC: KRW18,304,000 (US$18,085)	CEA	Treatment effectiveness (cases with bleeding episodes resolved)	rFVIIa: 87.1% aPCC: 64.0%	OD aPCC vs. rFVIIa	The authors did not provide an ICER but costs and effectiveness separately. rFVII is cost saving
Hay and Zhou [41]; funded by Baxter International Inc.	Cost per bleeding rFVIIa: US$35,838 25,969 (per bleeding)	Cost analysis	Treatment effectiveness (cases with bleeding episodes resolved)	rFVIIa and aPCC: 85.0%	OD aPCC vs. rFVIIa	aPCC is cost saving
Salaj et al. [42]; funded by Novo Nordisk A/S	Cost per bleeding rFVIIa: €12,760 aPCC: €19,802 (per bleeding)	CEA	Bleed resolution within $\leq$ 12 h	rFVIIa: 93.8% aPCC: 60.4% (of all rFVIIa- or aPCC-treated bleeds)	OD aPCC vs. rFVIIa	rFVIIa is cost saving
Jimenez-Yuste et al. [43]; funded by Novo Nordisk Pharma sA	Cost per bleeding rFVIIa: €8473 in children and €15,579 in adults aPCC: €8627 in children and €15,677 in adults	CEA	Cumulative joint bleed resolution after 24 and 36 h	rFVIIa: 88% in children and 95% in adults aPCC: 62% in children and 76% in adults	OD aPCC vs. rFVIIa	rFVIIa is cost saving
Villarrubia et al. [44]; funded by Baxter	Annual cost per patient: aPCC prophylaxis: €524,358 rFVIIa OD: €627,876	Cost analysis	–	–	PP with aPCC vs. OD with rFVIIa	Overall annual cost of prophylaxis was €524,358 per patient less expensive than the cost of OD treatment with rFVIIa

Table 2 continued

Reference and funding sources	Costs (quantification)	Type of analysis	Outcomes (description)	Outcome (quantification)	Treatment comparison	ICER (ratio)
Golestani et al. [45]; funded by Aryogen Biopharmaceutical Company	Cost per bleeding AryoSeven: US$2912 aPCC: US$3785	CEA	Success therapy (based on a scoring system evaluating pain and movement)	rFVIIa: 72% aPCC: 89% (per bleeding episode)	OD rFVIIa vs. OD aPCC	US$5146 per bleeding avoided
Mehta et al. [46]; funded by Baxalta US	Annual cost per patient (DOSE Registry) rFVIIa OD (median dose of 695 μg/kg per bleeding episode): US$34,009 aPCC PP: US$26,536	Cost analysis	Cost difference between aPCC PP vs. rFVIIa OD and number of annual bleeding events avoided (DOSE Registry)	Annual cost saving: US$7474 per kg and 20.8 bleeding episodes saved	aPCC prophylaxis vs. OD rFVIIa	aPCC prophylaxis saved US$360 per kg for each bleeding episode avoided
	Annual cost per patient (HTRS Registry) rFVIIa OD (median dose of 450 μg/kg per bleeding episode): US$22,020 aPCC PP: US$6536	Cost analysis	Cost difference between rFVIIa OD vs. aPCC PP and number of annual bleeding events avoided (HTRS Registry)	Annual cost saving with OD rFVIIa was US$4515 PP aPCC prevented 20.8 bleeding episodes	aPCC prophylaxis vs. OD rFVIIa	PP aPCC saved US$217 per kg for each bleeding episode avoided
	Annual cost per patient (HTRS Registry) rFVIIa OD (median dose of 786 μg/kg per bleeding episode): US$38,462 aPCC PP: US$26,536	Cost analysis	Cost difference between rFVIIa OD vs. aPCC PP and number of annual bleeding events avoided (HTRS Registry)	Annual cost saving with OD rFVIIa was US$11,926 PP aPCC prevented 20.8 bleeding episodes	aPCC prophylaxis vs. OD rFVIIa	PP aPCC saved US$573 per kg for each bleeding episode avoided
Leissinger et al. [14]; funded by Baxter Bioscience	OD: US$205,549 per patient SP: US$493,633 per patient (6 months)	Cost analysis	Mean number of bleeding episodes (6-month treatment period)	OD: 13.1 ± 7.1 bleeds SP: 5.0 ± 5.0 bleeds	OD vs. SP	The cost of prophylaxis was 2.4 times higher that of OD therapy. The cost of SP per bleeding episode avoided was US$35,565

aPCC activated prothrombin complex concentrates, *CEA* cost-effectiveness analysis, *FVIII* Factor VIII, *ICER* incremental cost-effectiveness ratio, *NA* not applicable, *NR* not reported, *OD* on demand, *QOD* every other day, *rFVII* recombinant Factor VII, *rFVIIa* recombinant activated Factor VII

Table 3 Studies on patients with inhibitors assessing immune tolerance induction (ITI)

