Thrombosis Research 199 (2021) 67–74

Contents lists available at ScienceDirect

Thrombosis Research

journal homepage: www.elsevier.com/locate/thromres

Review Article

Translating the success of prophylaxis in haemophilia to von Willebrand disease

Wolfgang Miesbach [a,*], Erik Berntorp [b]

[a] Haemophilia Centre, Medical Clinic II, Institute of Transfusion Medicine, Goethe University Hospital, Frankfurt am Main, Germany
[b] Department of Coagulation Disorders, Lund University, University Hospital, Malmo, Sweden

ARTICLE INFO

Keywords:
Blood coagulation disorder, inherited
Haematologic diseases
Haemophilia
Prophylaxis
von Willebrand disease

ABSTRACT

Introduction: There is limited awareness of von Willebrand disease (VWD), leading to challenges in both diagnosis and defining the optimal treatment approach for these patients. Patients with VWD are typically treated on-demand, with short-term prophylaxis used during surgery. In contrast, early initiation, and long-term use of prophylaxis is the standard of care in patients with severe haemophilia and can be successfully used to prevent joint bleeding and reduce chronic arthropathy.

Aim: To provide an understanding of the current evidence for the prophylactic treatment of patients with VWD and compare this to the management of patients with haemophilia.

Methods: Review of published literature using a non-systematic search of PubMed and reference lists of sourced articles.

Results: The successes seen with prophylaxis in haemophilia provide the rationale for long-term prophylaxis in patients with severe forms of VWD; preventing spontaneous, excessive and sometimes life-threatening bleeding, and reducing chronic joint disease. Currently, there are a few clinical trials assessing the long-term benefits of prophylaxis in VWD, and guidelines for the optimal prophylaxis treatment approach are lacking. Greater attempts to provide comprehensive, long-term care for patients with VWD are needed but still lacking within the community. This review highlights the success of prophylaxis in haemophilia and how this knowledge might be applied and translated to patients with VWD.

Conclusions: Lessons can be learned from the use of prophylaxis in haemophilia and prophylaxis should be considered the standard of care for a subgroup of patients with severe VWD.

1. Introduction

1.1. The role of prophylaxis in hereditary bleeding disorders

Prophylaxis is defined as the administration of factor concentrate to prevent anticipated bleeding [1]. In some individuals, short-term prophylaxis, surrounding surgery, pregnancy/labour, and menstruation may be required to prevent or control excessive bleeding. While in individuals with severe bleeding phenotypes, prophylaxis treatment is essential to prevent uncontrolled bleeding and reduce internal damage, e.g., to joints, and to prevent long-term sequelae. In patients with bleeding disorders such as von Willebrand disease (VWD), there is currently no consensus on the optimal use of prophylaxis, or the associated cost-benefit of long-term prophylaxis treatment.

The initiation of primary prophylaxis at an early age, before the second, or sometimes even first, clinically evident large joint bleed, and regular factor administration thereafter is considered the most effective treatment in patients with haemophilia [1], with randomised controlled trials confirming the efficacy and superiority of prophylaxis compared with patients treated on-demand [2–4]. In patients with severe haemophilia, primary prophylaxis is now considered the standard of care with the goal of treatment to maintain factor levels well above 1 IU/dL at all times [1,3,5]; thus, converting patients from a severe to a moderate/mild disease phenotype. Recent reports have suggested that maintaining higher factor levels (above 10 IU/dL) may be optimal to prevent subclinical bleeding [3,6,7]. Today, in patients with haemophilia, the goal of targeting a specific high factor level has evolved to personalised prophylaxis to achieve zero bleeds [8]. The prevention of bleeding is a key factor in preserving musculoskeletal function as well as reducing the severity and progression of joint damage in patients with

* Corresponding author at: Haemophilia Centre, Medical Clinic II, Institute of Transfusion Medicine, Goethe University Hospital, Frankfurt am Main, Germany.
E-mail address: wolfgang.miesbach@kgu.de (W. Miesbach).

https://doi.org/10.1016/j.thromres.2020.12.030
Received 24 August 2020; Received in revised form 22 December 2020; Accepted 29 December 2020
Available online 6 January 2021
0049-3848/© 2021 The Authors. Published by Elsevier Ltd. This is an open access article under the CC BY license (http://creativecommons.org/licenses/by/4.0/).

bleeding disorders [2,9]. Recurrent joint bleeds are known to cause cartilage and bone destruction, known as haemophilic arthropathy, which negatively impacts patient quality of life by causing chronic pain and disability [9,10]. This is also the case in other bleeding disorders, for example, a patient with congenital afibrinogenaemia, who experienced recurrent microbleeds into the hip joint, required total hip endoprosthesis at 13 years of age [11]. Since receiving long-term prophylactic replacement of the missing coagulation factor, the frequency and intensity of spontaneous bleeding have been significantly reduced versus on-demand treatment.

Although joint damage develops later in life in patients with VWD compared to those with haemophilia, prophylaxis may be equally as important for the reduction of joint haemorrhages and the subsequent development of arthropathy, particularly in patients with type 3 VWD; however, there are limited data reporting the existence and severity of arthropathy in VWD [12]. It is thought that joint bleeds occur in ~50% of patients with type 3 VWD and up to 10% in those with type 1 and type 2 VWD [13,14]. It is important to note that although FVIII levels are typically higher in patients with VWD than those with haemophilia, some patients with severe VWD have reduced FVIII levels, since VWF is a carrier for FVIII in circulation. The rationale for long-term prophylaxis in patients with severe forms of VWD is therefore similar to that in patients with severe haemophilia, preventing mucosal bleeding such as epistaxis, menstrual and gastrointestinal bleeding, and the potential to reduce haemophilia-like joint bleeds that may result in chronic morbidity and reduced quality of life.

This review aims to provide an understanding of the prophylactic treatment in patients with VWD and compare this to the management of patients with similar bleeding disorders, specifically, haemophilia. We also question whether prophylaxis should now be considered the standard of care for a subgroup of patients with VWD (e.g., patients with severe disease), and how the management of patients may change in the future. A prerequisite would be to develop more scientific evidence which could be included into guidelines.

1.2. VWD vs. haemophilia: distinct bleeding disorders with many similarities

VWD is the most common genetic bleeding disorder, occurring with equal frequency among men and women [15], while haemophilia is a well-known inherited bleeding disorder, affecting mostly men [1]. VWD trait is estimated to affect 1% of the population worldwide, of which it is thought that 0.1% are symptomatic and only 0.01% of the population have a confirmed VWD diagnosis; suggesting a high proportion of the population are unaware of their bleeding disorder [16,17]. In addition, not all of those individuals who have been diagnosed with VWD are receiving treatment. The prevalence of VWD and bleeding phenotypes are compared with haemophilia in Table 1. Notably the inheritance is usually autosomal dominant but the most severe form, type 3, is autosomal recessive and therefore very rare with highest prevalence in areas where consanguinity occurs. In addition, the variation in bleeding phenotypes in patients with milder disease suggest type 1 VWD is likely from polygenic inheritance [18].

