

Perioperative management for patients with von Willebrand disease: Defining the optimal approach

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Funding information

CSL Behring

Abstract

von Willebrand disease (VWD) is the most common inherited bleeding disorder characterised by a quantitative or qualitative deficiency in von Willebrand factor (VWF). During invasive surgical procedures, patients with VWD require additional treatment to maintain haemostasis; however, due to the complexity of VWD, there is a lack of consensus on the optimal management. In the perioperative period, patients are usually treated with VWF and factor FVIII (FVIII)-containing concentrates to provide an immediate haemostatic response to prevent excessive bleeding during both elective and emergency surgery. With the introduction of recombinant VWF (rVWF), there is a need for guidance on the use of the various VWF products in the perioperative period for all types of patients and surgeries. This review provides an overview of the current evidence for the surgical management of patients with VWD and, summarises the optimal treatment approach during the perioperative period, and highlights key unanswered questions and the research needed to address the evidence gaps.

KEYWORDS

haemostasis, perioperative period, surgical procedures, operative, von Willebrand diseases, von Willebrand factor

1 | INTRODUCTION

von Willebrand disease (VWD) is the most common genetic bleeding disorder, in which patients have low levels of functional von Willebrand factor (VWF), a large multimeric protein involved in platelet-to-sub-endothelium interactions and platelet-to-platelet cohesion during thrombus formation that also acts as a carrier for factor VIII (FVIII).¹ A deficiency in functional VWF, therefore, has a dual effect on haemostasis resulting in impaired coagulation.

VWF is synthesised as a polypeptide chain, and after post-translational modifications, the protein forms multimers before being released into plasma; multimers can be various sizes with high-molecular-weight multimers (HMWM) having the greatest activity

during haemostasis.² VWF can also be stored as HMWM in platelet α -granules until platelet activation and its subsequent release when required during haemostasis.² VWD is a heterogeneous disorder caused by a quantitative (types 1 and 3) or qualitative (type 2) deficiency of VWF (Figure 1).^{3,4} While type 3 VWD is associated with an absence of VWF in plasma, type 1 and type 2 VWD are associated with partial quantitative reduction in VWF protein and the presence of non-functional or abnormal VWF protein.³ Bleeding tendency is mainly driven by decreased functional VWF, and while some patients have no change in their plasma levels of VWF, rapid clearance (type 1 VWD) or structural and functional defects (type 2 VWD) result in reduced physical activity of VWF. Type 2 variants can be subclassified into 2A (lack of high- and

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intermediate-molecular-weight multimers and decreased binding to platelets), 2B (lack of HMWM and increased affinity for platelets), 2M (normal multimer distribution, partial reduced affinity for platelets) and 2N (normal multimer distribution and reduced affinity for FVIII).³ In haemostasis, VWF serves as a carrier protein for FVIII and acts to stabilise FVIII to protect it from rapid clearance, thus increasing its plasma half-life. In a patient with low levels of VWF, normal functioning FVIII could be cleared more rapidly, impairing the haemostatic response. It has also been suggested that there is a grading of VWF:FVIII binding capacity according to multimer size, with a gradual decrease in binding demonstrated with lower molecular-weight multimers.² The diagnostic approach to VWD requires measuring the amount of VWF in plasma and uses an assay to assess the function and levels of FVIII (normal range 50-150 IU/dL) to help determine whether the level and activity of VWF are reduced.^{4,5} This is particularly important for patients with mild/no symptoms and highlights the need to measure both VWF and FVIII in patients with VWD in the perioperative setting to maintain sufficient levels to achieve haemostasis, while minimising the risk of thrombosis as a result of high FVIII levels.^{4,5}

Although the severity of bleeding drives treatment decisions, the variability in clinical manifestations means treatment is not well defined and definitive diagnosis remains controversial within the different types of disease.⁶ In general, treatment strategies vary by type and severity of disease; in the majority of patients with mild/moderate disease, on-demand treatment with desmopressin is an

effective option for raising endogenous VWF levels. As such, desmopressin and/or tranexamic acid are often used for minor surgical procedures, including dental work.^{5,7}

In some patients, the response to desmopressin decreases after repeated doses (tachyphylaxis) with reduced efficacy observed after 3-4 days of treatment, which limits its use in settings where continuous treatment over several days is required, that is, during the perioperative period of major surgery.⁸ In addition, desmopressin is contraindicated in patients with type 2B VWD as it can lead to exacerbation of thrombocytopenia due to increased platelet binding, a distinctive feature of type 2B disease; however, it is used by some patients to treat minor bleeding episodes.⁹ Furthermore, patients with type 3 VWD are generally considered to be unresponsive to desmopressin and treatment is not recommended due to lack of endogenous VWF synthesis. Other contraindications for desmopressin use in VWD patients include cardiovascular disease, hypertension and the use of diuretics.¹⁰ Desmopressin should also be used with caution in patients <4 or >70 years and during pregnancy, as well as for patients with type 1C VWD in the setting of surgery.¹¹ Furthermore, all therapies are associated with their own benefits and possible side effects, and one of the major concerns of using desmopressin during surgery is severe water intoxication and concomitant hyponatremia.^{12,13} Although hyponatremia and volume overload are rare, there is an increased susceptibility in children and repeated doses of desmopressin may be fatal.¹²⁻¹⁴ In patients who are unresponsive or have

