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STATE OF THE ART REVIEW

Prophylaxis in von Willebrand disease with von Willebrand factor concentrate and nonfactor therapies

Calvin B. van Kwawegen | **Frank W. G. Leebeek**

Department of Hematology, Erasmus University Medical Center, Rotterdam, The Netherlands

Correspondence
Frank W. G. Leebeek, Department of Hematology, Erasmus University Medical Center, PO Box 2040, 3000 CA Rotterdam, The Netherlands.
Email: F.leebeek@erasmusmc.nl

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Abstract

This manuscript summarizes the current status of prophylaxis and novel potential therapies to prevent bleeding in patients with von Willebrand disease (VWD). VWD is the most common inherited bleeding disorder, which is associated mainly with mucocutaneous bleeding and bleeding during surgical and dental interventions. More severely affected VWD patients, mostly those with type 2 and type 3, can also suffer from joint, muscle, and gastrointestinal bleeds. Most patients with mild and moderate VWD are treated with desmopressin. The majority of patients with type 2 and 3 are treated with von Willebrand factor concentrates, with or without factor VIII. These patients suffer from severe and frequent bleeds and may require regular infusions of von Willebrand factor concentrate to prevent bleeding, so-called prophylaxis, 1 to 3 times per week. In this article, we review the current status of prophylaxis in VWD. We will also discuss emerging treatments that may be used as long-term prophylaxis in patients with severe VWD. We include relevant new data on this topic that were presented during the 2024 International Society on Thrombosis and Haemostasis (ISTH) Congress.

KEYWORDS
bleeding, nonfactor therapies, prophylaxis, treatment strategy, von Willebrand disease

1 | INTRODUCTION

von Willebrand disease (VWD) is the most common inherited bleeding disorder and is caused by a deficiency of von Willebrand factor (VWF) [1,2]. Type 1 VWD is the most prevalent type and is characterized by a quantitative reduction of VWF, whereas type 2 VWD is caused by a qualitative defect of VWF. Type 3 VWD is defined by a (near) complete absence of VWF [2]. VWD is mainly associated with mucosal and cutaneous bleeding, such as easy bruising, menorrhagia, epistaxis, and bleeding during and after surgical or dental procedures [3].

The bleeding phenotype of type 2 and 3 patients is generally more severe than that of type 1 VWD patients. Gastrointestinal (GI) bleeds, joint bleeds, and muscle bleeds occur more often in these more severely affected VWD patients. VWD patients are usually treated on-demand, at the time of bleeding, or before a surgical or dental procedure with desmopressin of plasma-derived (pd) or recombinant (r) factor (F)VIII/VWF-containing concentrates, aiming to increase and normalize VWF and FVIII levels [2]. Because of the frequency and severity of bleeds and the sequelae of bleeding, including anemia and arthropathy, children and adults with severe VWD have a reduced health-related quality of life (HRQoL) [4,5].

Prophylaxis is an important treatment option to prevent frequent or severe bleeding and consists of regular infusions with VWF concentrates, eg, once or twice weekly. In this State of the Art paper, we summarize the current status of prophylaxis in the field of VWD and discuss developments in nonfactor therapies with the potential to prevent bleeding in VWD patients in the future.

2 | BLEEDING PHENOTYPE OF VWD AND HRQOL

VWD is characterized mainly by mucocutaneous bleeding symptoms, including menorrhagia (heavy menstrual bleeding; HMB), epistaxis, easy bruising, and GI bleeding [3]. However, the bleeding phenotype is highly heterogeneous and influenced by multiple factors. In children, nosebleeds can occur frequently and can be so severe to the extent that they require blood transfusions [6]. In patients with type 2 and 3 VWD, the bleeding phenotype is not only determined by low VWF levels but also by reduced FVIII levels and is therefore more severe than in type 1. A large study of type 3 VWD patients showed that nearly all patients with FVIII levels < 10 IU/dL experienced frequent bleeding episodes and were in need of on-demand factor concentrate treatment [7]. Joint and muscle bleeds had occurred in 45% and 28% of patients, respectively.

In the Willebrand in the Netherlands (WiN) study, nearly 60% of type 3 patients and 12% of patients with type 2 self-reported joint bleeding, which may result in arthropathy in the long term [8]. In a study based on medical records of 49 VWD patients with treated joint bleeding in the past, arthropathy was found in 40%, resulting in pain and functional limitations [9]. Therefore, these bleeding episodes are preferably treated early and adequately with an on-demand treatment strategy or prevented by giving prophylaxis [10].

GI bleeding is reported in around 15% of VWD patients, but among patients with type 2 and type 3 VWD, the prevalence is up to 27% [3]. GI bleeding is frequently caused by the development of angiodysplasia and vascular lesions in the GI tract [11,12]. Several studies have indicated that this may be due to a lack of high-molecular-weight multimers of VWF, which have antiangiogenic properties [13,14]. Others have suggested another pathway in which a lack of intracellular VWF leads to enhanced angiogenesis through the release of angiopoietin from the endothelium [15]. Despite treatment of GI bleeding with VWF factor concentrates, these lesions are difficult to control, and recurrent bleeding is often encountered [3,12].

Several studies have shown that patients with VWD, especially those with frequent bleeding symptoms, have a reduced HRQoL. This was previously demonstrated in both children and adults with VWD [4,5]. A more severe bleeding phenotype is not only associated with reduced physical functioning and reduced scores on bodily pain but also reduced general health. Type 3 VWD patients had a significantly lower HRQoL than those with type 1 and 2. Frequently experienced HMB by VWD patients may have a strong impact on HRQoL [16]. Joint bleeds and arthropathy are strongly related to lower physical and mental health scores.

3 | TREATMENT OF VWD

Patients with VWD are mainly treated on-demand in case of bleeding or before surgical or dental interventions in order to reduce the risk of bleeding. Many of the nonseverely affected VWD patients can be treated with desmopressin, which increases VWF and FVIII levels 2- to 3-fold [2,17]. Patients who do not respond to desmopressin are treated with VWF-containing concentrates, including type 3 patients, type 1C patients with very low VWF and FVIII levels due to high clearance of VWF, and some patients with type 2. A similar treatment strategy is followed for patients in whom desmopressin is contraindicated, such as patients with type 2B VWD or cardiovascular disease [17].