VWD is a heterogeneous disorder caused by quantitative (types 1 and 3) and qualitative (type 2) deficiency of von Willebrand factor (VWF) [23]. Type 1 VWD is a partial reduction of VWF and is the most common, affecting 65–80% of symptomatic cases. Type 2 VWD constitutes 20–35% of patients; it is divided into four subtypes (2A, 2B, 2M and 2N) based on phenotype and involves the expression of functionally abnormal VWF. Type 3 VWD is the complete absence of VWF and affects ~1 in 1 million people. Haemophilia is a congenital disorder caused by deficiency or absence of coagulation factors VIII (FVIII, haemophilia A) or IX (FIX, haemophilia B); haemophilia A occurs in approximately 1 in 4000 male births [21] and patients with haemophilia A represent 80–85% of the haemophilia population. The severity of disease depends on the clotting factor level; severe disease is defined as ≤1 IU/dL factor level, patients with moderate disease have >1–5 IU/dL factor, and mild disease have >5–<40 IU/dL factor. Patients with severe disease require regular infusions of factor replacement therapy to raise and maintain high levels of clotting factors in circulation at all times, which would in turn reduce the frequency of spontaneous bleeding. A report by the World Federation of Hemophilia (WFH) suggests maintaining trough levels at 3–5 IU/dL could convert patients from a severe phenotype to a mild-moderate phenotype, as the way forward for treating patients with severe haemophilia [24,25]. It has also been suggested that maintaining factor levels at 15 IU/dL or higher may be beneficial in some patients with severe haemophilia [7,24]. In a recent study it was shown that keeping trough levels at 8–13 IU/dL substantially decreased bleeding frequency compared with keeping levels above 1–3 IU/dL [6].

Table 1
Comparing the incidence of VWD and haemophilia.

	VWD	Haemophilia
Patients diagnosed worldwide	~78,600 [19] (1:10,000) [20]	~210,500 [19] (1:4000[c]) [21]
Inheritance	Autosomal dominant[a] in most cases but recessive in type 3 VWD and some type 2 VWD	X-linked recessive
Estimated undiagnosed population (%)	~90	~50
Disease classification[b] (%) [1,20]	Type 3: 5–10 Type 2: 15–30 Type 1: 65–80	Severe: 60 Moderate: 15 Mild: 25
Average age of diagnosis	10–12 years [20]	1–2 years [1]
Predominantly affects [22]	Females and males	Males
Bleeding type/location [22]	Mucocutaneous bleeding (e.g., epistaxis, menorrhagia and gastrointestinal bleeding)	Joints and muscles
Estimated undertreated population (%)	Unknown	75 (globally) [22]

VWD, von Willebrand disease.
[a] Type 3 and type 2 N are inherited as a recessive trait.
[b] There may be phenotypic variations within each disease classification, e.g., not all patients with type 1 VWD exhibit a mild phenotype.
[c] Incidence of haemophilia A in males.

Bleeding history is critical to disease diagnosis in both VWD and haemophilia and there are distinct differences in the bleeding phenotype in patients with VWD or haemophilia, including the time of presentation, bleeding type/location and severity of bleeding (Table 1) [26]. Bleeding severity in VWD is variable and without treatment can be life-threatening, with severe complications associated with haemorrhages, such as gastrointestinal bleeding [27]. The hallmark of VWD is mucocutaneous bleeding (e.g., epistaxis, menorrhagia and gastrointestinal bleeding) and a deficiency of VWF is often not diagnosed until several years after the onset of bleeding symptoms or until a patient requires a medical procedure. The incidence of VWF deficiency in women with menorrhagia is around 10–20% [28] and it is thought that women with VWD are ~10 times more likely to die from postpartum haemorrhage and childbirth complications than women without VWD [29]. Bleeding after dental extraction is reported in 28–51% of patients with VWD, compared with 4–42% of healthy individuals [30]. The lack of VWD awareness among healthcare professionals and the general population, including how an individual interprets what might be considered a 'normal' level of spontaneous bleeding (e.g., during menstrual bleeding, or during epistaxis), and the lack of awareness of the guidelines for the management of patients with VWD, suggests a significant proportion of individuals are undiagnosed and undertreated. Today, VWD awareness is building among healthcare professionals; the introduction of the American College of Obstetricians and Gynecologists (ACOG) practice bulletins, and the Foundation for Women and Girls with Blood Disorders

(FWGBD) are helping to educate the community. In general, comprehensive guidelines are lacking due to the limited data available, particularly from randomised controlled trials assessing prophylaxis in patients with severe VWD. To aid diagnosis of VWD, bleeding assessment tools have been developed as a quantitative measure to rate bleeding symptoms, disease severity and family history of bleeding to inform diagnosis and treatment decisions [31–33]. The European Molecular and Clinical Markers for the Diagnosis and Management of type 1 VWD (MCMDM-1 VWD) Study reported that bleeding score was strongly inversely correlated with VWF level [32]. The condensed MCMDM-1 VWD bleeding questionnaire is a bleeding assessment tool used to quantify bleeding symptoms (individual components scored from 1 to 4) and predict when those symptoms are suggestive of a bleeding disorder. The condensed version of the MCMDM-1VWD questionnaire was used in a study of 30 women presenting with menorrhagia and was able to distinguish those with a bleeding disorder from those without a bleeding disorder (sensitivity 85%, specificity 90%) and was also able to distinguish disease severity; women with type 3 VWD had the highest bleeding scores [34]. These questionnaires and the resultant bleeding severity scores could help to predict clinical outcomes based on bleeding phenotype [35]; however, a lack of global awareness among physicians and patients, and limited uptake of the evaluation questionnaire could mean a high proportion of patients remain undiagnosed worldwide. Recently, the WFH have also developed draft clinical practice guidelines for the diagnosis and management of VWD. Although the guidelines recommend using long-term prophylaxis over no prophylaxis in patients with severe VWD, the evidence of effects are low certainty due to the limited data in this area and there is no clear definition regarding which patients with VWD should be considered suitable for prophylaxis. Importantly, the majority of individuals with VWD have a mild disease phenotype, which may account for the lack of diagnosis, nevertheless, these individuals may benefit from short-term prophylaxis to control bleeding, particularly during times of high bleeding risk e.g., menstruation. Of note, the index case described by Erik von Willebrand in 1926 died as a result of bleeding during her fourth menstruation at the age of 14 years [36]. In contrast, patients with severe haemophilia typically present with abnormal and prolonged bleeding at a young age and treatment approaches can be implemented in early life.

1.3. Current approaches to treatment

In patients with severe haemophilia, prophylactic administration of clotting factor concentrates is the basis of modern treatment and guidelines are widely accepted, whereas patients with VWD are typically treated on-demand and treatment guidelines for prophylaxis are less well-characterised [37]. Approximately 45% of patients with severe haemophilia A are thought to use some form of prophylaxis compared with only 10% of patients with severe VWD [30]. While prophylaxis is used for patients with severe VWD, historically, there has been less emphasis on the treatment of patients with mild-to-moderate disease and the use of prophylaxis in type 1 and 2 VWD is rare [38]. Although the heterogeneity of disease is variable, studies have shown that patients with moderate haemophilia A report similar annualised bleeding rates (ABRs) as those with severe haemophilia A [39], suggesting there is a significant unmet treatment need in this patient group, and raises an interesting question for individuals with less severe VWD and whether they are also relatively undertreated.