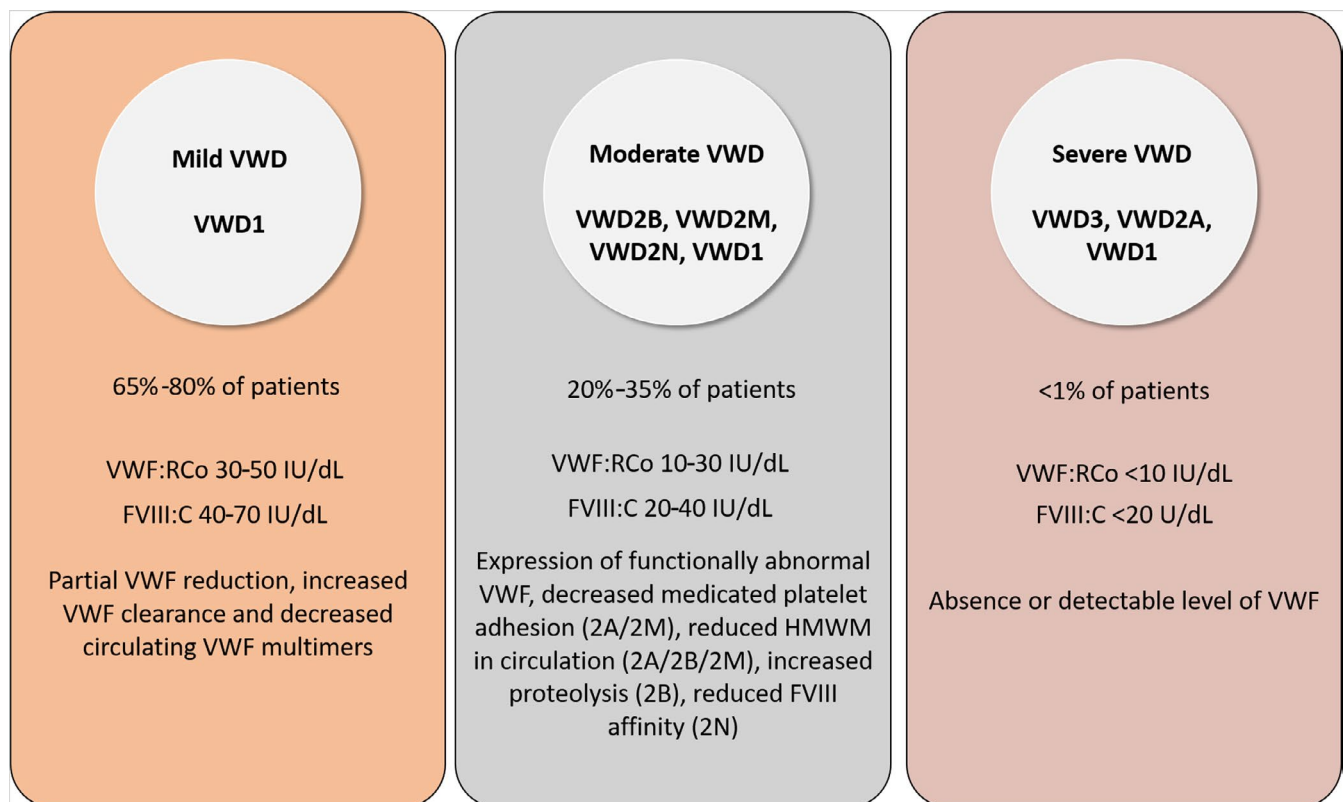


FIGURE 1 Types of VWD severity according to VWF and FVIII activities.⁴ FVIII:C, factor VIII procoagulant activity; HMWM, high-molecular-weight multimers; RCo, ristocetin cofactor; VWD, von Willebrand disease; VWF, von Willebrand factor. Patients with VWD1 and VWD2N may have VWF:RCo levels in the normal range

TABLE 1 Evidence-based recommendations for patients with VWD requiring replacement therapy

Setting	Replacement therapy recommendation ^a		Infusion frequency	Maintaining target VWF:RCo and VWF:FVIII levels
	Desmopressin responsive ^b	Desmopressin unresponsive		
<i>All concentrates containing VWF must be avoided in patients with VWD with alloantibodies because of the risk of anaphylactic reactions; recombinant FVIII can be used instead to restore haemostasis.^{5,4}</i>				
Plasma-derived products				
Minor surgery ^c	Desmopressin 0.3 µg/kg body weight	Loading dose: VWF 40 IU/kg (30–60 IU/kg) Maintenance dose: ^d VWF 30 IU/kg (20–40 IU/kg)	Daily or every other day doses; 12–48 h (for 1–5 d)	VWF:RCo levels and FVIII:C should be assessed at least once during the surgical procedure then daily Postoperative FVIII:C level >50 IU/dL until healing is complete (usually 2–5 d)
Major surgery ^c	Loading dose: VWF 50 IU/kg (40–60 IU/kg) Maintenance dose: ^d VWF 30 IU/kg (20–50 IU/kg) – Usual thrombo-prophylactic treatment with LMWH should be implemented in patients at high risk of venous thrombosis		Every 8–24 h (for 7–14 d)	Preoperative FVIII:C and VWF:RCo levels of 80–100 IU/dL Post-operative VWF:RCo and FVIII levels >50 IU/dL for at least 36 h – Measure plasma levels of FVIII:C and VWF:RCo every 12 h on the day of surgery, then every 24 h FVIII:C level >50 IU/dL for 12 h
Dental extractions or invasive procedures	Desmopressin 0.3 µg/kg body weight pre-procedure, and oral tranexamic acid in 3 doses of 15–25 mg/kg/d are advised	Loading dose: VWF 30 IU/kg (20–40 IU/kg) Maintenance dose: ^d VWF 40–60 IU/kg	Single dose	
Delivery and puerperium	50 IU/kg VWF, and oral tranexamic acid in 3 doses of 15–25 mg/kg/d are advised	Loading dose: VWF 50 IU/kg Maintenance dose: VWF 40 IU/kg	Daily doses; every 24 h (for 3–4 d)	FVIII:C level >50 IU/dL for 3–4 d
FVIII-poor plasma-derived VWF products				
Surgery ^{22,55}		Loading doses: VWF 50–60 IU/kg 12–24 h before surgery if FVIII levels <60 IU/dL, and VWF 50–60 IU/kg 1 h before surgery (in unscheduled procedures a single loading dose 1 h before surgery together with a dose of FVIII to obtain FVIII levels >60 IU/dL) Maintenance dose: 50–60 IU/kg	2 to 3 times a day, then daily or every other day	VWF:RCo and FVIII levels >50 IU/dL (assessed daily) until healing
A recombinant product ^e				
Major surgery ^c	Loading dose: rVWF 40–60 IU/kg		Infusion 12–24 h before surgery with an additional VWF and/or FVIII dose 1–2 h before surgery if needed	– Preoperative FVIII:C level ≥60 IU/dL, assessed within 3 h of surgery initiation – Postoperative FVIII:C level >50 IU/dL for up to 72 h – Postoperative VWF:RCo level >50 IU/dL for up to 72 h, then >30 IU/dL after 72 h