Besides increasing VWF and FVIII levels by infusion of VWF concentrate to treat or prevent bleeding, VWD patients may also benefit from supportive treatment. Inhibition of fibrinolysis may be beneficial, particularly for the management of mucocutaneous bleeding [17,18]. In patients with regular epistaxis or HMB, tranexamic acid (TXA) is often used successfully [19]. TXA given at a dose of 3 times daily 1000 mg (depending on body weight and renal function) during the menstrual period (5-7 days) has been shown to alleviate bleeding [20]. Menorrhagia may also be treated using hormonal treatment in VWD patients. After the exclusion of local uterine abnormalities or hormonal causes, oral contraceptives containing progesterone and estrogens are recommended as first-line treatment [21]. If oral contraceptives are ineffective or not preferred, a levonorgestrel-containing intrauterine device (Mirena) may be an alternative [19].

In patients with recurrent GI bleeding due to angiodysplasia, several drugs have been shown to be an effective addition to hemostatic treatment with VWF concentrates in case series, including octreotide, thalidomide, and statins [22–24].

4 | WHICH VWD PATIENTS ARE IN NEED OF PROPHYLAXIS?

In persons with severe and moderate hemophilia A and B who suffer from regular bleeds in joints and muscles or other severe bleeds, prophylactic treatment with intravenous (i.v.) administered factor concentrate 1 to 4 times per week has been the standard of care for many decades [25]. In hemophilia A and B, prophylaxis is started early in life, often after the first joint bleed. In recent years, most young children and adults with hemophilia A have switched to prophylactic treatment with emicizumab (Hemlibra, Roche). Emicizumab is a bispecific monoclonal antibody that has FVIIIa-like properties by binding FIXa and FX, thereby activating FX. Despite the fact that prophylaxis has been the standard for persons with hemophilia for decades, prophylaxis is only used in a small proportion of VWD patients and seems to be underutilized.

The first report on prophylactic use of VWF-containing concentrates in VWD patients was from Sweden in 2005 [26]. This study showed data from 35 patients, of which 30 had type 3 VWD, with VWF and FVIII levels < 10 IU/dL, who were treated with long-term prophylaxis for various bleeding indications. For children, the indications to start prophylaxis were mainly oral or nose bleeds, and for adults, most often joint bleeds. At the start of the study, the product used was a pdFVIII concentrate containing VWF; later, Haemate-P (CSL Behring) was administered.

In the Willebrand Disease Prophylaxis Network survey, performed in 2006, clinical data of 5300 VWD patients were reported. Only 99 VWD patients were on prophylaxis, predominantly for joint bleeding, oral/nasal bleeding, and GI bleeding [27]. This network also initiated the first prospective study on prophylaxis in 11 severe VWD patients and showed that VWF concentrate (50 VWF:RCo; Ristocetin cofactor IU/kg 1, 2, or 3 times per week) reduced the number of mucosal and joint bleeding episodes [28]. Holm et al. [29] analyzed the data of this prospective study in combination with a retrospective study in a total of 105 patients and showed a significant reduction of bleeding rates for epistaxis, GI bleeding, joint bleeding, and menorrhagia. However, most patients with GI bleeding needed prophylaxis 3 or more times per week, as well as higher dosages.

While the use of prophylaxis with VWF concentrates is generally effective, it is important to consider complications associated with this preventive strategy. Fortunately, there have been no reports of venous thrombosis during long-term prophylactic treatment with VWF concentrate. However, for patients with type 3 VWD, inhibitor formation in the form of alloantibodies against VWF may occur after treatment with VWF concentrate. Patients with alloantibodies against VWF generally show a limited increase and a rapid clearance of VWF after infusion of VWF concentrates. Alloantibodies to VWF may also lead to life-threatening anaphylactic allergic reactions, resulting in a contraindication to administer prophylaxis with VWF-containing concentrates in these patients. Although Berntorp et al. [26] reported inhibitors to VWF in 3 out of 48 patients on prophylaxis, the prevalence does not seem to increase in patients receiving long-term prophylaxis. The 3WINTER-IPS (type 3 von Willebrand International RegistrieS Inhibitor Prospective study) project, which included a large cohort of 260 type 3 VWD patients, also showed that the prevalence of alloantibodies was 6% in type 3 VWD patients [30].

In the Netherlands, we initiate prophylaxis for VWD patients suffering from severe and frequent bleeds. We inform patients about the benefits and potential side effects of treatment to reach a shared decision on treatment before starting prophylaxis [31]. Afterward, we teach patients self-infusion of the coagulation factor concentrate to enable home treatment. We start with 50 VWF:RCo U/kg i.v. twice a week and intensify to 3 times a week if bleeding still occurs. The efficacy and the experienced burden of regular infusions are evaluated with the patients at least twice per year. In our experience, most patients, particularly those with GI bleeding, are reluctant to discontinue treatment due to the observed benefits of prophylaxis, as previously reported [32].

In the WiN study, we included 834 patients with VWD who were known in one of the hemophilia treatment centers in the Netherlands. In 2023, the inclusion phase of a second nationwide study, the WiN-Pro study, was completed, and 670 patients, some of whom also participated in the WiN study, were included. WiN-Pro is a prospective study in which we collect patients' baseline characteristics at inclusion and data on bleeding symptoms, surgical interventions, side effects of treatment, and pregnancy during a 2-year follow-up period. Data from the WiN-Pro study revealed that currently, 10 patients are on prophylaxis (1.5%), of which 3 are children <12 years old. Most patients have type 3 VWD (60.0%), and the others have either type 2A or type 1C. The median ISTH-BAT (Bleeding Assessment Tool) bleeding score for these patients is 17 (range, 12-20).

Indications for prophylaxis are severe epistaxis, joint bleeding, and GI bleeding, and are comparable with previous studies. The majority of 2A patients (75%) on prophylaxis use this because of recurring GI bleeds. The indication for 2 children for prophylaxis was recurring and severe epistaxis. The third child started prophylaxis due to joint bleeding, but the dosage was increased because of HMB directly after the menarche. We were unable to retrieve a blood sample for 1 child, but historical levels were available, and genetic analysis revealed a homozygous stop gain variant to confirm the type 3 phenotype (Table 1).

5 | CURRENT GUIDELINE ON THE PROPHYLACTIC TREATMENT OF VWD PATIENTS

One of the reasons why prophylaxis has been underutilized in VWD patients may be the lack of reimbursement of VWF concentrates for long-term prophylaxis in many countries. Only a few high-quality studies, most with limited patient numbers, do not provide sufficient evidence for the reduced bleeding phenotype in VWD patients using prophylaxis. Therefore, in 2021, one of the prioritized questions for the management of VWD of the American Society of Hematology/International Society on Thrombosis and Haemostasis/National Hemophilia Foundation/World Federation of Hemophilia (ASH/ISTH/NHF/WFH) guideline was "In patients with VWD with a history of severe and frequent bleed, should routine prophylaxis with VWF concentrate or no routine prophylaxis (ie, treatment on-demand) be used?" [21].