For patients with haemophilia, plasma-derived (pd) and recombinant factor replacement products have been on the market for many years, and their use depends on availability and cost around the world [40]. The development of new long-acting factor concentrates has been shown to decrease the burden of treatment in haemophilia by allowing patients to reduce the number of weekly infusions while maintaining low bleed rates [41]. The health benefits of prophylactic dosing regimens for clotting factor therapy in patients with haemophilia include reduced joint damage and improved quality of life [9,42]. The severity of bleeding drives treatment decisions in both VWD and haemophilia; however, the variability in clinical manifestations in VWD means treatment and definitive diagnosis are not well defined within the different types of disease [26]. In VWD, patients are treated on-demand with desmopressin or pdVWF-containing concentrates for acute bleeding or trauma, or with short-term prophylaxis to prevent bleeding in the surgical setting (Table 2) [37,43–45].

In general, treatment strategies vary by the type and severity of disease; in the majority of patients with mild/moderate VWD, on-demand use of desmopressin is an effective treatment option, with intermittent use of prophylaxis with VWF/FVIII concentrates used for patients with a history of severe bleeding events (Fig. 1). It is important to note that closely spaced repeat doses of desmopressin in some patients can cause tachyphylaxis [43], and it is hypothesised that, in some cases, multiple doses over a long period of time could also lead to tachyphylaxis; this requires further investigation in patients requiring multiple long-term administration. Desmopressin is also contraindicated in patients with type 2B VWD as it can lead to exacerbation of thrombocytopenia, a distinctive feature of type 2B disease [47]. In VWD, pdVWF/FVIII products are most frequently used for VWF replacement therapy and have been widely approved [48]. In addition, a recombinant VWF (rVWF) product has recently been developed for use in adults in some settings, and has shown promising results in clinical trials [48,49]. This may become particularly useful in the future when considering patients who require a personalised treatment approach, including for patients with type 2N VWD (who express normal multimer distribution with reduced affinity for FVIII) whereby the replacement VWF could bind to FVIII, without increasing the risk of thrombosis associated with high VWF levels [50].

The initiation of prophylaxis in haemophilia is briefly classified, according to WFH, as primary (before the second clinically evident large joint bleed), secondary (after the second joint bleeding and before initiation of joint disease), short-term (typically used to control bleeding during planned procedures such as surgery), or tertiary (treatment started after the onset of joint disease documented by physical examination and plain radiographs of the affected joints) [1]; however, this definition cannot be readily transferred to VWD as disease is generally diagnosed much later [47]. In VWD, prophylaxis is defined as receiving factor infusions at least once per week to prevent or decrease the severity of bleeding with the intention of maintaining this regimen for 45 or more weeks per year (Fig. 1) [47].

In haemophilia, primary prophylaxis is recommended early in young patients before the onset of joint disease; however, adherence to prophylaxis treatment decreases with increased age [53]. The reasons for non-adherence/compliance issues for prophylaxis in patients with VWD and haemophilia may be different and could depend on various factors including the age of symptom presentation, disease diagnosis, treatment initiation, and less strict follow up compared with haemophilia. Evidence is emerging to suggest that even one bleed is too many in the progression of joint disease and prophylaxis should be encouraged in all patients with haemophilia [54]. A recent study in patients with haemophilia A found children who initiated FVIII prophylaxis before 2.5 years of age had significantly reduced MRI osteochondrial damage, and lower ABR and annualised joint bleeding rate, compared with those who delayed prophylaxis beyond 6 years of age [55]. This further supports the recommendation from the WFH to initiate primary prophylaxis before the first joint bleed in order to maintain joint health. In VWD, primary prophylaxis is less common compared with haemophilia and patients are typically only treated with VWF concentrates for short-term prophylaxis during the perioperative period [44,47]. There are currently no clear recommendations for prophylaxis outside the surgical setting in patients with VWD. Specific factor-containing concentrates can reduce the frequency of bleeding and provide long-term haemostatic efficacy; a potential benefit when considering the perioperative management of patients with VWD. While there are no randomised clinical studies assessing prophylaxis outside of the surgical setting, it is hypothesised

Table 2
Current treatment approaches in patients with VWD and haemophilia.

Treatment approach	VWD [37]			Haemophilia [1]	
	On-demand		Prophylaxis	On-demand	Prophylaxis
Estimated patients with severe disease	85%	5–10%	<10%	55%	45%
Therapy	Desmopressin	VWF-concentrates[a]	VWF-concentrates	FVIII or FIX concentrates; non-factor replacement concentrates	FVIII or FIX factor replacement concentrates; non-factor replacement concentrates
Indications	• Type 1 VWD • Some type 2 VWD with caution	• Type 3 VWD[b] • Type 2 VWD • Severe type 1 VWD • Type 1 VWD with contraindications to desmopressin	• Type 3 VWD[b]	• All patients with haemophilia A or B	• All patients with severe haemophilia A or B • Selected patients with moderate or mild haemophilia A or B
Advantages	• Easily available • Available in intranasal, subcutaneous and intravenous forms • Relatively inexpensive • Self-administration	• Effective in non-responders to desmopressin • Plasma-derived and recombinant VWF can be used • Short-term prophylaxis is beneficial during surgery	• Decreases bleeding episodes • Improved quality of life • Improved joint health • Long-term prophylaxis can reduce time spent in hospital	• Convenience • Few infusions	• Several novel therapies available, including factor and non-factor replacement products • Decreases bleeding episodes • Reduced haemophilic arthropathy and long-term morbidity • Improved physical activity • Improved quality of life and attendance at school/work • Reduced time spent in hospital
Disadvantages	• Short-term effect • Tachyphylaxis • Variable response • Potential side effects • Contraindications	• Short-term effect • Higher costs compared to desmopressin • Predominantly made from human plasma which may contain infectious agents (risk is minimised by donor screening, testing and virus inactivation/removal steps during manufacture)	• Prophylaxis with recombinant VWF is not well studied	• High bleed rates • Poor joint health • Pain and mobility issues • Lack of HTC follow ups	• Frequent intravenous/subcutaneous infusions from early life • Adherence to treatment • Venous access issues • Breakthrough bleeds may still occur
Incidence of inhibitors [46]	None	Severe (type 3) VWD: 5–10%	Unknown	Unknown	Severe haemophilia A: 20–30% Severe haemophilia B: 2–4%

FIX, factor IX; FVIII, factor VIII; HTC, Haemophilia Treatment Centre; VWD, von Willebrand disease; VWF, von Willebrand factor.
[a] In an adult patient undergoing elective surgery, doses quoted as average and may be 20% higher in paediatric patients.
[b] All plasma-derived concentrates containing VWF must be avoided in type 3 VWD patients with alloantibodies because of the risk of anaphylactic reactions. Recombinant FVIII, administered at very high doses by continuous intravenous infusion can be used instead.

that prophylaxis in VWD may have similar benefits to haemophilia, such as reduced long-term joint damage, reduced surgical complications, decreased annual factor consumption, reduced hospital resources and may also provide greater improvements in quality of life in some patients. The more variable bleeding presentation in VWD also suggests that clinical studies of prophylaxis treatment should focus on individual bleeding symptoms rather than ABR.