Reference and funding sources	Study design and time horizon	Country	Population	Treatment option	Perspective and year of cost	Clinical parameters (ITI success rate and bleeding)	Costs (description)
Odeyemi and Danø [47]; funded by Novo Nordisk A/S	Decision tree; 1–1.5 year (from detection to the elimination of inhibitors with ITI)	UK	Patients with haemophilia A with inhibitors	1. OD rFVIIa followed by ITI 2. OD aPCC followed by ITI	UK National Health Service; 2008	NA	Treatment costs
Rasekh et al. [48]; funded by Shahid Beheshti University of Medical Sciences	Decision analytic model; time horizon: 10 years	Iran	Patients with haemophilia A with high inhibitors	1. Boon ITI, 2. Low-dose ITI protocol, 3. Malmo ITI protocol 4. OD with rFVIIa	Iranian Ministry of Health; 2011	Success rate Bonn ITI: 72.85 Low-dose ITI: 43.0% Malmo: 53.3% Number of bleeding NR	Treatment costs
Berger et al. [49]; funded by Novo Nordisk Deutschland	Markov decision model; time horizon: 18 years	Germany	Children with severe haemophilia A with inhibitors, with a history of < 150 days of exposure to FVIII	1. High-dose ITI 2. Low-dose ITI 3. Risk-assessment ITI 4. OD with bypassing agents	German statutory health insurance; NR	Success rate High-dose ITI: 82% Low-dose ITI: 0.64% Risk-assessment ITI: 78.5% Number of bleeding events OD with bypassing agents: 15.05 bleeds	Direct costs (drug and hospitalisation)
Earnshaw et al. [50]; funded by Grifols	Decision analytical model; time horizon: lifetime	USA	Patients with haemophilia A with inhibitors	1. ITI 2. OD 3. PP with bypassing agents	Third-party payer; 2014	Success rate ITI: 69.8% Number of bleeding events OD: 26.2 PP: 1.3	Direct costs (drug and hospitalisation)

Table 3 continued

Reference and funding sources	Study design and time horizon	Country	Population	Treatment option	Perspective and year of cost	Clinical parameters (ITI success rate and bleeding)	Costs (description)
Rocino et al. [13]; funding NR	Retrospective multicentre study; time horizon: 7.5 years	Europe	71 patients with severe HA with inhibitors, with median (range) age of 3.8 (0.4–41.0) years at ITI start	1. ITI 2. No ITI	Third-party payer (public or private); NR	NA	Factor consumption
Kenet et al. [51]; funded by Shire	Economic model based on clinical trial data; time horizon: 12 months	USA	One patient who achieved a negative titre with either high-dose ITI and OD bypassing agents or low-dose ITI with BAP and an OD bypassing agent	1. Low-dose ITI with aPCC/FVII prophylaxis and OD 2. High-dose ITI with aPCC prophylaxis and aPCC/FVII OD	Third party payer perspective, 2016	Bleeds per month on ITI without BAP: high-dose ITI: 0.286/0.240 low-dose ITI: 0.626/0.340 Percent bleed reduction, ITI with BAP: high-dose ITI: 62%; low-dose ITI: 45%	Treatment costs

Reference and funding sources	Costs (quantification)	Type of analysis	Outcomes (description)	Outcome (quantification)	Treatment comparison	ICER (ratio)
Odeyemi and Danø [47]; funded by Novo Nordisk A/S	OD rFVIIa: £959,250 OD aPCC: £770,834 ITI after OD aPCC: £1,505,279 ITI after OD rFVIIa: £1,196,706 (cost per patient)	Cost analysis	Same efficacy was assumed for strategies	NA	OD rFVIIa followed by ITI vs. OD aPCC followed by ITI	The incremental cost in the aPCC-treated patients in the model, £129,367 (68%) represents additional ITI cost attributable to anamnestic response to earlier treatment with aPCC
Rasekh et al. [48]; funded by Shahid Beheshti University of Medical Sciences	10 years total cost per patient Bonn ITI: $5,528,650 Low-dose ITI: $2,243,650 Malmö ITI: $4,306,630 OD: $6,205,248	CUA	QALYs	Bonn ITI: 33.0 QALYs Low-dose ITI: 29.1 QALYs Malmö ITI: 28.1 QALYs OD: 25.1 QALYs	Boon ITI vs. OD with FVII Low-dose ITI vs. OD with FVII Malmo ITI vs. OD with FVII Boon ITI vs. low-dose ITI Boon ITI vs. Malmo ITI Low-dose ITI vs. Malmo ITI	Boon ITI is cost saving Low dose ITI is cost saving Malmo ITI is cost saving $842,307.69 per QALY gained $249,391.84 per QALY gained Low-dose ITI is cost saving

Table 3 continued

Reference and funding sources	Costs (quantification)	Type of analysis	Outcomes (description)	Outcome (quantification)	Treatment comparison	ICER (ratio)
Berger et al. [49]; funded by Novo Nordisk Deutschland	18 years total cost per patient High-dose ITI: €3.4 million Low-dose ITI: €2.4 million Risk-assessment ITI: €2.7 million OD with bypassing agents: €1.7 million	CEA	Total bleeds	High-dose ITI: 65. 1 Low-dose ITI: 93.7 Risk-assessment ITI: 67.5 OD with bypassing agents: 184.4	High-dose ITI vs. low-dose ITI	€34,965 per bleed avoided
					High-dose ITI vs. risk-assessment ITI	€291,667 per bleed avoided
					High-dose ITI vs. OD with bypassing agents	€14,250 per bleed avoided
					Low-dose ITI vs. risk-assessment ITI	Risk-assessment ITI is cost saving
					Low-dose ITI vs. OD with bypassing agents	€11,025 per bleed avoided
					Risk-assessment ITI vs. OD with bypassing agents	€8554 per bleed avoided
Earnshaw et al. [50]; funded by Grifols	ITI: US$19,904,815 OD: US$21,562,055 PP: US$43,106,359 (average lifetime costs)	CEA	Life-years	ITI: 74.5 OD: 70.3 PP: 70.3	ITI vs. OD vs. PP	ITI is cost saving
			Bleeding events	ITI: 427 OD: 1828 PP: 718	ITI vs. OD vs. PP	ITI is cost saving
		CUA	QALYs	ITI: 24.9 OD: 14.9 PP: 20.5	ITI vs. OD vs. PP	ITI is cost saving. In the probabilistic analysis: ITI vs. PP is cost saving 84.4% of the time and cost effective 100.0%; while ITI vs. OD is cost saving 52.7% of the time and cost effective 61.1% (ICER $\leq$ US$50,000).
Rocino et al. [13]; funding NR	€60,078.5 (during ITI) plus €13,210.9 (for the following year) [cost per patient per month]	Cost analysis	% of patients with successful ITI	Success rate 84%	ITI vs. no ITI	The ratio between the monthly cost of ITI and the cost of inhibitor treatment is 3.3. This high cost is dwarfed by comparison with the prospect of lifelong care of an inhibitor patient, in addition to gains in life expectancy and health-related quality of life