This guideline was based on an extensive systematic review of the available literature but revealed a limited number of studies [33]. It included only 1 randomized controlled trial and 12 prepost studies, of which only 5 contained an explicit comparison between time periods for prophylaxis vs no prophylaxis.

Prophylaxis was defined as a period of at least 6 months of treatment consisting of VWF concentrate treatment infused at least once every week. In the randomized clinical trial (PRO.WILL study), 19 patients were included, of whom 12 completed the study. Patients randomized to the intervention arm were treated with VWF concentrate at a dose of 60 VWF:RCo U/kg every 2 to 3 days (Fanhdi, Grifols) and were compared with patients who were treated on-demand [34]. The main outcome was that 100% (n = 10) of on-demand patients vs 60% (n = 9) of the prophylaxis patients experienced bleeding during 1 year. Prophylaxis reduced the risk of bleeding (rate ratio, 0.24 [95% CI, 0.17-0.35]), increased the time to first bleeding (66.0 ± 33.7 days vs 34.6 ± 10.5 days), and reduced the number of spontaneous epistaxis significantly. No adverse events or thrombotic events were seen during prophylaxis.

In the 5 observational studies with explicit comparative data, prophylaxis significantly reduced the risk of bleeding (relative risk,

TABLE 1 Patient characteristics of Willebrand in the Netherland Prospective study participants on prophylaxis.

Patient no.	Sex	Age[a]	Type	ISTH-BAT BS[a]	VWF:Ag[a,b]	VWF:Act[a,b]	FVIII:C[a,b]	Hist VWF:Ag[c]	Hist VWF:Act[c]	Hist FVIII:C[c]	Indication
1	Female	26	3	24	0.16	0.09	0.41	<0.10	<0.10	0.02	Recurring bleeding in multiple domains
2	Male	73	2A	9	0.42	0.06	0.62	0.09	<0.10	0.30	Recurring GI bleeds
3	Female	62	2A	19	1.63	0.49	1.52	0.38	0.12	0.60	Recurring GI bleeds
4	Female	90	2A	20	1.3	0.19	1.01	0.59	0.28	0.58	Recurring GI bleeds
5	Female	11	3	9	0.07	0.08	0.01	<0.10	<0.10	0.01	Recurring joint bleeds
6	Male	5	1C	14	0.09	0.07	0.08	<0.05	0.07	0.05	Recurring nose bleeds
7	Male	23	3	27	0.58	0.15	0.59	0.06	0	0.37	Recurring bleeding in multiple domains
8	Female	9	3	11	N/A	N/A	N/A	<0.10	<0.05	0.02	Recurring nose bleeds
9	Female	29	3	19	0.07	<0.04	0.55	<0.10	<0.15	0.01	Recurring bleeding in multiple domains
10	Male	58	3	15	0.1	<0.04	0.3	0.06	0.06	0.52	Recurring bleeding in multiple domains

FVIII:C, factor VIII activity; GI, gastrointestinal; HistAg, historical VWF antigen; HistFVIII:C, historical FVIII activity; ISTH-BAT BS, International Society on Thrombosis and Haemostasis Bleeding Assessment Tool Bleeding Score; N/A, not applicable; VWF, von Willebrand factor; VWF:Act, von Willebrand factor activity; VWF:Ag, von Willebrand factor antigen.

[a]Measured at study inclusion.

[b]Levels were measured 5 days after the last prophylactic dose with VWF concentrate.

[c]Hist stands for historically lowest levels.

0.34; 95% CI, 0.25-0.46), hospitalization, and HMB. No adverse events or harms, including thrombosis, were reported in these studies.

In conclusion, the guideline panel acknowledged the reduction of risk of bleeding and the potential improvement of quality of life. Prophylaxis was associated with high costs, but cost-effectiveness studies of prophylaxis had not been reported. Based on low-certainty evidence, long-term prophylaxis reduces the risk of developing recurrent bleeding episodes, including epistaxis and possibly spontaneous bleeding and hemarthrosis. Therefore, the guideline's conditional recommendation suggests using long-term prophylaxis rather than no prophylaxis in patients with VWD with a history of severe and frequent bleeds. In the guideline, additional research needs were identified, as specified in Table 2.

TABLE 2 Research needs for long-term prophylaxis in von Willebrand disease, as identified by the American Society of Hematology/International Society on Thrombosis and Haemostasis/National Hemophilia Foundation/World Federation of Hemophilia consensus guideline panel [21].

Large, randomized trials comparing prophylaxis to on-demand treatment
Use of prophylaxis for HMB and GI bleeding
Impact of prophylaxis on HRQoL (especially given the burden of regular i.v. injections)
Studies on pdVWF vs rVWF concentrate for prophylaxis
Studies on the use of additional treatment, including antifibrinolytic treatment
Studies on antiangiogenic therapies specifically for recurrent GI bleeding

GI, gastrointestinal; HMB, heavy menstrual bleeding; HRQoL, health-related quality of life; i.v., intravenous; pdVWF, plasma-derived VWF; rVWF, recombinant VWF; VWF, von Willebrand factor.

6 | RECENT STUDIES ON PROPHYLAXIS IN VWD

After the guideline was published in 2021, several additional studies have been performed, partly addressing the research needs that were previously identified, although large randomized clinical trials are still missing.

In 2022, Rugeri et al. [35] reported prospective data on 23 VWD patients included in the (Observatoire des Patients présentant une Maladie de Willebrand et traités par Voncento (OPALE) study who were treated with prophylaxis using a pdFVIII/VWF concentrate Voncento (CSL Behring) with a FVIII:VWF ratio of 1:2.4. These patients, mainly type 3 (n = 16), of whom 12 were female, with a median age of 16 (range, 1-85), were followed for a median of 19 months (range, 5-48).

Most patients (n = 19) were already on prophylaxis at OPALE study inclusion, and 4 started prophylaxis during follow-up. The most frequent indication for prophylaxis was joint bleeding (43%), epistaxis or oral bleeding (39%), or muscle hematoma (22%). The dosage of prophylaxis was a median of 45 IU VWF/kg twice per week, with a median weekly dosage of 96 IU/kg. The median annualized bleeding

rate for all patients on prophylaxis was 0.5 (range, 0-7.2) and was comparable between type 2A, type 2B, and type 3 patients. No adverse events, including thrombosis, allergic reactions, or inhibitors to VWF, were observed. Despite a lack of comparison with the preprophylaxis bleeding event rate, the authors concluded that prophylaxis was effective in preventing recurrent bleeding in VWD patients [35].