(Continues)

TABLE 1 (Continued)

Setting	Replacement therapy recommendation ^a		Infusion frequency	Maintaining target VWF:RCo and VWF:FVIII levels
	Desmopressin responsive ^b	Desmopressin unresponsive		
Minor surgery ^c	Loading dose: rVWF 40-60 IU/kg		Infusion 12-24 h before surgery with an additional VWF and/or FVIII dose 1-2 h before surgery if needed	<ul style="list-style-type: none"> - Preoperative FVIII:C level ≥ 30 IU/dL, assessed within 3 h of surgery initiation - Postoperative FVIII:C level >30 IU/dL for up to 72 h - Postoperative VWF:RCo level ≥ 30 IU/dL for up to 72 h
Dental extractions or invasive procedures	Loading dose: rVWF 40-60 IU/kg		Infusion 12-24 h before surgery, then 1-2 h before surgery if needed	<ul style="list-style-type: none"> - Postoperative FVIII:C level >30 IU/dL for up to 72 h - Postoperative VWF:RCo level ≥ 30 IU/dL for up to 72 h

Abbreviations: FVIII:C, factor VIII procoagulant activity; LMWH, low-molecular-weight heparin; NHLBI, National Heart, Lung and Blood Institute; RCo, ristocetin cofactor; rVWF, recombinant von Willebrand factor; UKHCDO, United Kingdom Haemophilia Centre Doctors' Organisation; VWF, von Willebrand factor.

^aRecommendations based on pooled data for an adult patient undergoing elective surgery, doses quoted as average (range); doses may be 20% higher in paediatric patients.

^bIn patients treated with desmopressin (DDAVP), a test infusion is recommended, especially in patients with VWF <30 IU/dL, measuring FVIII:C, VWF:Ag and VWF:RCo levels at 1 hour (peak) and at least 4 hours (clearance). If DDAVP is used repeatedly, measure the FVIII:C and VWF:RCo responses to monitor the development of tachyphylaxis. DDAVP should be used cautiously in children <2 years, due to the risk of hyponatremia (limit fluid intake); in elderly patients with atherosclerosis (risk of ischaemic complications); limit fluid intake (<1 L) in adults for 24 hours after DDAVP and at least 4 hours (clearance).

^cExamples of major surgeries may include craniotomy, cardiovascular, cardiothoracic, caesarean delivery, hysterectomy, open cholecystectomy; minor surgeries may include biopsies, complicated dental extractions, gingival procedures, central line placement and/or laparoscopic procedures.

^dMaintenance doses on postoperative days 1-3 given based on VWF:RCo levels; for minor surgery, if >100 no dose required, if 71-100 reduce dose by half, if 30-70 continue dose, if <30 increase dose by half; for major surgery >150 no dose required, if 101-150 reduce dose by half, if 61-100 continue dose, if 35-60 increase dose by half, if <35 double dose.³⁶

^ePossible indications for rVWF concentrates include major elective surgery, particularly when repeated infusions are foreseen in patients at high risk for thrombosis (old age, cancer surgery, orthopaedic surgery). If target FVIII:C levels are not achieved, rVWF was co-administered with rFVIII 1-2 hours before surgery to achieve peak level.



contraindications to desmopressin, VWF-containing concentrates are the choice of therapy and are effective in the perioperative setting.¹⁵

Treatment of surgical bleeding is challenging; there is no clear consensus on the dosage, frequency and duration of therapy, or the target levels of VWF and FVIII that should be achieved.^{5,7} The aim of this narrative review, therefore, is to provide guidance to clinicians on the use of FVIII and VWF concentrates in patients with VWD undergoing surgery based on the current available evidence. This includes the clinical implications of VWF concentrates devoid of FVIII compared with those products in which both VWF and FVIII are present.

2 | SURGICAL MANAGEMENT OF PATIENTS WITH VWD

Optimal surgical management in patients with VWD is dependent on multiple factors including the type of surgery, type of VWD, baseline VWF and FVIII levels, and the individual patient's history of bleeding. Bleeding assessment tools have been developed as a quantitative measurement to rate bleeding symptoms, disease severity and family history of bleeding, whereby the preoperative "bleeding score" can be used to predict postoperative bleeding outcomes.^{16,17} Preoperative scores range from -1 (absence of bleeding after significant haemostatic challenge such as two dental extractions or surgeries) to 4 (symptoms requiring the most significant medical intervention such as infusion of clotting factor concentrates or surgery to control bleeding); this approach can help reduce bleed complications by promoting timely interventions.^{16,17} Currently, consensus on the preferred surgical management for all patients is lacking and many of the recommendations regarding the use of replacement therapy are based primarily on expert opinion.¹⁵