Table 3 continued

Reference and funding sources	Costs (quantification)	Type of analysis	Outcomes (description)	Outcome (quantification)	Treatment comparison	ICER (ratio)
Kenet et al. [51]; funded by Shire	Cost per kg to achieve negative titre by ITI: low-dose ITI + aPCC (prophylaxis) + rFVIIa (OD): US$29,317 Low-dose ITI + rFVIIa (prophylaxis) + rFVIIa (OD): US$56,129 Low-dose ITI + rFVIIa (prophylaxis) + aPCC (OD): US$55,574 High-dose ITI + aPCC (OD): US$38,082 High dose ITI + rFVIIa (OD): US$38,310 Low-dose ITI + aPCC (prophylaxis) + aPCC (OD): US$28,933	Cost analysis	Bleeding event	High-dose ITI: 1.3 bleeds (average) over 4.6 months (median) Low-dose ITI using aPCC or rFVIIa: 2.2 or 3.1 bleeds (average) over 9.2 months (median)	Low-dose ITI with aPCC or rFVIIa (prophylaxis and OD) vs. high-dose ITI with aPCC (prophylaxis) and aPCC or rFVIIa (OD)	Low-dose ITI with aPCC (prophylaxis) and aPCC (OD) is less costly (24.0%) than high-dose ITI with aPCC OD Low-dose ITI with rFVIIa (prophylaxis) and rFVIIa OD is more costly (46.5%) than high-dose ITI with rFVIIa OD

aPCC activated prothrombin complex concentrates, *BAP* bypassing agent prophylaxis, *CEA* cost-effectiveness analysis, *CUA* cost-utility analysis, *FVII* Factor VII, *ICER* incremental cost-effectiveness ratio, *NA* not applicable, *NR* not reported, *OD* on demand, *P* prophylaxis, *QALYs* quality-adjusted life-years, *rFVIIa* recombinant Factor VII

other eight studies evaluated prophylaxis as the most effective and more expensive treatment. Whether prophylaxis is a cost-effective strategy mainly depends on the willingness to pay for an incremental unit of effect. Furthermore, other factors critically influencing results were type of factor used (e.g. recombinant or plasma-derived FVIII), the treatment efficacy (number of bleedings associated with or avoided by the investigated strategies), the choice of outcome indicators (e.g. bleeding events avoided or absence of joint damage, or QALYs) and the time horizon.

In the study by Castro Jaramillo et al., when primary prophylaxis was provided throughout life using recombinant FVIII (rFVIII), the additional cost per QALY gained vs. OD treatment was US$91,147, compared with US$54,995/QALY when plasma-derived FVIII was considered [35]. The use of different outcomes is mainly associated with the time horizon adopted in the analysis: studies using a short time horizon usually estimated the cost per bleed avoided, while studies with longer time horizons generally provided estimates in terms of cost per QALY gained [35]. Gringeri et al. reported an ICER of €7537 per bleeding event avoided comparing primary prophylaxis with OD treatment directly estimated within a randomised controlled trial following patients up to 7 years (median 4 years) after randomisation [1]. Risebrough et al. simulated the 5-year cost and outcomes in a cohort of patients with haemophilia from the age of 1 year, estimating an ICER of Can$3192 per joint bleeding avoided and of $Can244,085 per target joint avoided comparing escalation-dose prophylaxis with OD treatment. In the same study, when QALY was assessed as an outcome, the ICER was Can$542,938 per QALY gained [30]. In the only study conducted in patients with HB, Polack et al. reported an ICER of €22,605 per bleeding avoided comparing prophylaxis with OD treatment, comparing a mixed treatment (50% OD and 50% prophylaxis) provided with two types of FIX: recombinant vs. plasma derived [21].

3.1.2 Comparing Prophylaxis Regimens

In the analyses conducted on patients without inhibitors, three studies compared different prophylaxis regimens. All studies used only direct costs and most of these used the QALY as the outcome (Table 1). Risebrough et al. compared a standard-dose primary prophylaxis with an escalation-dose prophylaxis, a regimen that starts with a low dose and frequency of infusions, which is increased (adjusted), if a patient experiences bleeding events. In this study, the standard-dose primary prophylaxis was more effective and costly compared with escalation-dose prophylaxis with an ICER of Can$9046 per bleeding avoided and an ICER of Can$ > 1,000,000 per QALY gained [30]. In the study by Colombo et al., three prophylaxis regimens were simulated, with primary and secondary prophylaxis proving to be cost-effective options compared with a "hybrid strategy" [33].

Finally, Iannazzo et al. compared standard prophylaxis with a prophylactic regimen based on individual patients' pharmacokinetics in patients with HA, aged between 10 and 65 years. The pharmacokinetic-driven prophylaxis was a cost-saving option compared with standard prophylaxis, and this result was achieved through the optimal reallocation of rFVIII units used in the haemophilic population based on individual patients needs [37]. As reported by Iannazzo et al. [37], pharmacokinetic-driven prophylaxis proved to be a cost-saving approach to treat children with haemophilia, compared with standard prophylaxis, also in USA. Pharmacokinetic-driven prophylaxis decreased the cost of therapies and visits. The amount saved amounted to €8986 per patient/year [38].