In 2022, a phase 3 trial (NCT02973087) was performed to investigate the use of rVWF (VEYVONDI, Takeda Pharmaceutical Company Limited) as long-term prophylaxis to prevent bleeding [36]. rVWF was administered without additional FVIII. In this study, 23 VWD patients were included, of whom 17 completed the study. Most patients were type 3 patients (n = 18), and 48% were female, with a mean age of 40.6 (SD, 19.3) years. Thirteen patients were previously treated on-demand with pdVWF factor concentrate, and 10 were already on prophylaxis with a pdVWF concentrate. These groups were analyzed separately. Patients who were previously treated on-demand were given 50 IU rVWF/kg twice per week, and the patients who switched to rVWF were kept on the same regimen as the pdVWF they had received before entering this study.

Patients were treated for 12 months with rVWF, and data were compared with the 6-month period before starting prophylaxis. Compared with previous on-demand therapy, the bleeding rate (spontaneous annual bleeding rate, treated bleeds) decreased by 91.5% after initiation of rVWF prophylaxis from a mean spontaneous annual bleeding rate of 6.5 (95% CI, 2.5-17) to 0.3 (95% CI, 0.02-3.9). Eleven of the 13 patients (84.6%) had no bleeding episodes during prophylaxis. In the group that switched from pdVWF, the number of bleeds also decreased from a mean spontaneous annual bleeding rate of 0.51 (95% CI, 0.04-6.31) to 0.28 (95% CI, 0.02-3.85) after starting rVWF, but this was not statistically significant (55% reduction; 95% CI, 91.4%-252.3%). In this group, 70% of patients had no bleeding episodes during rVWF prophylaxis vs 60% during pdVWF prophylaxis.

A secondary analysis of the type 3 patients included in the rVWF study showed comparable outcomes with regard to reduction in bleeding episodes and additionally revealed data on VWF and FVIII trough levels during 12 months of treatment. Trough VWF:RCo, measured at 6 different time points, were low (<5 IU/dL). However, FVIII trough levels were remarkably high during prophylaxis with rVWF and increased from baseline at 2.5 IU/dL ± 0.9, measured during the first pharmacokinetic (PK) visit after washout, to 38.4 IU/dL ± 28.1 after 1 month of treatment [37]. Unfortunately, the indication for prophylaxis was mainly mucosal bleeding and only a limited number of patients were included with joint bleeds or recurrent GI bleeds as the prophylaxis indication. Therefore, additional data have to be obtained to confirm the rVWF benefit for these specific bleeding indications.

As mentioned, menorrhagia (ie, HMB) is the major clinical challenge in females with VWD and is associated with a reduced quality of life [38,39]. Especially in severely affected VWD patients, menorrhagia is difficult to treat. The 2021 ASH/ISTH/NHF/WFH VWD management guideline suggests either hormonal therapy or a levonorgestrel-releasing intrauterine system or TXA in addition to desmopressin to treat menorrhagia in these women. VWF concentrates may be necessary to treat or prevent HMB. Despite the fact that menorrhagia is a common indication for prophylaxis with VWF concentrates in previous observational studies, showing reduction of blood loss in many women, well-performed studies on the use of VWF concentrates as prophylaxis for HMB are lacking [29].

Recently, Ragni et al. [40] reported a phase 3, open-label, randomized crossover trial on rVWF concentrate vs TXA in patients with VWD with HMB in the USA. In this study, 39 women were randomly assigned to 40 IU/kg rVWF on day 1 of menstruation for 2 consecutive cycles (n = 18) or 5 days (days 1-5) of TXA 1300 mg 3 times daily for 2 cycles (n = 20), followed by a crossover for an additional 2 cycles. Menstrual blood loss was assessed using the pictorial blood assessment chart (PBAC). The median PBAC score in the rVWF group decreased from 597 (SD, 389) to 272 (SD, 223) across 2 cycles and from 483 (SD, 270) to 225 (SD, 207) in the TXA group. However, the scores did not normalize in either of the groups. Surprisingly, TXA resulted in significantly lower PBAC scores than prophylaxis with rVWF [35].

This study used a different treatment scheme and a lower dose of VWF concentrate than has been used in previously reported observational studies on prophylaxis for HMB [26,41]. The study was stopped prematurely because of COVID-19 restrictions and eventually included only women with moderate and mild VWD. The issue of optimal dosing of prophylaxis and prevention of HMB in VWD patients remains unsolved. Future studies are needed, given the remaining large burden of HMB for VWD patients [42].

The most recent study on long-term prophylaxis evaluated the use of Wilate (Octopharma), a VWF/FVIII concentrate with a ratio of 1:1, in children (≥6 years of age) and adults with severe VWD (WIL-31 study; Wilate-31) [43]. Bleeding episodes after initiation of prophylaxis were compared with an observational run-in study period (WIL-29) of 6 months prior to the start of prophylaxis. Patients experiencing at least 6 bleeds during the run-in period were eligible for inclusion in the prophylaxis study.

Of the 43 included patients, 33 patients were analyzed, and 30 completed the WIL-31 study. Twenty-two patients with type 3 were included. Patients received 20 to 40 IU VWF/kg of Wilate 2 to 3 times per week for 12 months. The median weekly administered dosage was 58 (range, 28-114) IU/kg. Bleeding was reduced by 84.4% after the initiation of prophylaxis. The mean spontaneous annual bleeding rate was 3.2 [43]. Most bleedings in the study were mucosal bleeds, including nose bleeds (51%), and only a minority were joint bleeds. HMB was evaluated in 4 females whose PBAC scores decreased by 43% during prophylaxis vs the on-demand period. The primary endpoint of the study was met: a >50% reduction in mean total annualized bleeding rate with Wilate prophylaxis vs prior on-demand treatment [43].

During the ISTH meeting in 2024, additional and more detailed data from the WIL-31 study were presented. A subanalysis of the WIL-31 study, including 22 type 3 VWD patients, showed similar outcomes as mentioned previously [43–45]. This study adds to the growing evidence that prophylaxis in VWD results in a reduction of bleeding. Remarkably, a relatively low dose of VWF concentrate was administered in this study compared with previous studies, which may reduce the costs of a preventive strategy without compromising its efficacy. However, this may

TABLE 3 Potential future developments for prophylactic treatment of von Willebrand disease.