The current published recommendations for target levels of both VWF and FVIII vary depending on the type of invasive procedure (Table 1); all guidelines recommend that surgeries are carried out in experienced centres with access to sufficient laboratory testing to monitor haemostasis. In the US guidelines, the therapeutic goal is to maintain trough FVIII levels >50 IU/dL for 7-14 days in patients undergoing major surgery and 3-5 days for those undergoing minor surgery.⁵ As such, VWF loading doses of 40-60 IU/kg for major surgery and 30-60 IU/kg for minor surgery are recommended, with additional maintenance doses of 20-40 IU/kg given after 8-24 or 12-48 hours (to maintain VWF ristocetin cofactor activity [VWF:RCo] and FVIII levels >50 IU/dL), respectively.⁵ The timing of loading dose administration is dependent on the product used, and maintenance doses are based on laboratory determination of VWF:RCo and FVIII levels following concentrate infusion, which should be regularly monitored as the duration of VWF elevation is highly variable in the surgical setting. In contrast, UK guidelines do not provide recommendations on doses of VWF and FVIII but recommend that during major surgical procedures, FVIII levels are maintained ≥ 100 IU/dL throughout the postoperative period, and both FVIII and VWF:RCo should be sustained above 50 IU/dL for 6-10 days post-surgery.⁷

A key issue is determining the optimal dosing of replacement therapy to ensure haemostatically adequate levels of VWF are achieved during surgical procedures. The most frequent recommendation is to monitor both the procoagulant activity of FVIII (FVIII:C) and VWF:RCo, with the aim of achieving similar peak and trough levels both intraoperatively and during the first few days postoperatively, without exceeding the desirable level.^{5,7} The US guidelines recommend that VWF:RCo and FVIII peak and trough levels are monitored daily around major surgical procedures and at least once following minor procedures.⁵ The UK guidelines are similar, recommending that FVIII levels are monitored regularly in all major surgery, and the majority of minor surgical procedures, while VWF:RCo should be monitored in major surgical procedures, particularly in the perioperative period.⁷

The US and UK guidelines differ in their recommendations for patients undergoing minor surgical procedures as the UK guidelines recommend management with desmopressin in the absence of laboratory testing, unless desmopressin is used more than three times within 72 hours, whereas the US guidelines recommend treatment with VWF concentrates, hence the need for rapid determination of VWF:RCo in addition to FVIII in these patients.^{5,7} The differences in guideline recommendations may in part be due to the time of publication; newer laboratory techniques and the distribution of high-quality testing facilities can improve precision and increase our understanding of the disease. In addition, management strategies vary by country, and recommendations may be influenced by the experience of the physicians contributing to the guidelines.

In clinical practice, monitoring of FVIII:C is preferred as it is thought to be the best predictor of bleeding, is commonly available and, in particular, is less time consuming and cheaper than alternative assays.⁶ In addition, low FVIII levels are associated with deep muscle haematomas and haemarthrosis, particularly in patients with type 3 VWD, highlighting the importance of monitoring FVIII levels during the surgical period. In contrast, low VWF levels correlate more with mucosal-based bleeding and assessing VWF may be a better predictor of perioperative bleeding in surgery such as tonsillectomy and in dental procedures.¹⁸ Current guidelines recommend that both VWF:RCo and FVIII:C levels are assessed daily for up to 7-14 days after major surgery, to avoid adverse events (AEs) such as thrombosis.^{5,7} This could be crucial when evaluating the bleeding rate in patients with low VWF levels but normal FVIII levels.

Commercially available plasma-derived concentrates differ in their VWF and FVIII content and hence their ability to achieve desired circulating levels of these factors in situations requiring repeated infusions.¹⁹ A review of available replacement therapies in Europe found that VWF/FVIII concentrates have VWF:RCo/FVIII:C levels ranging from 0.9 to 50.0 and VWF:RCo/Ag ratios ranging from 0.29 to 0.95 (Table 2).¹⁹ This suggests that similar doses provide substantially different increases in FVIII levels, which is crucial when considering treatment as plasma FVIII levels progressively increase over the course of VWF/FVIII concentrate administration.²⁰ VWF stabilises not only the exogenously administered FVIII but also the endogenous FVIII pool, which is synthesised at a normal rate

**TABLE 2** Safety and efficacy of replacement products in patients with VWD undergoing surgery

Product	VWF:RCo/ FVIII (ratio)	VWF:RCo/ Ag (ratio)	Study design and end points	Patients/surgical procedures
Plasma-derived products				
Antihemophilic factor/von Willebrand factor complex (Alphanate [®] ; Grifols) Mannucci et al ³⁸	0.91 ± 0.2	0.47 ± 0.1	Prospective study – Assess the efficacy of VWF/FVIII concentrate for bleeding episodes and prophylaxis during elective and invasive surgery in desmopressin contraindicated patients	39/71 VWD 1:6 VWD 2:19 VWD 3:14
Antihemophilic factor/von Willebrand factor complex (Haemate [®] P/Humate-P [®] ; CSL Behring) Hazendonk et al ³⁵ Gill et al ³⁶	2.45 ± 0.3	0.84	Retrospective study – Evaluate current perioperative management in relation to targets in national guidelines Prospective phase IV study – Evaluate the safety and efficacy of VWF/FVIII concentrate for the prevention of excessive bleeding in surgery	103/104 VWD 1:54 VWD 2:43 VWD 3:6 35/35 VWD 1:12 VWD 2:10 VWD 3:13
Thompson et al ³⁷			Prospective study – Evaluate the efficacy and safety of VWF/FVIII concentrate for the treatment of emergency, non-elective surgery	39/42 VWD 1:16 VWD 2:9 VWD 3:6 Unknown: 6
Human coagulation factor VIII/human von Willebrand factor (Immunate [®] ; Baxter AG) Auerswald et al. ⁵⁶	1.1	0.47	Prospective phase III study – Evaluate the clinical efficacy of VWF/FVIII concentrate for acute bleeds and surgical prophylaxis	14/14
von Willebrand factor/coagulation factor VIII complex (Wilate [®] ; Octapharma) Srivastava et al ³⁹	0.9	N/A	Prospective phase III study – Evaluate the haemostatic efficacy and safety of VWF/FVIII concentrate in maintaining intra- and postoperative haemostasis in surgery	30/30 VWD 1:7 VWD 2:2 VWD 3:21
Windyga et al. ⁵⁷			Prospective phase III study – Evaluate the haemostatic efficacy and safety of VWF/FVIII concentrate in maintaining intra- and postoperative haemostasis in surgery	32/57 VWD 1:4 VWD 2:9 VWD 3:19
Antihemophilic factor/von Willebrand factor complex (Wilfactin [®] ; LFB Biomedicament) Borel-Derlon et al ²²	50	0.95	Prospective, multicentre study – Assess the efficacy and safety of VWF/FVIII concentrate in the prevention of bleeding in scheduled/unscheduled surgical/invasive procedures	45/108
Antihemophilic factor/von Willebrand factor complex (Voncento [®] /Biostat [®] ; CSL Behring) Dunkley et al. ⁵⁸	2.4	0.87-0.95	Phase II/III study – Evaluate the efficacy and safety of VWF/FVIII concentrate for non-surgical bleeds and surgical procedures	23/29 VWD 1:7 VWD 2:9 VWD 3:7
Concentrates with limited/no published data in perioperative settings				
Antihemophilic factor/von Willebrand factor complex (Factor 8 Y, Bio Products Laboratory Limited)	0.81	0.29	N/A	N/A