3.1.3 Patients with Inhibitors

The included studies on patients with haemophilia with inhibitors reported heterogeneity in investigated treatments using different products and regimens (dose and frequencies) within the studies, making the results difficult to compare. On-demand treatments with different products (bypassing agents and rFVIII) were compared in six studies; while three studies compared prophylaxis regimens with OD treatment (Table 2). Immune tolerance induction treatments were assessed in six studies; in these studies, different ITI protocols were compared with each other and with OD treatment and/or prophylaxis with bypassing agents.

3.2 On-Demand Treatments with Different Products

Six studies investigated the cost and effectiveness associated with the rFVIIa compared with aPCC, for the management of bleeding episodes in adults and children with haemophilia and inhibitors. In three studies, rFVIIa proved more effective than aPCC in managing bleeding [40, 42, 43], while another three studies found aPCC to be more effective [39, 41, 45]. However, there was considerable heterogeneity in the outcomes considered, limiting the generalisability of results. As far as costs are concerned, we found conflicting evidence. According to Salaj and colleagues [42], You and colleagues [40], and Jimenez-Yuste and colleagues [43], rFVIIa was cost saving, while according to the groups of Hay and Zhou [41] and Steen Carlsson et al. [39], aPCC was less expensive than rFVIIa.

While part of the heterogeneity in results may be attributable to different patient characteristics (e.g. patients with mild-moderate vs. severe haemophilia), outcome parameters and treatment algorithms, based on evidence on the funding bodies, publication bias may have played a role in some of the papers. Many analyses used a single study or assumptions to estimate the dose/frequency and/or efficacy for the different products assessed. The selection of the study and the assumptions could have been influenced by various aspects, including the funding bodies, showing more favourable results for one product instead of another and creating a publication bias.

3.3 Prophylaxis vs. On-Demand Treatments

Of the three studies assessing the cost and effects of prophylaxis in patients with inhibitors, all studies compared aPCC-based prophylaxis with an OD strategy with aPCC or rFVIIa. [14, 44, 46]. Two studies were based on decision analytical models while one study was conducted within a randomised clinical trial (Table 2). Two studies compared aPCC prophylaxis with rFVIIa OD using a 1-year time horizon, reporting prophylaxis with aPCC as the less expensive treatment option [44, 46]. These studies were originally cost analyses, but also reported a clinical outcome, associating prophylaxis with aPCC with a lower number of bleeding episodes.

In a clinical trial, Lessinger et al. compared aPCC, infused prophylactically at a target dose of 85 U/kg of body weight (three times per week), with aPCC OD therapy at a target dose of 85 U/kg, used for bleeding episodes. The trial reported a significantly lower number of bleedings associated with 6 months of prophylaxis, with a cost per bleeding avoided of US$35,565 [14].

3.4 Immune Tolerance Induction Regimens vs. On-Demand and/or Prophylaxis Treatments with Bypassing Agents

Eradication of the inhibitor through ITI is generally recommended as the first treatment option, particularly in children with high-responding inhibitors because it provides the prospect of efficacious FVIII replacement therapy and the feasibility of prophylaxis with consequent preservation of joint status and quality of life [13].

Six studies evaluated the costs and effectiveness of different ITI protocols. Differences between studies were found with regard to methodology: (1) different time horizons, from 1 year to lifetime [47]; (2) different outcome measures, with QALYs, life-years saved, bleeding events, hospital stays and frequency of patients with inhibitor eradication; (3) different ITI regimes, e.g. low-dose ITI, high-dose ITI, risk-assessment ITI, Bonn ITI and Malmo ITI; mixed regimens including OD treatment with rFVIIa or aPCC followed by high- or low-dose ITI. Despite such methodologic differences, ITI was always less expensive and more effective compared with the alternative, i.e. OD or prophylaxis with bypassing agents. Within the different ITI protocols assessed, low-dose ITI and risk-assessment ITI seemed to have the most favourable cost-effectiveness profile [51].

Rocino et al. reported that the high cost of ITI treatment was counterbalanced by a high rate of success in the treatment of patients with inhibitors, which is associated with an additional gain in life expectancy and health-related quality of life reported by patients without inhibitors [13]. However, a low-dose ITI may be more economically convenient than a high-dose ITI when it is combined with aPCC prophylaxis. A synergistic effect of ITI with aPCC reflected a potential to reduce morbidity by lowering the risk for breakthrough bleeds [51]. Odeyemi and Danø [47] applied a cost-minimisation technique to compare the economic impact of using aPCC or rFVIIa to manage bleeding that occurred during the time between the appearance of the inhibitor and the start of ITI (pre-ITI), to improve the patients' probability of achieving success with a low-dose ITI, instead of a high-dose ITI. The authors concluded that rFVIIa reported lower treatment costs (−£188,405) compared with aPCC, suggesting the management of bleeding pre-ITI with rFVIIa to increase the use of low-dose ITI and reduce costs.