Agent	Mode of administration	Working mechanism	Phase of development
Efanesoctocog alfa (BIVV-001)	i.v.	FVIII increase	Phase 1 trial in VWD type 2N and type 3 (NCT 04770935). No results reported yet
Emicizumab	s.c.	mAb with FVIII-like activity	Only registered for inherited hem A with or without inhibitor; case series off-label use
VGA039	s.c.	mAb targeting protein S	Phase 1 studies in healthy volunteers and in VWD patients
Rondaptivo pegol/BT200	s.c.	Pegylated aptamer targeting the A1 domain of VWF	Clinical studies in VWD type 2A and 2B patients
Nanobody KB-V13A12	s.c.	Cross-linking VWF with albumin	Mouse models [49]
Synthetic nanoparticles	i.v.	Binding to VWF collagen and platelets	Mouse models [50]
siRNA	s.c	Knockout mutated alleles	Preclinical studies in mice with VWD type 2B
Gene editing	n.a.	Restoring VWF production by CRISPR/CAS9 mediated gene editing	Canine models [51]
Gene editing	n.a.	Knockout of mutant allele	ECFC [52]

CRISPR, clustered regularly interspaced short palindromic repeats; FVIII, factor VIII; hem A, hemophilia A; i.v., intravenous; mAb, monoclonal antibody; n.a, not applicable; s.c., subcutaneous; siRNA, small interfering RNA; VWD, von Willebrand disease; VWF, von Willebrand factor.

also depend on the type of bleeding indication, as only a few patients with GI bleeding and joint bleeds were included.

7 | COST-EFFECTIVENESS OF PROPHYLAXIS IN VWD

Recently, a study on the cost-effectiveness of prophylaxis was reported comparing rVWF vs pdVWF in severe VWD in the United States [46]. The authors built a Markov cohort of adult severe VWD patients. Data were based on a recent study of prophylaxis, including severe VWD patients who were previously infused with pdVWF and were switched to rVWF [37]. The authors concluded that, at current pricing in the US, prophylaxis with rVWF was cost-saving for those patients currently averaging more than 2.7 weekly pdVWF infusions. This may be caused by the longer half-life (1.4-fold) of rVWF vs pdVWF [47,48].

A per-unit rVWF/pdVWF cost ratio of >1.51 is the critical threshold for a given pdVWF product to become favored over rVWF. However, this outcome is US health care specific and, given the global variation in VWF concentrate pricing, may be different for other countries. Unfortunately, the cost-effectiveness of prophylaxis was not compared with on-demand treatment strategies.

8 | FUTURE DEVELOPMENTS IN THE TREATMENT OF SEVERE VWD PATIENTS

In recent years, new options for long-term treatment of VWD have emerged. Some of them, such as gene therapy, are still in an early phase, while others are in a preclinical phase or have already been used off-label in patients with VWD (Table 3).

One of the developments presented during the ISTH congress was the To-WiN study, a prospective study on the use of PK modeling in the treatment of VWD. This study aims to improve treatment with desmopressin, or VWF concentrates, perioperatively and during prophylaxis. Dosing regimens are based on individual PK parameters using the population PK model by Bukkems et al. [53]. The prophylaxis part of the study is still ongoing [54].

BT200 (rondoraptivon pegol) is a pegylated aptamer that binds to the A1 domains of VWF. It was originally developed as an antihemostatic drug, interfering with VWF-platelet interaction by blocking the A1 domain, and it turned out to be of potential use for patients with VWD and (mild) hemophilia A [55]. In a recently published study in patients with type 2B VWD, a dose of 3 mg subcutaneously (s.c.) administered BT200 3 times per week, followed by 6 to 9 mg once per week for 28 days, resulted in a 2- to 3-fold increase of von Willebrand factor antigen (VWF:Ag) and FVIII, a 3-fold increase of the platelet count, and a normalization of the VWF multimer pattern [56].

Another mechanism of action of BT200 is to reduce macrophage-dependent VWF clearance, thereby increasing the half-life of VWF and FVIII [57]. This has been shown elegantly in 2 recent studies, including healthy volunteers and persons with hemophilia A [58,59]. In the latter study [59], it was shown that the VWF:RCo/VWF:Ag ratio decreases after BT-200 treatment, as is expected from blocking the A1 domain. Further studies are needed in patients with VWD type 2B or other types to investigate the clinical efficacy of the functional changes caused by BT200 treatment.

Recently, the first results were presented for VGA039, a s.c. administered, fully human immunoglobulin G4 monoclonal antibody

that binds protein S and attenuates its cofactor activity for tissue factor pathway inhibitor alpha and activated protein C. By modulating protein S cofactor activity for tissue factor pathway inhibitor alpha and activated protein C, VGA039 augments and restores thrombin generation during the initiation and propagation phase of coagulation [60]. *In vitro* studies showed increased thrombin generation in plasma samples from VWD patients, regardless of type. Studies in nonhuman primates showed that s.c. or i.v. administered VGA039 reduced mucosal bleed times and blood loss in an experimentally induced severe VWD model [60]. A randomized, double-blind, placebo-controlled, first-in-human, phase 1a trial in healthy volunteers revealed an increase in thrombin generation after i.v. and s.c. administration of various doses. Drug concentration profiles demonstrate suitability for weekly or less frequent s.c. prophylactic dosing for various bleeding disorders, including VWD patients [61].

Recently, several cases have been reported on the use of emicizumab in patients with VWD, of whom the first was reported by Weyand et al. [62]. They treated a 5-year-old boy with type 3 VWD and alloantibodies against VWF successfully with emicizumab over a period of 10 months. The rationale for treating patients with emicizumab is that the severity of the bleeding phenotype in type 3 patients is not only the result of VWF absence but also due to the concomitant very low FVIII levels. Since emicizumab generates a FVIII-like activity, this may attenuate bleeding in VWD patients, even in the absence of VWF.

Since this first report, at least 7 other cases of pediatric and adult VWD patients treated with emicizumab have been reported [63]. Most patients were treated according to the standard dosing scheme for severe hemophilia A, including the loading doses. The duration of treatment was reported to be between 6 and 12 months and showed a major reduction of bleeding events, although breakthrough bleeding did occur in most patients. Fatal bleeding in an elderly VWD patient was reported during emicizumab treatment but was attributed to hypertension [64]. Future clinical studies on the use of emicizumab in VWD patients, with and without VWF alloantibodies, are planned.

Up until now, studies on gene therapy for VWD have only been performed in a preclinical setting and so far have never reached clinical application [65]. Unfortunately, in the last decade, limited advances have been made. de Jong et al. [66] developed a small interfering RNA (siRNA) strategy in endothelial colony-forming cells (ECFCs). They aim to silence mutant heterozygous *VWF* alleles causing dominant type 1 or type 2 VWD, thereby restoring normal multimeric VWF. Efficient endothelial delivery of these siRNAs and the effectivity of allele-selective inhibition of *VWF* had been successfully shown in mice models [67]. Theoretically, administration of these siRNAs may restore VWF functional activity in VWD patients; however, this strategy has not yet been applied in clinical studies.