It is also important to acknowledge the differences in EMA clinical trial requirements between haemophilia and VWD. For FVIII trials in patients with severe haemophilia A, the clinical trial development concept is clearly defined and initial studies require a minimum of 12 adult/adolescent previously treated patients (PTPs) to undergo PK analysis, followed by an additional 38 patients to undergo efficacy and safety analysis for at least 50 exposure days (EDs). Similarly, 12 paediatric PTPs must undergo PK analyses with an additional 13 PTPs also undergoing efficacy and safety analyses for at least 50 EDs. On the other hand, clinical trials in patients with VWD require 12 adult/adolescent patients with severe VWD, including at least six type 3 VWD patients, to undergo PK analysis; for trials assessing new products, there is no requirement for patients to have been previously treated and the authorities acknowledge that it may be difficult to obtain six type 3 VWD patients due to the rarity of the disease. Furthermore, an additional 20 patients are required for the efficacy and safety analyses and, for prophylaxis assessment, a minimum of five type 3 VWD patients should be followed for one year, assessing safety, efficacy and immunogenicity. The assessment in paediatric patients should not be started until interim data of one year of exposure are available in 10 patients older than 12 years, who are included in the efficacy trial. PTPs would be the most suitable candidates to test the product-related immunogenicity of a modified VWF product; however, this is not a requirement for clinical studies.

1.4. Long-term prophylaxis in VWD

It is hypothesised that long-term prophylaxis in patients with severe VWD could reduce/prevent recurrent mucosal bleeds, such as gastrointestinal bleeding and heavy menstrual bleeding, which can reduce patient quality of life or even be life-threatening if untreated. In addition, with the progression of joint damage, early initiation of prophylaxis could be crucial for the reduction of joint haemorrhages with development of arthropathy, particularly in patients with type 3 VWD. Prophylaxis is feasible to implement early in life in a home setting and can have numerous long-term benefits.

The von Willebrand Disease Prophylaxis Network (VWD-PN) conducted a survey of treatment practice in patients with VWD among a group of investigators in Europe and North America. Of the 1.6%

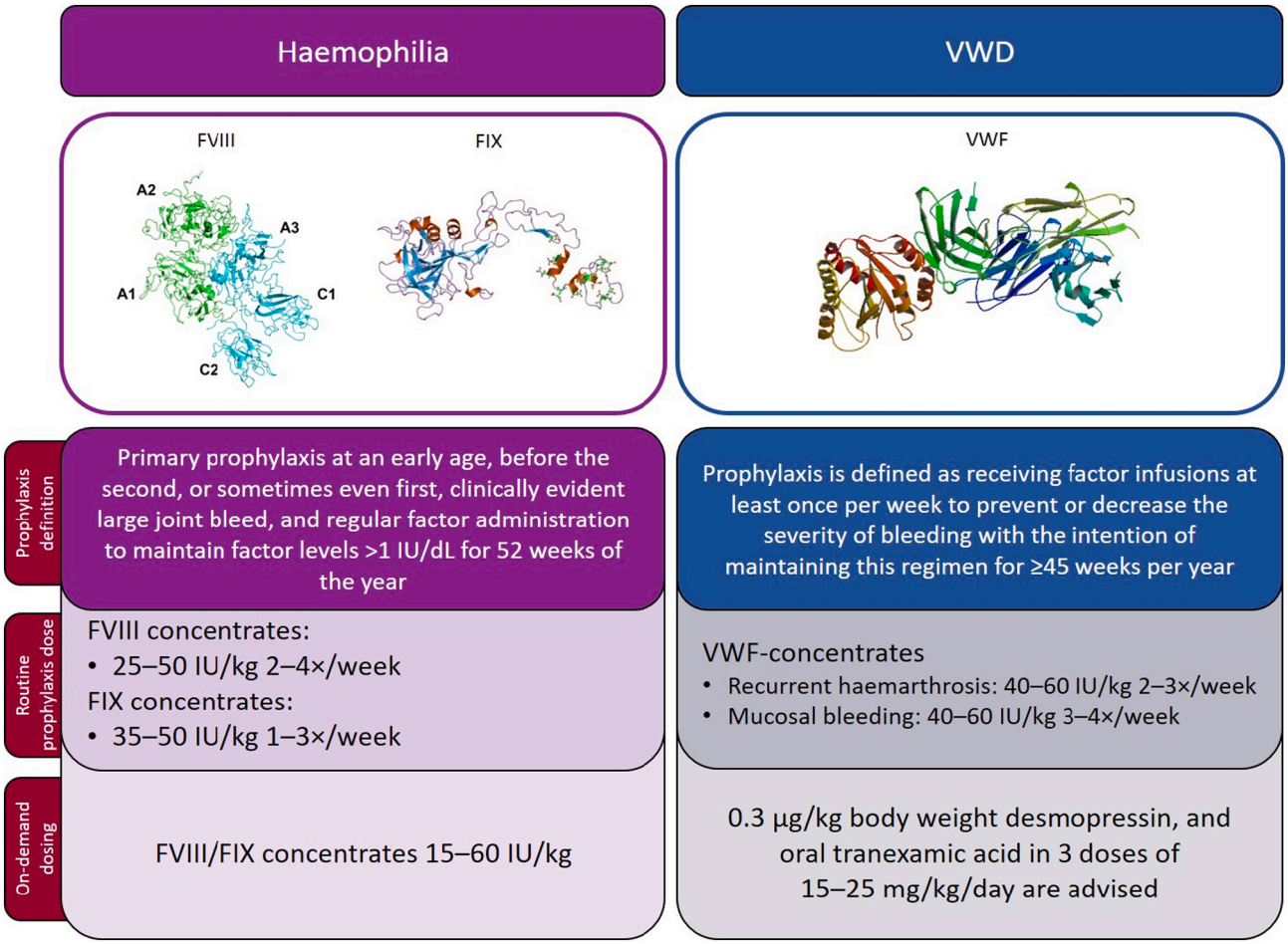

Fig. 1. Current treatment approaches[†] in patients with haemophilia and VWD [1,49,51,52].
FIX, factor IX; FVIII, factor VIII; VWD, von Willebrand disease; VWF, von Willebrand factor.
[†]Doses based on current guidelines for haemophilia and vary depending on disease severity and product; newer products have meant dosing frequency can be reduced further than those stated above while maintaining sufficient factor levels.

patients receiving prophylaxis, the majority had type 3 VWD (74.5%); however, a higher proportion of patients with type 3 VWD received prophylaxis in Europe (28.7%) than in North America (12.2%). Only 7.8% and 17.6% of the patients on prophylaxis were type 1 and type 2 VWD, respectively [38]. The most commonly reported reasons for initiating prophylaxis were joint bleeding (40%), epistaxis/oral bleeding (23%), gastrointestinal (GI) bleeding (14%) and menorrhagia (5%) [38]; however, the current prophylaxis regimens (optimal dose and frequency) used to treat different clinical bleeding phenotypes are not well defined. In addition, it is important to note that the VWD-PN study was retrospective and may be subject to selection bias as the distribution of types of VWD varied in the US and EU, and prophylaxis was only initiated in selected cases. Studies reporting on long-term prophylaxis in VWD have previously been summarised [52]. In addition to these studies, a 12-month analysis compared on-demand and prophylaxis treatment with VWF/FVIII concentrates and demonstrated a lower risk of bleeding (relative attributable risk estimate: −0.667) in those assigned to a prophylaxis regimen [51]. Further to this, based on the current literature, the frequency of prophylaxis and dose indication for VWD bleeding phenotypes in patients with type 3 VWD are noted in Table 3 [56], and bleeding rates have been shown to reduce for each bleeding phenotype in patients treated using prophylaxis [47,57]. However, it is important to note that despite the evidence of long-term prophylaxis with VWF/FVIII concentrates, there are a lack of recommendations for prophylaxis regimens in those with type 1 and 2 VWD, and these patients are typically treated with desmopressin.