4 Discussion

Although haemophilia is a rare condition, several economic evaluations of haemophilia treatments have been performed in the last decade. Not surprisingly, a relevant number of studies were conducted in patients with inhibitors, considering the high acquisition price of bypassing agents. All studies in patients without inhibitors, except one, were carried out on HA treatments, possibly reflecting the relative epidemiologic and economic burden of the condition. As reported in other studies, the variability in the methods used and the differences in the treatments under assessment often make the identification of general trends difficult [26, 29, 52]. This aspect is also reflected in our review, which only provides a clear answer to the question: "Is ITI for patients with inhibitors cost effective?". In our study, only ITI in patients with inhibitors showed consistent and concordant results on its cost-saving or dominant profile, compared with the treatment with bypassing agents. However, when we tried to answer the question: "Is it cost-effective to provide recombinant factor prophylaxis for severe HA or HB without inhibitors, or is OD therapy a more cost-effective option?", prophylaxis with rFVIII

seemed a cost-effective option, compared with OD treatment. However, this observation depends on several factual variables, including (1) annual background bleeding rate, (2) relative efficacy, (3) dosing regimens and (4) price of rFVIII [30, 31, 33, 34, 50]. A difference in values and assumptions made for these variables created a significant variability in the cost of OD and prophylaxis treatment reported in the studies; which seems not related to the time of publication. When we analysed four studies conducted in the same country (Italy), the cost of rFVIII prophylaxis was different even within studies published in the same year. In 2011, the study by Colombo et al. reported a 1-year prophylaxis cost per patient of €23,738 (regimen: 30 IU kg-1 2.5 times a week; €0.68 per IU) [33], while Gringeri et al. reported a cost of €79,668 (regimen: 25–40 IU kg-1 two or three times a week; €0.75 per IU) [1]. In 2016, Iannazzo et al. reported a cost of €265,859 (regimen: 30 IU kg-1 every 48 h; €0.65 per IU) [37] and Coppola et al. a cost of €29,006 (regimen: 25 IU kg-1 three times a week; 0.65 per IU) [36].

However, the uncertainty related to the results of these analyses is even more influenced by methodological variables, including: (1) the use of a short time horizon (e.g. 1 year, 6 months and even a single bleed) that is not able to detect the effect of a treatment for the entire life of a patient with haemophilia; (2) the use of outcomes with little generalisability (e.g. bleed avoided, target joint and pain intensity); (3) the use of a clinical effect related to a single study, conducted in a small sample of patients; (4) the use of non-standardised doses and the frequency of clotting factor infusion; (5) poor definition of the uncertainty related to the results and the parameters, and (6) differences in the cost and outcome discount rates.

Further, another issue to consider in the retrieved studies is the potential risk of publication bias that can lead to publication of only favourable results. Within the included studies, 19 of 26 (73%) analyses were funded by industry (Tables 1, 2, 3), raising the potential risk of publication bias. Unfortunately, the heterogeneity of the outcomes used in the evaluations make the assessment of publication bias very difficult. The use of a more standardised outcome in future analysis could make it possible to better assess this aspect.

Our observations are in line with those reported by Drummond et al. regarding the quality of reporting methods of economic evaluations in haemophilia [26]. The improvement in the quality of evaluations can be observed in some of the recently published studies included in our analyses, potentially positively influenced by consensus initiatives [27, 53]. Although the methodological quality seems to be improving, weaknesses still exist, and a fruitful collaboration between clinical experts, budget holders and health economists is indispensable to best guide clinicians and decision makers. In fact, in patients without inhibitors, the initial economic evaluations conducted in the 1990s and in the first part of the millennium were usually short-term analyses comparing prophylaxis with OD treatment using cost per bleeding avoided as an outcome [29], with few exceptions such as the paper published in this journal in 2002 by Miners et al. [54].

More recent evaluations have evolved and become more sophisticated in different ways. First, the time horizon has been significantly extended, with more recent analyses adopting a lifetime approach, as natural for a genetic, chronic and lifelong disease like haemophilia. Second, outcomes of choice have moved away from bleedings avoided and moved towards QALYs, an evolution made possible thanks to the increasing availability of long-term evidence on outcomes, particularly on the association between frequency and severity of bleedings, development of haemophilic arthropathy and the global health status of patients, including utility. Third, the concept of prophylaxis itself has changed from standard regimens towards a personalised approach based on the individual patient's pharmacokinetic and social expectations (e.g. physical exercise and sport) [37].

4.1 Future Directions

New concerns about cost effectiveness and the sustainability of old, new and future treatment options are being raised among clinicians and budget holders dealing with patients with haemophilia. The body of evidence directly or indirectly generated by economic evaluations published in recent years is now being applied to new treatment strategies already on the market or that will be marketed in the near future [55]. For decades, the treatment of haemophilia has been straightforward: simply replace the deficient protein with an available intravenous factor concentrate or use bypassing agents [56]. New categories of haemophilia therapy are now available or in late phases of development: engineered factor concentrates with extended half-lives, gene therapy and non-factor replacement haemostasis strategies. These products can make it possible to address gaps in the current approach to haemophilia management but do not provide a one-size-fits-all opportunity [56]. For example, the extended half-lives of rFVIII and rFIX could simplify the prophylactic regimens in HA and HB without inhibitors, reducing the frequency of infusions and extending the protection from bleeding, making the treatment more tolerable to the patient (and to parents) with a consequent improvement of therapeutic adherence. The use of novel non-replacement products, such as emicizumab, [55, 57] could be an alternative strategy in patients with or without inhibitors but can be used only for prophylaxis regimens and not to manage

bleeding. Further, these therapies require much less frequent dosing than most factor products and are administrated subcutaneously rather than intravenously [56]. Gene therapy could offer a definitive cure but is still in the early clinical development stage, and the long-term safety and efficacy issues have already been raised. Finally, all of these treatments should be assessed considering their safety profiles and the possible immunological responses.