During the ISTH meeting in 2024, interesting presentations were given on VWD treatment strategies based on gene editing. One approach performed in ECFCs is to use clustered regularly interspaced short palindromic repeats (CRISPR)/Cas9 technology to reestablish the production of VWF in type 3 canine models [51]. Bär et al. [52] performed long-read sequencing to target single nucleotide polymorphisms on the same allele as a specific type 2A mutation (p.C1190R) in *VWF* and successfully restored the phenotype of patient ECFCs using CRISPR/Cas9. Gene-editing strategies may lead to interesting, possibly more permanent, or curative treatment options for VWD in the future.

Last year, Roullet et al. [50] published a study on a novel non-replacement strategy using synthetic platelet nanoparticles decorated with peptides that enable them to bind to collagen, VWF, and activated platelets. They used several murine models, with type 2B and type 3 VWD and human platelets, to show the efficacy of synthetic platelets in the improvement of thrombus formation. They showed that this strategy has the potential to significantly reduce blood loss and that strong clots were formed, similar to clots obtained from wild-type mice. Another promising nanobody, effectively cross-linking VWF to albumin, was presented at the ISTH meeting in 2023. These murine experiments showed functional hemostasis for up to 10 days after a single s.c. injection of the KBV13A12 particle [49]. These *in vivo* experiments demonstrate another potential approach for future VWD treatment.

9 | FUTURE STUDIES

Despite the addition of several novel studies on the use of long-term prophylaxis in VWD with VWF concentrates in the past few years, indicating that it reduces the number of bleeding episodes, there are still persisting issues. Uncertainties that remain include 1) which dose should be given to patients, 2) whether the dose intensity should be tailored to the type of bleeding in patients (mucosal vs joint vs GI bleeds), 3) whether PK dosing, based on VWF and FVIII levels, improve outcome and cost-effectiveness of prophylaxis, and 4) whether and to what extent long-term prophylaxis improves HRQoL. For innovative, nonfactor, long-term treatments, clinical studies in VWD patients are necessary to show the safety and benefit of these treatments.

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AUTHOR CONTRIBUTIONS

C.B.v.K. collected the Willebrand in the Netherlands Prospective data, performed statistical analyses, interpreted the data, and wrote and critically revised the manuscript. F.W.G.L. conceived and designed the study, interpreted data, and wrote and critically revised the manuscript. All authors gave their consent to the final version of the manuscript.

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F.W.G.L. received research support from CSL Behring and Shire/Takeda for performing the Willebrand in the Netherlands (WiN) study and is a consultant for uniQure, Takeda, CSL Behring, and BioMarin, of

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REFERENCES

[1] Sadler JE, Mannucci PM, Berntorp E, Bochkov N, Boulyjenkov V, Ginsburg D, et al. Impact, diagnosis and treatment of von Willebrand disease. *Thromb Haemost*. 2000;84:160–74.

[2] Leebeek FW, Eikenboom JC. Von Willebrand's disease. *N Engl J Med*. 2016;375:2067–80.

[3] de Wee EM, Sanders YV, Mauser-Bunschoten EP, van der Bom JG, Degenaar-Dujardin ME, Eikenboom J, et al. Determinants of bleeding phenotype in adult patients with moderate or severe von Willebrand disease. *Thromb Haemost*. 2012;108:683–92.

[4] de Wee EM, Fijnvandraat K, de Goede-Bolder A, Mauser-Bunschoten EP, Eikenboom JC, Brons PP, et al. Impact of von Willebrand disease on health-related quality of life in a pediatric population. *J Thromb Haemost*. 2011;9:502–9.

[5] de Wee EM, Mauser-Bunschoten EP, Van Der Bom JG, Degenaar-Dujardin ME, Eikenboom HC, Fijnvandraat K, et al. Health-related quality of life among adult patients with moderate and severe von Willebrand disease. *J Thromb Haemost*. 2010;8:1492–9.

[6] Sanders YV, Fijnvandraat K, Boender J, Mauser-Bunschoten EP, van der Bom JG, de Meris J, et al. Bleeding spectrum in children with moderate or severe von Willebrand disease: relevance of pediatric-specific bleeding. *Am J Hematol*. 2015;90:1142–8.

[7] Metjian AD, Wang C, Sood SL, Cuker A, Peterson SM, Soucie JM, et al. Bleeding symptoms and laboratory correlation in patients with severe von Willebrand disease. *Haemophilia*. 2009;15:918–25.

[8] van Galen KPM, Sanders YV, Vojinovic U, Eikenboom J, Cnossen MH, Schutgens REG, et al. Joint bleeds in von Willebrand disease patients have significant impact on quality of life and joint integrity: a cross-sectional study. *Haemophilia*. 2015;21:e185–92. https://doi.org/10.1111/hae.12670

[9] van Galen KPM, de Kleijn P, Foppen W, Eikenboom J, Meijer K, Schutgens REG, et al. Long-term impact of joint bleeds in von Willebrand disease: a nested case-control study. *Haematologica*. 2017;102:1486–93.

[10] McLaughlin JM, Munn JE, Anderson TL, Lambing A, Tortella B, Witkop ML. Predictors of quality of life among adolescents and young adults with a bleeding disorder. *Health Qual Life Outcomes*. 2017;15:67. https://doi.org/10.1186/s12955-017-0643-7

[11] Tsagianni A, Comer DM, Yabes JG, Ragni MV. Von Willebrand disease and gastrointestinal bleeding: a national inpatient sample study. *Thromb Res*. 2019;178:119–23.

[12] Makris M, Federici AB, Mannucci PM, Bolton-Maggs PHB, Yee TT, Abshire T, et al. The natural history of occult or angiodysplastic gastrointestinal bleeding in von Willebrand disease. *Haemophilia*. 2015;21:338–42.

[13] Starke RD, Ferraro F, Paschalaki KE, Dryden NH, McKinnon TA, Sutton RE, et al. Endothelial von Willebrand factor regulates angiogenesis. *Blood*. 2011;117:1071–80.

[14] Randi AM, Laffan MA. Von Willebrand factor and angiogenesis: basic and applied issues. *J Thromb Haemost*. 2017;15:13–20.

[15] Chornenki NLJ, Ocran E, James PD. Special considerations in GI bleeding in VWD patients. *Hematology Am Soc Hematol Educ Program*. 2022;2022:624–30.

[16] Govorov I, Ekelund L, Chaireti R, Elfvinge P, Holmström M, Bremme K, et al. Heavy menstrual bleeding and health-associated quality of life in women with von Willebrand's disease. *Exp Ther Med*. 2016;11:1923–9.

[17] Mannucci PM. Treatment of von Willebrand's disease. *N Engl J Med*. 2004;351:683–94.