Table 3
Long-term prophylaxis in patients with type 3 VWD in the VWD-PN prospective study [47,58].

Bleeding phenotype	Percentage of patients initiating prophylaxis (n = 50)	VWF: RCo dose IU/kg body weight	Dose(s) per week[a]	When to initiate
Joint	21.8%	10–50	2–3	After first bleeds
GI	23.6%	20–60	2–4	After 2–3 severe bleeds per year
Epistaxis	23.6%	20–60	1–3	After 3–4 severe bleeds per year
Menorrhagia	7.3%	20–50	3–4 during menstruation	If required
Other[b]	14.6%	10–70	1–3	If required

GI, gastrointestinal; RCo, ristocetin cofactor; VWD, von Willebrand disease; VWF, von Willebrand factor.
[a] Doses based on individual patient bleeding phenotype.
[b] Other bleeding phenotypes included intracranial haemorrhage, haematomas in soft tissue, oral, dental extraction, scraped knees, ovarian cysts or bleeding.

For short- and long-term prophylaxis, a commonly used concentrate is a pdVWF concentrate, with a VWF:FVIII ratio of 2.4:1 (Haemate® P, CSL Behring, Germany; Humate-P® in the US and Canada), at doses ranging from 12 to 50 IU FVIII/kg body weight, with infusions given 1–3 times per week [59]. Patients with VWD treated with long-term prophylaxis with Haemate® P have demonstrated reduced bleeding episodes compared with those treating on-demand, and treatment was well-tolerated, indicating that Haemate® P may be efficacious in patients treated prophylactically [60,61]. In addition, in children who began prophylaxis with VWF/FVIII concentrates before the age of 5 years, there have been no reports of joint bleeds or signs of arthropathy [62]. Furthermore, the bleeding frequency in patients with type 3 VWD treated with another VWF/FVIII concentrate (Wilate®, Octapharma, Austria) with a balanced VWF:FVIII ratio (1:1) has been assessed [63,64]. Wilate® has been shown to be effective for on-demand treatment (25–50 IU/kg) and routine prophylaxis (20–40 IU/kg 2–3×/week), and can be administered at lower VWF doses compared with other concentrates owing to its 1:1 ratio [64]. After initiating long-term prophylaxis, patients reported a reduction in bleeding frequency, from 4 bleeds per month (range 1–30) to 0 bleeds per month (0–2) on prophylaxis [63]. In addition, Wilate® has demonstrated excellent tolerability with no thromboembolic events in adults or paediatrics [64]. Another pdVWF/FVIII concentrate (Voncento®, CSL Behring, Germany) is available for the prophylaxis and treatment of haemorrhage or surgical bleeding when desmopressin treatment alone is contraindicated or ineffective [65,66]. Paediatric patients with VWD treated prophylactically with Voncento® reported reduced incidence of major bleeds (3.3%) compared with patients treated on-demand (27.1%); the incidence of joint bleeds were also reduced (3.3% vs. 11.5%, respectively) [66]. Moreover, the pdVWF/FVIII concentrate (Wilfactin®, LFB Biopharmaceuticals Limited, France) almost devoid of FVIII has demonstrated effective bleed control in clinical trials, with a treatment interval of 50–60 IU/kg 2–3×/week for long-term treatment of spontaneous bleeding events [67]. Additionally, in a recently published case, a patient with a history of serious haemorrhage was treated with 32 IU/kg of this concentrate and demonstrated a significant reduction in the frequency and intensity of spontaneous bleeding, further supporting the use in clinical practice [68]. Further clinical studies would be desirable to determine the optimal prophylaxis regimen for each bleeding phenotype in VWD, and the first dose-escalation study in patients with severe VWD treated with prophylaxis could help establish the optimal prophylaxis regimen [58]. This is of particular importance because in patients who receive multiple doses of VWF/FVIII concentrate over a short period of time, plasma FVIII levels may progressively increase, as VWF stabilises not only the exogenously administered FVIII but also the endogenous FVIII pool [69]. Resulting high FVIII levels have been associated with an increased risk of thromboembolic complications, although these events are rare in VWD [70,71]. Nevertheless, although this may be a concern if patients require multiple doses following surgery, long-term prophylaxis at a frequency of 1–3 times per week would allow FVIII levels to decrease between doses. In addition, in more than 36 years of clinical experience, there have been no instances of inhibitor development and few thrombotic events in patients treated with Haemate® P prophylaxis [62].

Patients treated with factor concentrates may develop inhibitory antibodies, with the incidence typically associated with type 3 VWD patients (5–10% of patients) [46], but does not seem to be a main issue in VWD compared with the situation in haemophilia. Theoretically, a rVWF concentrate, or a purified VWD concentrate with no FVIII, could be beneficial for prophylaxis to raise FVIII to haemostatically relevant levels without additional FVIII replacement infusions [49,67]; however, concentrates with a high VWF/FVIII ratio (≥2:1) have been proved to ensure the haemostatic balance, without an accumulation of FVIII due to the short half-life of FVIII. In addition, the benefits of regular prophylactic use with rVWF have yet to be proven in larger trials [51], and prophylaxis is not currently indicated in the label. Furthermore, emicizumab, a monoclonal antibody indicated for use in patients with haemophilia A with or without inhibitors, has been investigated in patients with type 3 VWD who develop antibodies to VWF/FVIII concentrates. While this is a rare occurrence, the development of antibodies further limits the treatment options in these patients. Patient studies have shown that prophylaxis with emicizumab can reduce the frequency of spontaneous bleeding and therefore improve quality of life; this may become the favoured treatment approach in a number of patients, including for patients with severe VWD who have a high treatment burden and bleeding phenotypes similar to patients with haemophilia [72].

1.5. *Future implications for prophylaxis in VWD*

The successful implementation of long-term prophylaxis regimens in haemophilia provides a rationale for the use in patients with VWD. Evidence of the ability of VWF/FVIII concentrates to provide adequate and timely haemostasis in patients with VWD treated with prophylaxis is accumulating. In contrast to haemophilia, there is a significant lack of studies assessing the pharmacokinetic and pharmacoeconomic impact of treatment in patients with severe VWD, and limited studies comparing the efficacy of on-demand versus long-term prophylactic regimens. Despite this, it is thought that a selected population of patients with VWD and a severe bleeding phenotype may benefit from long-term prophylaxis with VWF concentrates, and as bleeding frequency increases with age, there is an increased need to provide personalised prophylaxis to manage disease comorbidities [20,73]. Based on the effects seen in patients with haemophilia treated with prophylaxis, similarities may be drawn for the benefits and barriers of long-term prophylaxis (Fig. 2) to reduce morbidity and improve patient quality of life, e.g., does prophylaxis in VWD reduce the need for hospitalisation [74]. The unmet needs for patients with VWD and haemophilia treated on prophylaxis will shape our approach to treatment as we move towards personalised prophylaxis, targeting zero bleeds. In addition, the standardisation and validation of the bleeding score in VWD and its application to evaluate the patient's tendency to bleed will likely aid individualising prophylaxis therapy and may minimise treatment burden. Furthermore, novel treatment approaches such as gene therapy are ongoing and could further improve the standard of care.