Major/minor surgery	Loading dose, IU/ kg, median (range)	Efficacy	Safety
13 major (4 abdominal, 9 orthopaedic) 58 minor (22 dental, 10 gastric, 2 ENT)	60 (20-76)	Overall good clinical response; 2 patients showed reduced recovery suggestive of alloantibody formation Actual vs expected blood loss was lower in 68/71 procedures (-31.7 mL)	2 VTE; 1 mild 1 severe
110 major 38 minor	VWD 1:36 (27-49) VWD 2:43 (37-52)	Clinically relevant bleeding occurred in 5 (3.4%) surgical procedures; 4 required transfusion	No thrombotic events
25 major (10 tissue/organ excisions, 6 multiple tooth extractions, 3 plastic surgeries, 2 orthopaedic surgeries and 4 other) 10 minor (3 dental, 3 hernia repair, 3 port insertion, 1 gynaecological)	Major: 61.2 (17.4-113.9) Minor: 49.9 (23.7-135.3)	Effective haemostasis in 32/35 (91.4%) immediately after surgery; 3 patients (8.6%) with multiple tooth extractions rated moderate/poor 3 patients developed major haemorrhage in the postoperative period. Actual vs expected blood loss was lower in major (65 vs 81 mL) and minor (9 vs 18 mL) surgeries	107 AEs reported in 30 patients in the surgical phase; 7 SAEs reported but not related to treatment. No deaths or thrombotic events occurred
25 major 17 minor	82.3 (32.5-216.8)	Excellent/good haemostasis (100%)	55 AEs in 24/42 (57.1%) procedures; 3 considered treatment related; 4 SAEs in 3 procedures, none considered related to treatment No thrombotic events
Procedures not reported	30-80	Excellent/good haemostasis (100%)	No SAE. Bleeding complications occurred in 3 patients
21 major (8 orthopaedic, 5 gynaecological, 4 gastrointestinal, 2 dental, 2 ENT) 9 minor (5 dental, 2 orthopaedic, 1 ophthalmology, 1 ENT)	57.3 (27-169)	Excellent haemostasis (95.2% major, 100% minor) Actual vs expected blood loss was lower in 28/30 procedures (-294.9 mL). No thrombotic events or inhibitors to FVIII/VWF	8 AEs in 5 patients considered probably related to treatment (hypersensitivity, chest discomfort, decreased blood pressure, feeling hot/dizzy)
27 major procedures in 21 patients (10 abdominal, 7 orthopaedic, 3 gynaecological, 4 dental, 2 plastic, 1 cardiovascular) 30 minor procedures in 16 patients	49 (7-79)	Excellent/good haemostasis (51/53; 96%)	2 AEs in 1 patient No SAE
45 (14 orthopaedic, 10 gynaecological, 7 general, 14 dental)	40 (14-74)	Excellent/good haemostasis (100%)	No SAE
10 major 19 minor	Major: 40-60 Minor: 40-50	Excellent haemostasis (100% major, 93.3% minor) Actual blood loss was considered less or equal to the predicted blood loss in 85% of surgeries. Blood transfusion was required in 2 major surgeries	3 patients reported an AE possibly related to treatment No deaths or thrombotic events occurred
N/A	N/A	N/A	N/A

(Continues)



TABLE 1 (Continued)

Product	VWF:RCo/ FVIII (ratio)	VWF:RCo/ Ag (ratio)	Study design and end points	Patients/surgical procedures
Antihemophilic factor/von Willebrand factor complex (Fandhi [®] ; Grifols)	1.04 ± 0.1	0.47 ± 0.1	N/A	N/A
Antihemophilic factor (Koate [®] -DVI; Kedrion Biopharma)	1.1	0.48	N/A	N/A
Recombinant products				
von Willebrand factor (Recombinant) (Vonvendi [®] ; Takeda) Peyvandi et al ²³	>10	>1	Prospective, Phase III non-randomised study – Evaluate the efficacy and safety of rVWF with/without rFVIII for patients undergoing elective surgery	15/15 VWD 1:3 VWD 2:4 VWD 3:8

Abbreviations: AE, adverse event; Ag, antigen; ENT, ear nose and throat surgery; FVIII, factor VIII; FVIII:C, factor VIII procoagulant activity; N/A, not available; RCo, ristocetin cofactor; rVWF, recombinant VWF; SAE, serious adverse event; VTE, venous thromboembolism; VWD, von Willebrand disease; VWF, von Willebrand factor.