[18] van Galen KP, Engelen ET, Mauser-Bunschoten EP, van Es RJ, Schutgens RE. Antifibrinolytic therapy for preventing oral bleeding in patients with haemophilia or von Willebrand disease undergoing minor oral surgery or dental extractions. *Cochrane Database Syst Rev*. 2019;12:CD011385. https://doi.org/10.1002/14651858.CD011385.pub2

[19] Brignardello-Petersen R, El Alayli A, Husainat N, Kalot MA, Shahid S, Aljabirii Y, et al. Gynecologic and obstetric management of women with von Willebrand disease: summary of 3 systematic reviews of the literature. *Blood Adv*. 2022;6:228–37.

[20] Bonnar J, Sheppard BL. Treatment of menorrhagia during menstruation: randomised controlled trial of ethamsylate, mefenamic acid, and tranexamic acid. *BMJ*. 1996;313:579–82.

[21] Connell NT, Flood VH, Brignardello-Petersen R, Abdul-Kadir R, Arapshian A, Couper S, et al. ASH ISTH NHF WFH 2021 guidelines on the management of von Willebrand disease. *Blood Adv*. 2021;5:301–25.

[22] Engelen ET, van Galen KP, Schutgens RE. Thalidomide for treatment of gastrointestinal bleedings due to angiodysplasia: a case report in acquired von Willebrand syndrome and review of the literature. *Haemophilia*. 2015;21:419–29.

[23] Sohal M, Laffan M. Von Willebrand disease and angiodysplasia responding to atorvastatin. *Br J Haematol*. 2008;142:308–9.

[24] Alikhan R, Keeling D. Von Willebrand disease, angiodysplasia and atorvastatin. *Br J Haematol*. 2010;149:159–60.

[25] Berntorp E. History of prophylaxis. *Haemophilia*. 2013;19:163–5.

[26] Berntorp E, Petrini P. Long-term prophylaxis in von Willebrand disease. *Blood Coagul Fibrinolysis*. 2005;16:S23–6.

[27] Berntorp E, Abshire T, vWD PN Steering Committee. The von Willebrand disease prophylaxis network (vWD PN): exploring a treatment concept. *Thromb Res*. 2006;118:S19–22.

[28] Abshire T, Cox-Gill J, Kempton CL, Leebeek FW, Carcao M, Kouides P, et al. Prophylaxis escalation in severe von Willebrand disease: a prospective study from the von Willebrand Disease Prophylaxis Network. *J Thromb Haemost*. 2015;13:1585–9.

[29] Holm E, Abshire TC, Bowen J, Álvarez MT, Bolton-Maggs P, Carcao M, 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*. 2015;26:383–8.

[30] Pagliari MT, Budde U, Baronciani L, Eshghi P, Ahmadinejad M, Badiee Z, et al. von Willebrand factor neutralizing and non-neutralizing alloantibodies in 213 subjects with type 3 von Willebrand disease enrolled in 3WINTERS-IPS. *J Thromb Haemost*. 2023;21:787–99.

[31] NVvH. Richtlijn Diagnostiek en behandeling van de ziekte van Von Willebrand: NVHB. 2024. https://publicatie.hematologienederland.nl/#138. [accessed October 9, 2024].

[32] Saccullo G, Makris M. Prophylaxis in von Willebrand disease: coming of age? *Semin Thromb Hemost*. 2016;42:498–506.

[33] El Alayli A, Brignardello Petersen R, Husainat NM, Kalot MA, Aljabiri Y, Turkmani H, et al. Outcomes of long-term von Willebrand factor prophylaxis use in von Willebrand disease: a systematic literature review. *Haemophilia*. 2022;28:373–87.

[34] Peyvandi F, Castaman G, Gresele P, De Cristofaro R, Schinco P, Bertomoro A, 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*. 2019;17:391–8.

[35] Rugeri L, Harroche A, Repessé Y, Desprez D, Petesch BP, Chamouni P, et al. Effectiveness of long-term prophylaxis using pdFVIII/VWF concentrate in patients with inherited von Willebrand disease. *Eur J Haematol*. 2022;109:109–17.

[36] Leebeek FWG, Peyvandi F, Escobar M, Tiede A, Castaman G, Wang M, et al. Recombinant von Willebrand factor prophylaxis in patients with severe von Willebrand disease: phase 3 study results. *Blood*. 2022;140:89–98.

[37] Leebeek FWG, Peyvandi F, Tiede A, Castaman G, Escobar M, Wang M, et al. Prophylaxis with recombinant von Willebrand factor

in patients with type 3 von Willebrand disease: results of a post hoc analysis from a phase 3 trial. *Eur J Haematol*. 2023;111:29–40.

[38] De Wee EM, Knol HM, Mauser-Bunschoten EP, van der Bom JG, Eikenboom JC, Fijnvandraat K, et al. Gynaecological and obstetric bleeding in moderate and severe von Willebrand disease. *Thromb Haemost*. 2011;106:885–92.

[39] Kadir RA, Sabin CA, Pollard D, Lee CA, Economides DL. Quality of life during menstruation in patients with inherited bleeding disorders. *Haemophilia*. 1998;4:836–41.

[40] Ragni MV, Rothenberger SD, Feldman R, Nance D, Leavitt AD, Malec L, et al. Recombinant von Willebrand factor and tranexamic acid for heavy menstrual bleeding in patients with mild and moderate von Willebrand disease in the USA (VWDMin): a phase 3, open-label, randomised, crossover trial. *Lancet Haematol*. 2023;10:e612–23. https://doi.org/10.1016/S2352-3026(23)00119-9

[41] Castaman G, Coppola A, Zanon E, Boeri E, Musso M, Siragusa S, et al. Efficacy and safety during formulation switch of a pasteurized VWF/FVIII concentrate: results from an Italian prospective observational study in patients with von Willebrand disease. *Haemophilia*. 2013;19:82–8.

[42] Leebeek FWG. Heavy menstrual blood loss in patients with von Willebrand disease: an unsolved problem. *Lancet Haematol*. 2023;10:e561–2. https://doi.org/10.1016/S2352-3026(23)00165-5

[43] Sidonio Jr RF, Boban A, Dubey L, Inati A, Kiss C, Boda Z, et al. von Willebrand factor/factor VIII concentrate (Wilate) prophylaxis in children and adults with von Willebrand disease. *Blood Adv*. 2024;8:1405–14.

[44] Sidonio Jr RF, Dubey L, Vilchevska KV, Inati A, Khayat CD. Efficacy and safety of prophylaxis with a plasma-derived von Willebrand factor/factor VIII concentrate in children and adolescents with von Willebrand disease - a sub-analysis of data from the Wil-31 study. *Blood*. 2023;142:3992. https://doi.org/10.1182/blood-2023-180513

[45] Sidonio RF. Bleeding sites in von Willebrand disease patients on prophylaxis with a plasma-derived von Willebrand factor/factor VIII concentrate – a sub-analysis of data from the WIL-31 study [abstract]. *Res Pract Thromb Haemost*. 2024.