2. Conclusions

Prophylaxis has significantly changed the lives of many patients with haemophilia and knowledge gained from the use of prophylaxis in haemophilia could be applied to some patients with VWD to reduce the burden of disease. There are still unmet needs for prophylaxis in haemophilia, e.g., in moderate forms of the disease, and a similar situation could be the case in VWD. Currently, there is no firm definition of prophylaxis in VWD and the frequency and dose of concentrate needs to be further defined. As knowledge of VWD increases, in particular the progression of joint damage in untreated patients, guidelines should be updated to provide comprehensive care for individuals with VWD. Studies within the frame of VWD-PN have paved the way showing clear benefits for prophylaxis, and further studies would aid in the development of evidence-based guidelines for this approach, but it can already be proposed that long-term prophylaxis should be implemented in patients with repeated bleeds impacting quality of life and increasing burden on healthcare especially those with type 3, but occasionally also in patients with phenotypically severe type 2 and type 1 VWD.

Declaration of competing interest

Professor Miesbach has received funding support for research and has acted as a paid consultant to LFB, CSL Behring, Octapharma and Takeda/Shire. Professor Berntorp has received funding support for research from Takeda/Shire and acted as paid consultant to LFB, CSL

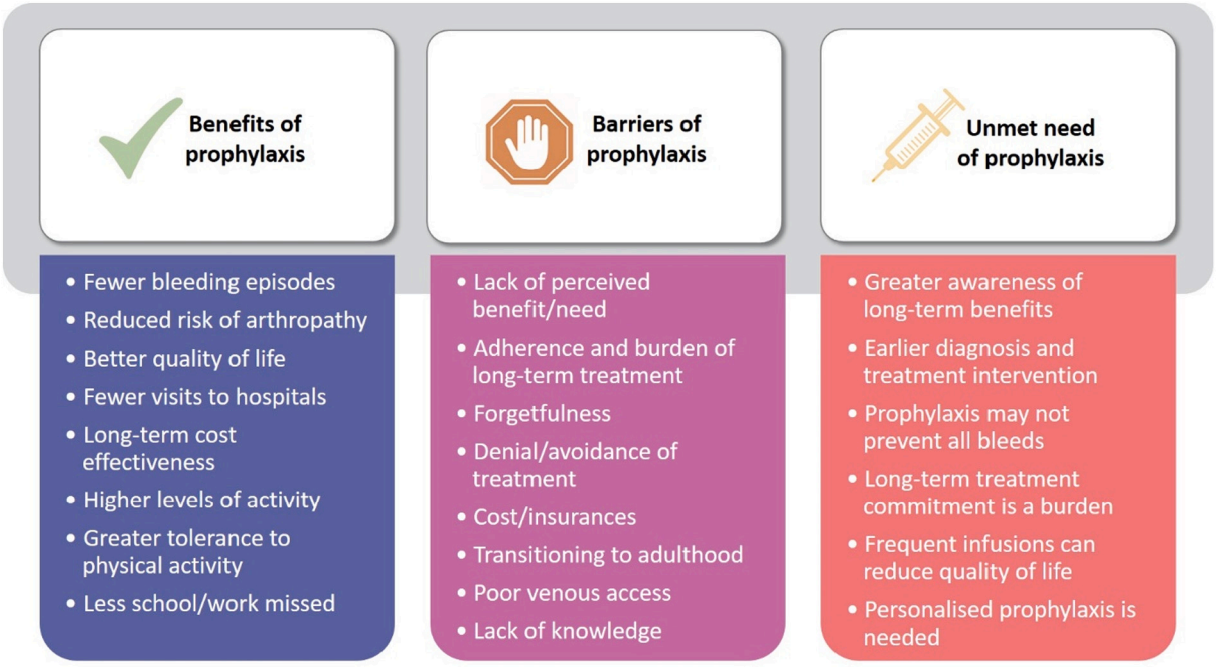

Fig. 2. Benefits, barriers and unmet needs of patients treated on prophylaxis are similar in VWD and haemophilia [3,4].

Behring, Octapharma and Takeda/Shire.

Acknowledgements

WM and EB contributed equally to the development of this review manuscript. Medical writing assistance was provided by Meridian HealthComms Ltd. in accordance with good publication practice (GPP3), funded by CSL Behring.