^aOverall dose 12-24 hours before surge.

in patients with VWD.²¹ Specific VWF concentrates with low FVIII levels have been developed, and studies have found that these concentrates can be used safely and effectively for perioperative management (as described in Table 1) as well as to treat acute bleeds and spontaneous bleeds in patients with severe VWD.^{21,22} It is, therefore, hypothesised that low FVIII concentrates may be beneficial at reducing the complications of excessive high FVIII levels observed when repeated doses of concentrate are required over a short interval, such as during emergency surgery.

In addition, a rVWF product with no FVIII has been developed and treatment is thought to instantly normalise VWF levels without an immediate rise in FVIII levels; the increase in FVIII occurs at a slower rate as VWF binds endogenous FVIII.²³ However, in the case of excessive bleeding or emergency/unscheduled surgery, patients require VWF and FVIII levels to be instantly raised meaning loading doses are not feasible. This has led to concerns regarding the use of VWF concentrates devoid of FVIII,²⁴ and before patients undergo an unscheduled procedure, co-administration (preoperative loading dose 40-60 IU/kg) with a priming dose of FVIII may be required to attain a FVIII peak of at least 60 IU/dL.^{21,22} A summary of rVWF concentrate dosing frequency and the laboratory monitoring that may be required in these circumstances is outlined in Table 1. It is important to note there are no recommendations for the dose or duration of additional FVIII, during and/or following a surgical procedure, and co-administration may be influenced by the accessibility of FVIII:C assessment tools during surgery, as well as the length and intensity of the surgical procedure.^{25,26}

3 | THE RISK OF THROMBOEMBOLIC COMPLICATIONS

A further challenge to treatment with replacement therapy is to maintain VWF levels high enough to offer protection against haemorrhage, while minimising long-term exposure to very high VWF

and FVIII levels, which have been reported to be associated with an increased risk of arterial and venous thrombosis, respectively.^{27,28} Although the threshold levels of FVIII above which significant risk exists for thromboembolic events have not been clearly defined, long-term exposure to FVIII is known to increase the risk of thrombosis.²⁹ Current US guidelines recommend that to decrease the risk of thrombosis, levels should not exceed 200 IU/dL for VWF:RCo and 250 IU/dL for FVIII.⁵ All patients receiving VWF concentrates should be assessed for thrombotic risk factors and appropriate preventive strategies should be implemented to avoid maximal levels of VWF:RCo and FVIII being exceeded.⁵

While the theoretical risk of thromboembolic complications exists, few thrombotic complications have been reported in patients receiving VWF/FVIII replacement therapy, especially in the setting of known risk factors for thrombosis in the general population, such as surgery, older age, obesity and a history of thromboembolic events.⁵ Low rates of thrombosis have been shown in patients with transiently elevated FVIII levels³⁰; however, the actual incidence of thrombotic events in patients receiving VWF/FVIII concentrates is unknown and close monitoring for thrombotic complications is recommended. A high degree of safety is supported by findings from a systematic review of 71 prospective studies, which evaluated the incidence of thrombotic events in 361 patients with VWD receiving replacement factor concentrates.³¹ Overall, seven venous thrombotic events, which were judged at least probably related to factor administration, were observed including two major venous thromboembolic episodes in patients receiving prolonged replacement therapy for surgery.³¹ Furthermore, a 25-year retrospective observational study in patients treated with a plasma-derived VWF concentrate (Haemate[®] P, CSL Behring; Humate-P[®] in the US and Canada) reported only one thromboembolic event in 663 treatment events in 71 patients.³² In addition, 33 years of pharmacovigilance data reported only 33 cases of thrombotic complications in 78 787 standard dose administrations.³³

There are no evidence-based guidelines to direct therapy in patients at high thrombotic risk, and for the majority of patients,



Major/minor surgery	Loading dose, IU/kg, median (range)	Efficacy	Safety
N/A	N/A	N/A	N/A
N/A	N/A	N/A	N/A
10 major (5 orthopaedic, 2 dental, 3 other) 5 minor (4 general, 1 oral)	55 (36.1-59.9) ^a	Excellent/good haemostasis (100%) Actual vs predicted blood loss was 70% for all surgeries (mean actual blood loss 94 mL vs mean predicted blood loss 106 mL)	12 AEs in 6 patients and 2 SAEs in 2 patients, none considered related to treatment

the use of graduated compression stockings and early mobilisation can be sufficient to prevent venous thromboembolism. The use of anticoagulant prophylaxis should be considered for patients with relevant additional risk factors for thrombosis, and treatment strategies incorporating anticoagulation must balance the risk of haemorrhage in a patient who is already at increased risk against the potential consequences of not treating the thrombotic event. In addition, using a rVWF product to raise FVIII levels slowly may reduce the risk of thrombosis in some patients; however, there is a need for guidance on the use of such products in the perioperative setting. Nonetheless, it has been suggested that FVIII:C is assayed at the time of VWF/FVIII administration, then after 12 hours on the day of infusion, and every 24 hours thereafter.³⁴ In addition, prophylactic low-molecular-weight heparin regimens, such as those routinely employed in patients without VWD undergoing similar procedures, have been advocated but are not included in the current US and UK guidelines for the treatment of patients with VWD.³⁴

4 | PERIOPERATIVE MANAGEMENT OF VWD IN CLINICAL STUDIES

Since optimal guidelines on the perioperative management of patients with VWD are lacking, the experience from clinical trials is important to inform clinical practice. An overview of studies evaluating the perioperative management of patients with VWD with VWF/FVIII concentrates is summarised in Table 2.