[46] Waldron C, Ito S, Wang D, Allen C, Viswanathan G, Bona RD, et al. Cost-effectiveness of prophylaxis with recombinant vs plasma-derived VWF in severe von Willebrand disease in the United States. *Blood*. 2024;143:2332–5.

[47] Gill JC, Castaman G, Windyga J, Kouides P, Ragni M, Leebeek FW, et al. Hemostatic efficacy, safety, and pharmacokinetics of a recombinant von Willebrand factor in severe von Willebrand disease. *Blood*. 2015;126:2038–46.

[48] Bauer A, Friberg-Hietala S, Smania G, Wolfsegger M. Pharmacokinetic-pharmacodynamic comparison of recombinant and plasma-derived von Willebrand factor in patients with von Willebrand disease type 3. *J Blood Med*. 2023;14:399–411.

[49] Peyron I, Casari C, Cristophe O, Lenting P, Denis C. KB-V13A12, a novel nanobody-based therapeutic molecule for the treatment of von Willebrand disease [abstract]. *Res Pract Thromb Haemost*. 2023;7:100545.

[50] Roullet S, Luc N, Rayes J, Solarz J, Disharoon D, Ditto A, et al. Efficacy of platelet-inspired hemostatic nanoparticles on bleeding in von Willebrand disease murine models. *Blood*. 2023;141:2891–900.

[51] Barraclough A, Nichols T, Merricks E, Vanhoorelbeke K, De Meyer SF, Leebeek FWG, et al. Re-establishing von Willebrand factor production in endothelial cells derived from von Willebrand disease type 3 canine models through CRISPR-Cas9 mediated gene editing [abstract]. *Res Pract Thromb Haemost*. 2024.

[52] Bär I, Bürgisser P, van Moort I, van Kwawegen CB, Voorberg J, Eikenboom J, et al. Allele specific knock-out of mutant von Willebrand factor in heterozygous Von Willebrand disease type 2A patient-derived ECFCs [abstract]. *Res Pract Thromb Haemost*. 2024.

[53] Bukkems LH, Heijdra JM, de Jager NCB, Hazendonk HCAM, Fijnvandraat K, Meijer K, et al. Population pharmacokinetics of the von Willebrand factor-factor VIII interaction in patients with von Willebrand disease. *Blood Adv*. 2021;5:1513–22.

[54] Al Arashi W, Cloesmeijer M, Leebeek FWG, Nieuwenhuizen L, Heubel-Moenen FCJI, Meijer K, et al. Personalized treatment by pharmacokinetic-guided dosing in von Willebrand disease; a prospective multicenter study, OPTI-CLOT/To WiN study [abstract]. *Res Pract Thromb Haemost*. 2024.

[55] Zhu S, Gilbert JC, Hatala P, Harvey W, Liang Z, Gao S, et al. The development and characterization of a long acting anti-thrombotic von Willebrand factor (VWF) aptamer. *J Thromb Haemost*. 2020;18:1113–23.

[56] Ay C, Pabinger I, Kovacevic KD, Gelbenegger G, Schörgenhofer C, Quehenberger P, et al. The VWF binding aptamer rondoraptivon pegol increases platelet counts and VWF/FVIII in type 2B von Willebrand disease. *Blood Adv*. 2022;6:5467–76.

[57] Chion A, Byrne C, Atiq F, Doherty D, Aguila S, Fazavana J, et al. Aptamer BT200 blocks interaction of K1405-1408 in the VWF-A1 domain with macrophage LRP1. *Blood*. 2024;144:1445–56.

[58] Kovacevic KD, Grafeneder J, Schörgenhofer C, Gelbenegger G, Gager G, Firbas C, et al. The von Willebrand factor A-1 domain binding aptamer BT200 elevates plasma levels of von Willebrand factor and factor VIII: a first-in-human trial. *Haematologica*. 2022;107:2121–32.

[59] Ay C, Kovacevic KD, Kraemmer D, Schoergenhofer C, Gelbenegger G, Firbas C, et al. The von Willebrand factor-binding aptamer rondaptivon pegol as a treatment for severe and non-severe hemophilia A. *Blood*. 2023;141:1147–58.

[60] Huck I, Leong L, Byun T, Kim B, He A, Chan J, et al. Prophylactic efficacy of VGA039, an anti-protein s monoclonal antibody, in a novel non-human primate model of acquired von Willebrand disease [abstract]. *Res Pract Thromb Haemost*. 2023;7:101253.

[61] Schoergenhofer C, Moser MM, Firbas C, Leach TS, Tercero A, Covert K, et al. VGA039, a protein S-targeting monoclonal antibody, demonstrates in a Phase Ia healthy volunteer trial the potential of subcutaneous weekly or less frequent prophylactic dosing for bleeding disorders [abstract]. *Res Pract Thromb Haemost*. 2024.

[62] Weyand AC, Flood VH, Shavit JA, Pipe SW. Efficacy of emicizumab in a pediatric patient with type 3 von Willebrand disease and alloantibodies. *Blood Adv*. 2019;3:2748–50.

[63] Giuffrida AC, Siboni SM, Baronciani L, Poli G, Gandini G, Peyvandi F. Emicizumab in type 3 von Willebrand disease: report of a case with an alloantibody and literature review. *Semin Thromb Hemost*. 2024; in press. https://doi.org/10.1055/s-0044-1787662

[64] LeMaistre FI, Chiang E, Streiff MB, Yui JC. Efficacy of emicizumab therapy in two adult patients with type 3 von Willebrand disease. *Blood Coagul Fibrinolysis*. 2024;35:206–8.

[65] Portier I, Vanhoorelbeke K, Verhenne S, Pareyn I, Vandeputte N, Deckmyn H, et al. High and long-term von Willebrand factor expression after Sleeping Beauty transposon-mediated gene therapy in a mouse model of severe von Willebrand disease. *J Thromb Haemost*. 2018;16:592–604.

[66] de Jong A, Dirven RJ, Oud JA, Tio D, van Vlijmen BJM, Eikenboom J. Correction of a dominant-negative von Willebrand factor multimerization defect by small interfering RNA-mediated allele-specific inhibition of mutant von Willebrand factor. *J Thromb Haemost*. 2018;16:1357–68.

[67] Jongejan YK, Schrader Echeverri E, Dirven RJ, Paunovska K, Linthorst NA, de Jong A, et al. Small interfering RNA-mediated allele-selective silencing of von Willebrand factor *in vitro* and *in vivo*. *Blood Adv*. 2023;7:6108–19.