References

[1] A. Srivastava, A.K. Brewer, E.P. Mauser-Bunschoten, et al., Guidelines for the management of hemophilia, Haemophilia 19 (2013) e1–47.
[2] D. Nugent, B. O'Mahony, G. Dolan, International Haemophilia Access Strategy Council, Value of prophylaxis vs on-demand treatment: application of a value framework in hemophilia, Haemophilia 24 (2018) 755–765.
[3] G. Castaman, The benefits of prophylaxis in patients with hemophilia B, Expert. Rev. Hematol. 11 (2018) 673–683.
[4] M. Makris, Prophylaxis in haemophilia should be life-long, Blood Transfus. 10 (2012) 165–168.
[5] I. den Uijl, D. Biesma, D. Grobbee, K. Fischer, Turning severe into moderate haemophilia by prophylaxis: are we reaching our goal? Blood Transfus. 11 (2013) 364–369.
[6] R. Klamroth, J. Windyga, V. Radulescu, PK-guided Rurioctocog Alfa Pegol Prophylaxis in Patients With Severe Hemophilia A Targeting two FVIII Trough Levels: Results From the Phase 3 PROPEL Study. Presented at the International Society on Thrombosis and Haemostasis (ISTH) Biennial Congress, July 6–10, 2019; Melbourne, Australia, 2019.
[7] I.E. den Uijl, K. Fischer, J.G. Van Der Bom, D.E. Grobbee, F.R. Rosendaal, I. Plug, Analysis of low frequency bleeding data: the association of joint bleeds according to baseline FVIII activity levels, Haemophilia 17 (2011) 41–44.
[8] M.W. Skinner, D. Nugent, P. Wilton, et al., Achieving the unimaginable: health equity in haemophilia, Haemophilia 26 (2020) 17–24.
[9] J. Oldenburg, Optimal treatment strategies for hemophilia: achievements and limitations of current prophylactic regimens, Blood 125 (2015) 2038–2044.
[10] K. Fischer, J.G. van der Bom, E.P. Mauser-Bunschoten, et al., The effects of postponing prophylactic treatment on long-term outcome in patients with severe hemophilia, Blood 99 (2002) 2337–2341.
[11] T. Simurda, L. Stanciakova, J. Stasko, M. Dobrotova, P. Kubisz, Yes or no for secondary prophylaxis in afibrinogenemia? Blood Coagul. Fibrinolysis 26 (2015) 978–980.
[12] K.P.M. van Galen, P. de Kleijn, W. Foppen, et al., Long-term impact of joint bleeds in von Willebrand disease: a nested case-control study, Haematologica 102 (2017) 1486–1493.
[13] K.P. van Galen, Y.V. Sanders, U. Vojinovic, et al., Joint bleeds in von Willebrand disease patients have significant impact on quality of life and joint integrity: a cross-sectional study, Haemophilia 21 (2015) e185–e192.
[14] K.P.M. van Galen, M. Timmer, P. de Kleijn, et al., Long-term outcome after joint bleeds in Von Willebrand disease compared to haemophilia A: a post hoc analysis, Thromb. Haemost. 118 (2018) 1690–1700.
[15] F. Peyvandi, I. Garagiola, L. Baronciani, Role of von Willebrand factor in the haemostasis, Blood Transfus. 9 (Suppl. 2) (2011) s3–s8.
[16] M. Bowman, W.M. Hopman, D. Rapson, D. Lillicrap, P. James, The prevalence of symptomatic von Willebrand disease in primary care practice, J. Thromb. Haemost. 8 (2010) 213–216.
[17] World Federation of Hemophilia, von Willebrand Disease FAQ, Available at: https://www.wfh.org/en/page.aspx?pid=680. (Accessed April 2020).
[18] J. Stockley, S.P. Nisar, V.C. Leo, et al., Identification and characterization of novel variations in platelet G-protein coupled receptor (GPCR) genes in patients historically diagnosed with type 1 von Willebrand disease, PLoS One 10 (2015), e0143913.
[19] World Federation of Hemophilia, Annual global survey 2018, Available at: https://www.wfh.org/en/our-work-research-data/annual-global-survey. (Accessed April 2020).
[20] J.M. Heijdra, M.H. Cnossen, F.W.G. Leebeek, Current and emerging options for the management of inherited von Willebrand disease, Drugs 77 (2017) 1531–1547.
[21] A. Iorio, J.S. Stonebraker, H. Chambost, et al., Establishing the prevalence and prevalence at birth of hemophilia in males: a meta-analytic approach using national registries, Ann. Intern. Med. 171 (2019) 540–546.
[22] National Haemophilia Foundation, Fast facts 2020, Available at: https://www.hemophilia.org/About-Us/Fast-Facts. (Accessed April 2020).
[23] D. Lillicrap, von Willebrand disease: advances in pathogenetic understanding, diagnosis, and therapy, Blood 122 (2013) 3735–3740.
[24] M.W. Skinner, WFH: closing the global gap–achieving optimal care, Haemophilia 18 (Suppl. 4) (2012) 1–12.
[25] A. Iorio, E. Iserman, V. Blanchette, et al., Target plasma factor levels for personalized treatment in haemophilia: a Delphi consensus statement, Haemophilia 23 (2017) e170–e179.
[26] P. Schinco, G. Castaman, A. Coppola, et al., Current challenges in the diagnosis and management of patients with inherited von Willebrand's disease in Italy: an Expert Meeting Report on the diagnosis and surgical and secondary long-term prophylaxis, Blood Transfus. 16 (2018) 371–381.
[27] S. Selvam, P. James, Angiodysplasia in von Willebrand disease: understanding the clinical and basic science, Semin. Thromb. Hemost. 43 (2017) 572–580.
[28] The American Society of Hematology, Clinical practice guideline on the evaluation and management of von Willebrand Disease (VWD) 2012, Available at: www.hematology.org/Clinicians/Guidelines-Quality/Quick-Ref/528.aspx. (Accessed April 2020).
[29] Centers for Disease Control and Prevention, Research on von Willebrand Disease (VWD) 2018, Available at: https://www.cdc.gov/ncbddd/vwd/research.html. (Accessed April 2020).
[30] National Heart Lung and Blood Institute, The diagnosis, evaluation, and management of von Willebrand Disease 2007, Available at: https://www.nhlbi.nih.gov/files/docs/guidelines/vwd.pdf. (Accessed April 2020).
[31] J. Spradbrow, S. Letourneau, J. Grabell, et al., Bleeding assessment tools to predict von Willebrand disease: utility of individual bleeding symptoms, Res. Pract. Thromb. Haemost. 4 (2020) 92–99.