However, proper clinical and economic investigation of these strategies is also necessary, considering the different prices of these products and the possible impact of the sustainability of the treatment in patients with haemophilia. Considering the key role of factor concentrate costs in haemophilia healthcare [23], the assessment of the cost effectiveness of new and old products is crucial to understand the possible impact on the management of patients with haemophilia. To perform economic evaluations of these products, reliable data input and assumptions will be necessary, especially for the long-term effects, the expected adherence (reduced number of infusions, and more comfortable administration routes associated with the new products), the impact of (non)adherence in terms of clinical effect, product consumption and patients' quality of life. In particular, transforming the reduced number of infusions, the lower treatment burden and a better route of administration into an improvement of the utility value will be the crucial challenge to be addressed while we are waiting for the future results of ad-hoc research. Future research on patients with haemophilia treated with the new products should be aimed at providing a real estimation of quality of life and utility impact reported by the patients, and at associating this impact with the different characteristics of these new products: reduced number of infusions, lower treatment burden, better adherence and better route of administration. All the discussed aspects should be taken into account if we want to answer the new questions that have been raised on the proposed value of new recombinant factor products (which have extended half-lives) or non-factor replacement strategies compared with existing recombinant products.

5 Conclusions

Haemophilia is a complex medical and social condition with high treatment costs. As reported in other studies, economic evaluations in this field are increasing in number and quality, highlighting the need for more robust analyses based on reliable methods, assumptions and data inputs [26, 29, 52].

Analysis of the retrieved studies indicates that prophylaxis seems a cost-effective treatment option compared with OD treatment for patients with HA and HB without inhibitors, particularly when more adequate, comprehensive and long-term analyses are considered and, second, when personalised prophylaxis is compared with a one-size-fits-all approach. For patients with inhibitors, ITI is dominant compared with any alternative course of care in which patients are placed on a regimen with bypassing agents and, again, an approach to ITI based on individual risk has the potential to be superior. In patients without inhibitors, we found a less clear picture when different regimens with bypassing agents were compared, as the available analyses either present conflicting comparative evidence on the cost of bleeding only, or express the outcomes in terms of cost per bleeding avoided, i.e. something that is not comparable to other healthcare interventions.

The introduction of new treatments will mandate assessment based on solid evidence. In light of the evolution of the haemophilia health economic literature, future analyses based on a short-term time span and intermediate outcomes will neither match current scientific standards nor fulfil requirements from policy-making bodies. Further, more reliable assessments that translate the new treatment options characteristics (e.g. reduced frequency of infusions, extended protection from bleeding and different routes of administration) in terms of cost-effectiveness profiles are needed to optimise the resources available for the management of patients with haemophilia.

Author contributions PAC, LGM and LSD contributed to the study design and preparation of the manuscript; LA and MM performed the literature searches and data abstraction, and contributed to the study design and preparation of the manuscript; GC provided a critical revision for important intellectual content; and all authors critically reviewed the article.

Compliance with Ethical Standards

Funding No sources of funding were received to conduct this research or prepare this article.

Conflict of interest Paolo A. Cortesi received a research grant from Baxalta now part of Shire and speaking honoraria from Pfizer, outside the submitted work. Lorenzo G. Mantovani reports personal fees from Pfizer and Bayer Healthcare, outside the submitted work. Lucia S. D'Angiolella, Alessandra Lafranconi, Mariangela Micale, and Giancarlo Cesana have no conflicts of interest directly relevant to the content of this article.

Data Availability Statement All relevant data are included in the article.

References

1. Gringeri A, Lundin B, von Mackensen S, Mantovani L, Mannucci PM, Group ES. A randomized clinical trial of prophylaxis in