Of the available replacement factor concentrates, studies assessing their use in the surgical management of patients are generally limited. There is broad clinical experience in patients treated with a plasma-derived VWF/FVIII concentrate (Haemate[®] P), with data from 160 major surgeries and 65 minor surgeries reported over the past two decades (Table 2).³⁵⁻³⁷ Following administration, FVIII coagulation activity was measured and haemostatic efficacy was assessed and rated as excellent/good in the majority of surgeries,

with no patients reporting a thrombotic event. In the most recent study of 103 patients with VWD (type 1, n = 54; type 2, n = 43; type 3, n = 6), which included 110 major and 38 minor surgeries, only 5 (3.4%) patients experienced clinically relevant bleeding during surgery.³⁵ An additional study of 35 patients undergoing surgery utilised individually tailored pharmacokinetic (PK) loading and maintenance dosing, and adjustment of maintenance doses (eg when doses should be increased/decreased/continued or skipped) was based on VWF:RCo and FVIII levels.³⁶ Actual vs expected blood loss was lower in both major (65 vs 81 mL) and minor (9 vs 18 mL) surgeries, showing haemostasis can be well managed using tailored PK dosing.³⁶ Based on the results of this study, authors' recommendations for pre- and post-surgical dosing infusions are included in this review. These results are similar to studies of other products. In one study (Alphanate[®]; Grifols), PK-guided dosing, with the aim of raising VWF levels to 100 IU/dL, in 71 surgical procedures (13 major and 58 minor) demonstrated actual vs expected blood loss was lower in 68/71 procedures (-31.7 mL).³⁸ Furthermore, in another study of 30 patients (Wilate[®]; Octapharma), doses were calculated by targeting VWF:RCo levels of 100 IU/dL for major surgery and 50 IU/dL for minor surgery.³⁹ In these patients, intraoperative blood loss was lower than the expected blood loss in 28/30 procedures (-294.9 mL).³⁹ It is important to note that these studies assessed the efficacy of VWF concentrates in elective surgery, and overall demonstrated that careful planning of the doses and management of patients can reduce the risk of complications during the perioperative period with any VWF/FVIII concentrate.

The complex variation between available VWD concentrates, VWD disease severity and the difference in VWF and/or FVIII levels after concentrate replacement makes population PK and personalised care more difficult to develop in patients with VWD, and some believe the use of population PK assessments to predict factor levels during surgery may not be reliable, due to the variability of individual PK parameters such as in vivo recovery values.⁴⁰ A recent study developed a population PK model to predict FVIII levels over time



after administration of a plasma-derived VWF/FVIII concentrate (Haemate[®] P) to 97 patients.⁴¹ This model was successfully used to monitor FVIII levels and could prove beneficial for tailoring treatment using PK-guided dosing with this product.⁴¹ However, using the patient's preoperative PK values, along with regular VWF/FVIII assessments as part of a comprehensive treatment plan throughout the perioperative period, is essential to predict post-infusion circulating levels of VWF and FVIII required to achieve haemostasis.

In the majority of clinical studies, few AEs and serious AEs (SAEs) have been reported in patients with VWD undergoing surgical procedures. Nonetheless, AEs have been reported in patients treated with several of the available products, and while the majority of events are evaluated to be not treatment related, some have been associated with replacement therapies, including transient minor elevation of liver function tests, moderate dyspnoea and injection site thrombophlebitis and deep venous thromboembolism possibly related to an elevated FVIII level.³⁸ In addition, in a Phase III study of 15 patients receiving rVWF concentrate, 12 AEs in 6 patients and two SAEs in two patients (including one patient with deep vein thrombosis [DVT] and one with diverticulitis) were reported, none of which were considered related to rVWF treatment.²³ The DVT was initially considered to be related to confounding risk factors, including obesity, surgical procedure and immobilisation; however, continued treatment in the postoperative period led to reassessment of the event as "possibly related" to treatment.²³ In addition, this study supported the efficacy of rVWF with the majority of surgical procedures rated as excellent/good.²³

A meta-analysis of 54 studies evaluating the efficacy of VWF/FVIII concentrates and desmopressin in patients undergoing invasive procedures showed that both are effective for bleeding prevention during surgery.⁴² In patients undergoing elective surgery, when using rVWF, the concentrate infusion should be administered at least 6-8 hours before the procedure to allow FVIII levels to rise adequately.¹¹ On the other hand, some VWF/FVIII products can be administered 1-2 hours before surgery,⁴³ which can be particularly important for patients requiring emergency surgery. In addition, patients with low FVIII may require an additional priming infusion of FVIII to ensure levels are high enough in emergency situations.²² Furthermore, antifibrinolytics can be used in patients undergoing surgery to minimise the risk of bleeding and the need for blood transfusions as well as the incidence of thromboembolic events.⁴⁴ In patients with VWD, the co-administration of tranexamic acid (15-25 mg/kg body weight three times a day) in some settings, such as dental procedures, has been shown to be beneficial at reducing the occurrence of bleeds and need for additional coagulation factor replacement.⁴⁵

5 | RECOMMENDATIONS FOR PERIOPERATIVE DOSING AND MANAGEMENT

An overview of the current guidance for patients with VWD undergoing surgery is summarised in Table 1. VWF levels (VWF:RCo)

should be assessed following infusion, then at least once daily following surgery, and plasma levels of FVIII:C should be measured every 12 hours on the day of surgery, then every 24 hours post-surgery until discharge.⁵ Gill et al provided additional maintenance dose modifications based on postoperative VWF:RCo levels and could provide a basis for PK-tailored dosing, as patients in this study were well managed with bleeding generally reported as mild-moderate in severity.³⁶ In addition, in patients treated with VWF/FVIII concentrate (Haemate[®] P), PK assessments were demonstrated to be independent over a range of doses, supporting the feasibility of PK-guided dosing.⁴⁶

The optimal therapeutic approach is yet to be defined for each disease phenotype, and there are a number of outstanding clinical questions that remain regarding the implementation of therapy and assessment during the perioperative period. Further research is needed to assess the use of VWF/FVIII and FVIII-poor VWF concentrates in real-life settings, particularly in emergency settings, including its impact on patients and costs, for example, postoperative days in hospital, in order to provide comprehensive treatment guidance to clinicians.