[32] A. Tosetto, F. Rodeghiero, G. Castaman, et al., A quantitative analysis of bleeding symptoms in type 1 von Willebrand disease: results from a multicenter European study (MCMDM-1 VWD), J. Thromb. Haemost. 4 (2006) 766–773.
[33] American Society of Hematology, The Diagnosis, Evaluation, and Management of von Willebrand Disease, National Heart, Lung, and Blood Institute, NIH, 2012.
[34] H.A. Azzam, H.R. Goneim, A.M. El-Saddik, E. Azmy, M. Hassan, S. El-Sharawy, The condensed MCMDM-1 VWD bleeding questionnaire as a predictor of bleeding disorders in women with unexplained menorrhagia, Blood Coagul. Fibrinolysis 23 (2012) 311–315.
[35] A.B. Federici, P. Bucciarelli, G. Castaman, et al., The bleeding score predicts clinical outcomes and replacement therapy in adults with von Willebrand disease, Blood 123 (2014) 4037–4044.
[36] A.B. Federici, E. Berntorp, C.A. Lee, The 80th anniversary of von Willebrand's disease: history, management and research, Haemophilia 12 (2006) 563–572.
[37] W.L. Nichols, M.B. Hultin, A.H. James, et al., von Willebrand disease (VWD): evidence-based diagnosis and management guidelines, the National Heart, Lung, and Blood Institute (NHLBI) Expert Panel report (USA), Haemophilia 14 (2008) 171–232.
[38] E. Berntorp, T. Abshire, von Willebrand Disease Prophylaxis Network Steering Committee, The von Willebrand disease prophylaxis network: exploring a treatment concept, J. Thromb. Haemost. 4 (2006) 2511–2512.
[39] M.J. Scott, H. Xiang, D.P. Hart, et al., Treatment regimens and outcomes in severe and moderate haemophilia A in the UK: the THUNDER study, Haemophilia 25 (2019) 205–212.
[40] M. Escobar, E. Santagostino, M.E. Mancuso, et al., Switching patients in the age of long-acting recombinant products? Expert. Rev. Hematol. 12 (2019) 1–13.
[41] K. Lieuw, Many factor VIII products available in the treatment of hemophilia A: an embarrassment of riches? J. Blood Med. 8 (2017) 67–73.
[42] S. von Mackensen, J. Shah, W. Seifert, G. Kenet, Health-related quality of life in paediatric haemophilia B patients treated with rIX-FP, Haemophilia 25 (2019) 45–53.
[43] M.A. Laffan, W. Lester, J.S. O'Donnell, et al., The diagnosis and management of von Willebrand disease: a United Kingdom Haemophilia Centre Doctors Organization guideline approved by the British Committee for Standards in Haematology, Br. J. Haematol. 167 (2014) 453–465.
[44] W. Miesbach, E. Berntorp, Von Willebrand disease - the 'Dos' and 'Don'ts' in surgery, Eur. J. Haematol. 98 (2017) 121–127.
[45] R. Sasaki, Y. Horimoto, J. Mizuno, et al., Administration of plasma-derived coagulation factor VIII during the perioperative period of mastectomy for breast cancer with acquired von Willebrand syndrome, Surg. Case Rep. 4 (2018) 118.
[46] P.D. James, D. Lillicrap, P.M. Mannucci, Alloantibodies in von Willebrand disease, Blood 122 (2013) 636–640.
[47] E. Berntorp, Prophylaxis in von Willebrand disease, Haemophilia 14 (Suppl. 5) (2008) 47–53.
[48] F. Peyvandi, P. Kouides, P.L. Turecek, E. Dow, E. Berntorp, Evolution of replacement therapy for von Willebrand disease: from plasma fraction to recombinant von Willebrand factor, Blood Rev. 38 (2019) 100572.
[49] F. Peyvandi, A. Mamaev, J.D. Wang, et al., Phase 3 study of recombinant von Willebrand factor in patients with severe von Willebrand disease who are undergoing elective surgery, J. Thromb. Haemost. 17 (2019) 52–62.
[50] E.J. Favaloro, Towards personalised therapy for von Willebrand disease: a future role for recombinant products, Blood Transfus. 14 (2016) 262–276.
[51] F. Peyvandi, G. Castaman, P. Gresele, et al., A phase III study comparing secondary long-term prophylaxis versus on-demand treatment with vWF/FVIII concentrates in severe inherited von Willebrand disease, Blood Transfus. 17 (2019) 391–398.
[52] G. Saccullo, M. Makris, Prophylaxis in von Willebrand disease: coming of age? Semin. Thromb. Hemost. 42 (2016) 498–506.
[53] S. Zappa, M. McDaniel, J. Marandola, G. Allen, Treatment trends for haemophilia A and haemophilia B in the United States: results from the 2010 practice patterns survey, Haemophilia 18 (2012) e140–e153.
[54] L.F.D. van Vulpen, K. Holstein, C. Martinoli, Joint disease in haemophilia: pathophysiology, pain and imaging, Haemophilia 24 (Suppl. 6) (2018) 44–49.
[55] B.B. Warren, D. Thornhill, J. Stein, et al., Young adult outcomes of childhood prophylaxis for severe hemophilia A: results of the Joint Outcome Continuation Study, Blood Adv. 4 (2020) 2451–2459.
[56] T.C. Abshire, A.B. Federici, M.T. Alvarez, et al., Prophylaxis in severe forms of von Willebrand's disease: results from the von Willebrand Disease Prophylaxis Network (VWD PN), Haemophilia 19 (2013) 76–81.
[57] E. Holm, T.C. Abshire, J. Bowen, et al., Changes in bleeding patterns in von Willebrand disease after institution of long-term replacement therapy: results from the von Willebrand Disease Prophylaxis Network, Blood Coagul. Fibrinolysis 26 (2015) 383–388.
[58] T. Abshire, J. Cox-Gill, C.L. Kempton, et al., Prophylaxis escalation in severe von Willebrand disease: a prospective study from the von Willebrand Disease Prophylaxis Network, J. Thromb. Haemost. 13 (2015) 1585–1589.
[59] Humate-P® Prescribing Information, Available at: https://labeling.cslbehring.com/PI/US/Humate-P/EN/Humate-P-Prescribing-Information.pdf, 2017. (Accessed April 2020).
[60] A. Coppola, E. Cimino, P. Conca, et al., Long-term prophylaxis with intermediate-purity factor VIII concentrate (Haemate P) in a patient with type 3 von Willebrand disease and recurrent gastrointestinal bleeding, Haemophilia 12 (2006) 90–94.
[61] E. Berntorp, Haemate P/Humate-P: a systematic review, Thromb. Res. 124 (Suppl. 1) (2009) S11–S14.
[62] E. Berntorp, P. Petrini, Long-term prophylaxis in von Willebrand disease, Blood Coagul. Fibrinolysis 16 (Suppl. 1) (2005) S23–S26.
[63] S. Halimeh, A. Krumpel, H. Rott, et al., Long-term secondary prophylaxis in children, adolescents and young adults with von Willebrand disease. Results of a cohort study, Thromb. Haemost. 105 (2011) 597–604.
[64] E. Berntorp, J. Windyga, European Wilate Study Group, Treatment and prevention of acute bleedings in von Willebrand disease - efficacy and safety of Wilate, a new generation von Willebrand factor/factor VIII concentrate, Haemophilia 15 (2009) 122–130.
[65] T.J. Lissitchkov, E. Buevich, K. Kuliczkowski, et al., Pharmacokinetics, efficacy, and safety of a plasma-derived VWF/FVIII concentrate (VONCENTO) for on-demand and prophylactic treatment in patients with von Willebrand disease (SWIFT-VWD study), Blood Coagul. Fibrinolysis 28 (2017) 152–162.
[66] G. Auerswald, C. Djambas Khayat, O. Stasyshyn, et al., Pharmacokinetics, efficacy and safety of a plasma-derived VWF/FVIII concentrate (formulation V) in pediatric patients with von Willebrand disease (SWIFTLY-VWD study), J. Blood Med. 11 (2020) 213–225.
[67] A. Borel-Derlon, A.B. Federici, V. Roussel-Robert, et al., Treatment of severe von Willebrand disease with a high-purity von Willebrand factor concentrate (Wilfactin): a prospective study of 50 patients, J. Thromb. Haemost. 5 (2007) 1115–1124.
[68] T. Simurda, M. Dobrotova, I. Skornova, J. Sokol, P. Kubisz, J. Stasko, Successful use of a highly purified plasma von Willebrand factor concentrate containing little FVIII for the long-term prophylaxis of severe (type 3) von Willebrand's disease, Semin. Thromb. Hemost. 43 (2017) 639–641.
[69] P.M. Mannucci, M. Franchini, Laboratory monitoring of replacement therapy for major surgery in von Willebrand disease, Haemophilia 23 (2017) 182–187.
[70] I. Martinelli, von Willebrand factor and factor VIII as risk factors for arterial and venous thrombosis, Semin. Hematol. 42 (2005) 49–55.
[71] P.A. Kyrle, E. Minar, M. Hirschl, et al., High plasma levels of factor VIII and the risk of recurrent venous thromboembolism, N. Engl. J. Med. 343 (2000) 457–462.
[72] A.C. Weyand, V.H. Flood, J.A. Shavit, S.W. Pipe, Efficacy of emicizumab in a pediatric patient with type 3 von Willebrand disease and alloantibodies, Blood Adv. 3 (2019) 2748–2750.
[73] W. Miesbach, E. Berntorp, When von Willebrand disease comes into age - a matter of change? Eur. J. Haematol. 86 (2011) 496–501.
[74] E. Holm, K.S. Carlsson, S. Lovdahl, A.E. Lail, T.C. Abshire, E. Berntorp, Bleeding-related hospitalization in patients with von Willebrand disease and the impact of prophylaxis: results from national registers in Sweden compared with normal controls and participants in the von Willebrand Disease Prophylaxis Network, Haemophilia 24 (2018) 628–633.