children with hemophilia A (the ESPRIT Study). J Thromb Haemost. 2011;9(4):700–10.
2. Barr RD, Saleh M, Furlong W, Horsman J, Sek J, Pai M, et al. Health status and health-related quality of life associated with hemophilia. Am J Hematol. 2002;71(3):152–60.
3. Gringeri A, Leissinger C, Cortesi PA, Jo H, Fusco F, Riva S, et al. Health-related quality of life in patients with haemophilia and inhibitors on prophylaxis with anti-inhibitor complex concentrate: results from the Pro-FEIBA study. Haemophilia. 2013;19(5):736–43.
4. Bolton-Maggs PH, Pasi KJ. Haemophilias A and B. Lancet. 2003;361(9371):1801–9.
5. Roberts H, Key N, Escobar M. Hemophilia A and hemophilia B. In: Kaushansky K, Lichtman M, Beutler E, Kipps T, Prchal J, Seligsohn U, editors. Williams hematology. 8th ed. New York (NY): McGraw Hill; 2010.
6. Valentino LA, Hakobyan N, Enockson C, Simpson ML, Kakodkar NC, Cong L, et al. Exploring the biological basis of haemophilic joint disease: experimental studies. Haemophilia. 2012;18(3):310–8.
7. Franchini M. The modern treatment of haemophilia: a narrative review. Blood Transfus. 2013;11(2):178–82.
8. Srivastava A, Brewer AK, Mauser-Bunschoten EP, Key NS, Kitchen S, Llinas A, et al. Guidelines for the management of hemophilia. Haemophilia. 2013;19(1):e1–47.
9. Ljung R, Gretenkort AN. The current status of prophylactic replacement therapy in children and adults with haemophilia. Br J Haematol. 2015;169(6):777–86.
10. Rota M, Cortesi PA, Steinitz-Trost KN, Reininger AJ, Gringeri A, Mantovani LG. Meta-analysis on incidence of inhibitors in patients with haemophilia A treated with recombinant factor VIII products. Blood Coagul Fibrinolysis. 2017. https://doi.org/10.1097/MBC.0000000000000647 **(Epub ahead of print)**.
11. Castaman G, Bonetti E, Messina M, Morfini M, Rocino A, Scaraggi FA, et al. Inhibitors in haemophilia B: the Italian experience. Haemophilia. 2013;19(5):686–90.
12. Dimichele D. Inhibitors: resolving diagnostic and therapeutic dilemmas. Haemophilia. 2002;8(3):280–7.
13. Rocino A, Cortesi PA, Scalone L, Mantovani LG, Crea R, Gringeri A, et al. Immune tolerance induction in patients with haemophilia a and inhibitors: effectiveness and cost analysis in an European Cohort (The ITER Study). Haemophilia. 2016;22(1):96–102.
14. Leissinger C, Gringeri A, Antmen B, Berntorp E, Biasoli C, Carpenter S, et al. Anti-inhibitor coagulant complex prophylaxis in hemophilia with inhibitors. N Engl J Med. 2011;365(18):1684–92.
15. Di Minno MN, Di Minno G, Di Capua M, Cerbone AM, Coppola A. Cost of care of haemophilia with inhibitors. Haemophilia. 2010;16(1):e190–201.
16. Guh S, Grosse SD, McAlister S, Kessler CM, Soucie JM. Health care expenditures for Medicaid-covered males with haemophilia in the United States, 2008. Haemophilia. 2012;18(2):276–83.
17. Guh S, Grosse SD, McAlister S, Kessler CM, Soucie JM. Healthcare expenditures for males with haemophilia and employer-sponsored insurance in the United States, 2008. Haemophilia. 2012;18(2):268–75.
18. Rocha P, Carvalho M, Lopes M, Araújo F. Costs and utilization of treatment in patients with hemophilia. BMC Health Serv Res. 2015;15:484.
19. O'Hara J, Hughes D, Camp C, Burke T, Carroll L, Diego DG. The cost of severe haemophilia in Europe: the CHESS study. Orphanet J Rare Dis. 2017;12(1):106.
20. Chen SL. Economic costs of hemophilia and the impact of prophylactic treatment on patient management. Am J Manag Care. 2016;22(5 Suppl.):s126–33.
21. Polack B, Calvez T, Chambost H, Rothschild C, Goudemand J, Claeyssens S, et al. EQOFIX: a combined economic and quality-of-life study of hemophilia B treatments in France. Transfusion. 2015;55(7):1787–97.
22. Gringeri A, Mantovani LG, Scalone L, Mannucci PM, Group CS. Cost of care and quality of life for patients with hemophilia complicated by inhibitors: the COCIS Study Group. Blood. 2003;102(7):2358–63.
23. Heemstra HE, Zwaan T, Hemels M, Feldman BM, Blanchette V, Kern M, et al. Cost of severe haemophilia in Toronto. Haemophilia. 2005;11(3):254–60.
24. O'Mahony B, Noone D, Prihodova L. Survey of coagulation factor concentrates tender and procurement procedures in 38 European Countries. Haemophilia. 2015;21(4):436–43.
25. Peyvandi F, Menegatti M. Treatment of rare factor deficiencies in 2016. Hematol Am Soc Hematol Educ Program. 2016;2016(1):663–9.
26. Drummond M, Houwing N, Slothuus U, Giangrande P. Making economic evaluations more helpful for treatment choices in haemophilia. Haemophilia. 2017;23(2):e58–66.
27. Nicholson A, Berger K, Bohn R, Carcao M, Fischer K, Gringeri A, et al. Recommendations for reporting economic evaluations of haemophilia prophylaxis: a nominal groups consensus statement on behalf of the Economics Expert Working Group of The International Prophylaxis Study Group. Haemophilia. 2008;14(1):127–32.
28. Husereau D, Drummond M, Petrou S, Carswell C, Moher D, Greenberg D, et al. Consolidated Health Economic Evaluation Reporting Standards (CHEERS): explanation and elaboration: a report of the ISPOR Health Economic Evaluation Publication Guidelines Good Reporting Practices Task Force. Value Health. 2013;16(2):231–50.
29. Miners AH. Economic evaluations of prophylaxis with clotting factor for people with severe haemophilia: why do the results vary so much? Haemophilia. 2013;19(2):174–80.
30. Risebrough N, Oh P, Blanchette V, Curtin J, Hitzler J, Feldman BM. Cost-utility analysis of Canadian tailored prophylaxis, primary prophylaxis and on-demand therapy in young children with severe haemophilia A. Haemophilia. 2008;14(4):743–52.
31. Miners A. Revisiting the cost-effectiveness of primary prophylaxis with clotting factor for the treatment of severe haemophilia A. Haemophilia. 2009;15(4):881–7.
32. Daliri AA, Haghparast H, Mamikhani J. Cost-effectiveness of prophylaxis against on-demand treatment in boys with severe hemophilia A in Iran. Int J Technol Assess Health Care. 2009;25(4):584–7.
33. Colombo GL, Di Matteo S, Mancuso ME, Santagostino E. Cost-utility analysis of prophylaxis versus treatment on demand in severe hemophilia A. Clinicoecon Outcomes Res. 2011;3:55–61.
34. Farrugia A, Cassar J, Kimber MC, Bansal M, Fischer K, Auserswald G, et al. Treatment for life for severe haemophilia A: a cost-utility model for prophylaxis vs. on-demand treatment. Haemophilia. 2013;19(4):e228–38.
35. Castro Jaramillo HE, Moreno Viscaya M, Mejia AE. Cost-utility analysis of primary prophylaxis, compared with on-demand treatment, for patients with severe hemophilia type A in Columbia. Int J Technol Assess Health Care. 2016;32(5):337–47.
36. Coppola A, D'Ausilio A, Aiello A, Amoresano S, Toumi M, Mathew P, et al. Cost-effectiveness analysis of late prophylaxis vs. on-demand treatment for severe haemophilia A in Italy. Haemophilia. 2017;23(3):422–9.
37. Iannazzo S, Cortesi PA, Crea R, Steinitz K, Mantovani LG, Gringeri A. Cost-effectiveness analysis of pharmacokinetic-driven prophylaxis vs. standard prophylaxis in patients with severe haemophilia A. Blood Coagul Fibrinolysis. 2017;28(6):425–30.