Furthermore, when used prophylactically, specific factor containing concentrates can reduce the frequency of recurrent bleeding and provide long-term haemostatic efficacy; a potential benefit when considering the perioperative management of patients with VWD.⁴⁷ In general, long-term prophylaxis outside of surgical settings is rarely used in patients with VWD due to the heterogeneity in disease phenotype; however, several reports have demonstrated the clinical value of long-term prophylactic treatment with VWF-containing concentrates in patients with severe disease, and its early implementation can prevent frequent epistaxis in childhood, as well as joint disease progression.⁴⁸ Prophylaxis may also be beneficial for women during menorrhagia; however, some patients may experience more challenging complications, such as recurrent gastrointestinal bleeds, which remain a challenge and are associated with significant morbidity in VWD.⁶ While there are no current guidelines for the optimal prophylaxis treatment regimen, VWF concentrate doses typically range between 30 and 60 IU/kg and require up to three infusions per week, depending on the bleeding severity.^{49,50} In addition, while the annual cost of prophylaxis may initially seem high, benefits such as reduced surgical complications, decreased annual factor consumption, reduced hospital resources and greater improvements in quality-of-life in some patients suggest there is a growing interest in the implementation of prophylaxis.⁵⁰ It should be noted that prophylaxis with desmopressin is not recommended and may have several side effects.

6 | EVIDENCE GAPS IN THE PERIOPERATIVE MANAGEMENT OF PATIENTS WITH VWD

The surgical management of patients with VWD is complex and several questions remain unanswered, with further research needed to define the optimal treatment approach during various surgical



Unanswered questions in the surgical management of patients with VWD	Suggestions for how these questions may be resolved
With a vast amount of products available, what is the optimal therapy / treatment approach for emergency vs. elective surgical procedures? Should treaters become familiar with one or two brands to ensure appropriate dosing?	Further studies are needed to find clinical consensus on the optimal treatment approach and raising awareness of the disease may help clinicians treat patients faster and more effectively
What assessments should be made before surgery? Does it differ depending on the concentrate used?	
How do FVIII levels before surgery determine the dose of replacement VWF/FVIII concentrate that is administered pre-surgery and would low FVIII levels limit the use of FVIII-poor VWF concentrates?	A database could be used to record real-world pharmacokinetics in patients treated with different products and this could help find the optimal treatment for various disease phenotypes and clinical settings
What are the recommendations for the use of rVWF concentrates in emergency vs. elective surgery and should they only be used in patients with a mild VWF deficiency?	
How do the post-infusion pharmacokinetics of FVIII differ among products?	
Do children have a lower rate of adverse events than adult patients and how does the treatment approach differ compared to adult patients?	As the awareness of VWD increases, patients are being diagnosed at a younger age allowing for longer duration of assessment which may help find the optimal treatment for children
What is the optimal treatment approach for patients with inhibitors to VWF?	Further studies evaluating the efficacy of treatment in patients with inhibitors are needed
In patients without a diagnosis of VWD but with low VWF levels (30–50 IU/dL), is the co-administration of desmopressin and tranexamic acid the optimal approach, instead of using VWF-containing concentrates?	Case reports on the management of patients with low VWF levels may provide evidence for alternative treatment approaches
Long-term prophylaxis may be beneficial in controlling spontaneous bleeding in patients with severe VWD; will this reduce factor consumption during surgery and what is the optimal treatment approach?	Clinical studies are needed to assess the long-term benefits of prophylaxis with VWF concentrates

FIGURE 2 Further research is needed to define the optimal treatment approach for patients with VWD undergoing surgery. FVIII, factor VIII; VWD, von Willebrand disease; VWF, von Willebrand factor.

settings (Figure 2). In particular, few studies have addressed the efficacy and safety of different protocols in the surgical management of VWD in paediatric patients. Additional clinical trials are ongoing to assess the safety and efficacy of rVWF concentrates for prophylaxis in the VWD paediatric population.^{51,52} In addition, treatment in some patients may be complicated by the development of antibodies against VWF, with most cases reported in patients with type 3 VWD.⁵³ All plasma concentrates containing VWF should be avoided in VWD patients with alloantibodies because of the risk of anaphylactic reactions; they can be effectively treated with rFVIII alone in order to restore haemostasis.⁵⁴ Furthermore, few studies have evaluated the perioperative factor consumption and as expected, consumption varies substantially, from 27 to 146 IU/kg/d, depending on the type of surgical procedure and the type of VWD.³⁵ It is, however, hypothesised that patients undergoing minor surgery have higher factor consumption due to less frequent but higher loading doses within a shorter period of time.

The surgical management of patients with low VWF levels continues to pose a significant clinical challenge as patients present with variable bleeding phenotypes; treatment should, therefore, also consider personal and family bleeding histories in addition to VWF levels in order to optimise therapy.⁴⁵

7 | CONCLUSIONS

Given the complexity of VWD, clinical consensus is lacking for the treatment of patients undergoing surgery. Evidence of the effectiveness of VWF/FVIII concentrates to provide adequate and timely haemostasis in patients undergoing surgery is accumulating. The use of VWF concentrates for the reduction of excessive bleeding in surgery is generally accepted and on-demand treatment with 30–60 IU/kg can control haemostasis during major and minor surgeries. However, treatment strategies vary by the type and severity of disease, as well as the product used and duration of treatment, and a number of unanswered questions require further clarification to fully understand the clinical implications and provide further guidance to clinicians. This review provides an overview of the current optimal treatment for patients with VWD in the perioperative period, and future research initiatives should focus on the knowledge gaps identified in this article.

ACKNOWLEDGEMENTS

Medical writing assistance was provided by Meridian HealthComms Ltd in accordance with good publication practice (GPP3), funded by CSL Behring.



CONFLICTS OF INTEREST

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

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How to cite this article: Miesbach W. Perioperative management for patients with von Willebrand disease: Defining the optimal approach. *Eur J Haematol*. 2020;105:365-377. <https://doi.org/10.1111/ejh.13462>