38. Pasca S, Milan M, Sarolo L, Zanon E. PK-driven prophylaxis versus standard prophylaxis: when a tailored treatment may be a real and achievable cost-saving approach in children with severe hemophilia A. Thromb Res. 2017;157:58–63.
39. Steen Carlsson K, Astermark J, Donfield S, Berntorp E. Cost and outcome: comparisons of two alternative bypassing agents for persons with haemophilia A complicated by an inhibitor. Thromb Haemost. 2008;99(6):1060–7.
40. You CW, Lee SY, Park SK. Cost and effectiveness of treatments for mild-to-moderate bleeding episodes in haemophilia patients with inhibitors in Korea. Haemophilia. 2009;15(1):217–26.
41. Hay JW, Zhou ZY. Economical comparison of APCC vs. rFVIIa for mild-to-moderate bleeding episodes in haemophilia patients with inhibitors. Haemophilia. 2011;17(5):e969–74.
42. Salaj P, Penka M, Smejkal P, Geierova V, Ovesná P, Brabec P, et al. Economic analysis of recombinant activated factor VII versus plasma-derived activated prothrombin complex concentrate in mild to moderate bleeds: haemophilia registry data from the Czech Republic. Thromb Res. 2012;129(5):e233–7.
43. Jimenez-Yuste V, Núñez R, Romero JA, Montoro B, Espinós B. Cost-effectiveness of recombinant activated factor VII vs. plasma-derived activated prothrombin complex concentrate in the treatment of mild-to-moderate bleeding episodes in patients with severe haemophilia A and inhibitors in Spain. Haemophilia. 2013;19(6):841–6.
44. Villarrubia R, Oyagüez I, Álvarez-Román MT, Mingot-Castellano ME, Parra R, Casado MA. Cost analysis of prophylaxis with activated prothrombin complex concentrate vs. on-demand therapy with activated factor VII in severe haemophilia A patients with inhibitors, in Spain. Haemophilia. 2015;21(3):320–9.
45. Golestani M, Eshghi P, Rasekh HR, Cheraghali AM, Salamzadeh J, Naderi M, et al. Cost-effectiveness analysis of biogeneric recombinant activated Factor VII (AryoSeven™) and activated prothrombin complex concentrates (FEIBA™) to treat hemophilia A patients with inhibitors in Iran. Iran J Pharm Res. 2016;15(2):669–77.
46. Mehta DA, Oladapo AO, Epstein JD, Novack AR, Neufeld EJ, Hay JW. A budget impact model of hemophilia bypassing agent prophylaxis relative to recombinant Factor VIIa on-demand. J Manag Care Spec Pharm. 2016;22(2):149–57.
47. Odeyemi IAO, Danø AM. Optimising immune tolerance induction strategies in the management of haemophilia patients with inhibitors: a cost-minimisation analysis. Curr Med Res Opin. 2009;25(1):239–50.
48. Rasekh HR, Imani A, Karimi M, Golestani M. Cost-utility analysis of immune tolerance induction therapy versus on-demand treatment with recombinant factor VII for hemophilia A with high titer inhibitors in Iran. Clinicoecon Outcomes Res. 2011;3:207–12.
49. Berger K, Schopohl D, Eheberg D, Auerswald G, Kurnik K, Schramm W. Treatment of children with severe haemophilia A and inhibitors: a health economic evaluation for Germany. Klin Padiatr. 2013;225(3):152–8.
50. Earnshaw SR, Graham CN, McDade CL, Spears JB, Kessler CM. Factor VIII alloantibody inhibitors: cost analysis of immune tolerance induction vs. prophylaxis and on-demand with bypass treatment. Haemophilia. 2015;21(3):310–9.
51. Kenet G, Oladapo A, Epstein JD, Thompson C, Novack A, Nugent DJ. Estimating the potential cost of a high dose immune tolerance induction (ITI) therapy relative to the cost of a combined therapy of a low dose ITI therapy with bypassing agent prophylaxis. Haemophilia. 2017;23(5):e394–402.
52. Valente M, Cortesi PA, Lassandro G, Mathew P, Pocoski J, Molinari AC, et al. Health economic models in hemophilia A and utility assumptions from a clinician's perspective. Pediatr Blood Cancer. 2015;62(10):1826–31.
53. Feldman BM, Aledort L, Bullinger M, Delaney FM, Doria AS, Funk S, et al. The economics of haemophilia prophylaxis: governmental and insurer perspectives. Haemophilia. 2007;13(6):745–9.
54. Miners AH, Sabin CA, Tolley KH, Lee CA. Cost-utility analysis of primary prophylaxis versus treatment on-demand for individuals with severe haemophilia. Pharmacoeconomics. 2002;20(11):759–74.
55. Peyvandi F, Garagiola I, Young G. The past and future of haemophilia: diagnosis, treatments, and its complications. Lancet. 2016;388(10040):187–97.
56. Hartmann J, Croteau SE. 2017 clinical trials update: innovations in hemophilia therapy. Am J Hematol. 2016;91(12):1252–60.
57. Oldenburg J, Mahlangu JN, Kim B, Schmitt C, Callaghan MU, Young G, et al. Emicizumab prophylaxis in hemophilia A with inhibitors. N Engl J Med. 2017;377(9):809–18.