# Perioperative management of patients with von Willebrand disease

*James S. O'Donnell*[1,2] *and Michelle Lavin*[1,2]

[1]*Irish Centre for Vascular Biology, Royal College of Surgeons in Ireland, Dublin, Ireland; and* [2]*National Coagulation Centre, St. James' Hospital, Dublin, Ireland*

**Surgical procedures represent a serious hemostatic challenge for patients with von Willebrand disease (VWD), and careful perioperative management is required to minimize bleeding risk. Risk stratification includes not only the nature of the surgery to be performed but the baseline plasma von Willebrand factor (VWF) levels, bleeding history, and responses to previous challenges. Baseline bleeding scores (BSs) may assist in identification of patients with a higher risk of post-surgical bleeding. There remains a lack of consensus between best practice guidelines as to the therapeutic target and assays to be monitored in the postoperative period. Hemostatic levels are maintained until bleeding risk abates: usually 3 to 5 days for minor procedures and 7 to 14 days for major surgery. Hemostatic supplementation is more complex in VWD than in other bleeding disorders owing to the combined but variable deficiency of both plasma VWF and factor VIII (FVIII) levels. For emergency surgery, coadministration of VWF and FVIII is required to ensure hemostasis; however, for elective procedures, early infusion of VWF replacement therapy will stabilize endogenous FVIII. Because endogenous FVIII production is unaffected in patients with VWD, repeated VWF supplementation (particularly with plasma-derived FVIII-containing products) may lead to accumulation of FVIII. Frequent monitoring of plasma levels and access to hemostatic testing are, therefore, essential for patients undergoing major surgery, particularly with more severe forms of VWD.**

**Learning Objectives**

- Review preoperative risk assessment strategies to guide hemostatic cover at the time of surgery for people with von Willebrand disease
- Understand the distinctions between differing von Willebrand factor replacement therapies and the timing of administration preoperatively

## Clinical case

A 70-year-old man with type 2M von Willebrand disease (VWD) has failed to attend for a number of years and now requires a right total knee replacement (TKR). Recorded baseline results from the original time of diagnosis at 32 years of age were von Willebrand factor (VWF):antigen (Ag) 26 IU/dL, ristocetin cofactor assay (VWF:RCo) 12 IU/dL, collagen binding (VWF:CB) 24 IU/dL, and factor VIII (FVIII) one stage clotting assay (FVIII:C) 30 IU/dL. Plasma VWF multimer distribution confirmed the presence of normal high-molecular weight multimers (HMWMs). His mother and elder brother were also registered with a diagnosis of VWD. He has no previous surgical history. However, he has a significant bleeding history that includes recurrent epistaxis (requiring multiple cauterizations), bleeding after dental extraction (requiring packing and suturing), and lifelong easy bruising. He has undergone a previous 1-deamino-8-D-arginine vasopressin (DDAVP) trial that demonstrated a partial response (1 hour post-DDAVP: VWF:Ag 78 IU/dL, VWF:RCo 46 IU/dL; 4 hours post-DDAVP: VWF:Ag 52 IU/dL, VWF:RCo 32 IU/dL). Consequently, DDAVP and tranexamic acid (TXA) have previously been used to manage severe episodes of epistaxis. He is now referred for advice regarding a perioperative hemostatic management plan.

## Characterization of VWD subtype and assessment of bleeding phenotype

VWD is a heterogenous disorder encompassing both quantitative (type 1 and type 3 VWD) and qualitative deficiencies in VWF (type 2 VWD). The resultant bleeding diathesis is characterized by mucocutaneous bleeding, with easy bruising menorrhagia and epistaxis frequent manifestations of the condition. Importantly, however, significant phenotypic variability exists between patients with VWD, even within the same subtype. Consequently, to develop a perioperative management plan for patients with VWD, it is important to not only determine the VWD subtype involved but also consider the patient's bleeding history.

The development of bleeding assessment tools (BATs) has simplified and standardized the approach to VWD phenotypic evaluation.[1] Moreover, markedly elevated bleeding scores (BSs) have been reported to predict future bleeding risk.[2] In addition, positive scores in specific BAT domains have been shown to predict surgical bleeding risk. For example, Tosetto et al[3] found that the prediagnosis mucocutaneous

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BS (epistaxis, cutaneous bleeding, and bleeding from minor wounds) derived from the Condensed Molecular and Clinical Markers for the Diagnosis and Management of Type 1 von Willebrand Disease (MCMDM-1VWD) score was a better predictor of surgical bleeding than plasma VWF or FVIII levels in patients with type 1 VWD. Although limited data have been reported to date, these findings suggest that it is useful to objectively assess bleeding phenotype for any patient with VWD undergoing an elective procedure. Limitations exist with the use of BATs, with the possibility of underestimation of bleeding phenotype in younger patients or those who have undergone minimal previous hemostatic challenges.[1] In contrast, the use of prophylactic treatment to cover previous procedures may result in a falsely elevated BS. Finally, BATs are easily saturable so that the same score is derived for a severe bleeding episode (eg, epistaxis requiring cautery) irrespective of whether it occurred on 1 or multiple occasions.[1] For our patient, this represents his first major surgical challenge. Based on his historical plasma VWF assays, he has correctly been assigned with a diagnosis of type 2M VWD. For this patient, the Condensed MCMDM-1VWD and International Society on Thrombosis and Hemostasis BAT scores are concordant at 8 (normal reference for males $<4$),[4,5] with a mucocutaneous BS of 5. Given that the maximum mucocutaneous BS with the Condensed MCMDM-1VWD is 10, this patient may be at risk of postoperative bleeding, and a careful plan for hemostatic management is warranted.

## Preoperative assessment of plasma VWF levels

In normal individuals, plasma VWF levels increase with aging.[6] This age-related increase in levels has also been observed in some patients with VWD.[7-9] For patients with low VWF and type 1 VWD, plasma VWF:Ag increases at a mean rate of 1.9 to 3 IU/dL per year. Consequently, plasma VWF:Ag levels may correct into the normal range for some patients with quantitative VWD.[7,8] Aging-associated increases in plasma VWF:Ag levels have also been observed in some patients with type 2 VWD. Perhaps unsurprisingly, however, the effects of progressive aging on VWF:RCo and VWF:CB functional assays in patients with qualitative VWD were less marked.[9] Although data are limited, it seems that age-related increases in plasma VWF levels may not necessarily be associated with an attenuation in surgical bleeding risk.[9] Given that our patient has not had VWF levels checked for many years, laboratory assays were repeated to guide his preoperative hemostatic plan. This repeat testing confirmed that his plasma VWF levels remained significantly reduced (VWF:Ag 32 IU/dL, VWF:RCo 10 IU/dL, and FVIII:C of 38 IU/dL). These levels coupled with his significant personal bleeding history mean that perioperative hemostatic therapy will be required for this forthcoming orthopedic surgery.

## Stratification of surgical risk in patients with VWD

Stratification of surgical risk is essential to define a treatment plan for patients with VWD undergoing elective procedures. In particular, higher target plasma VWF levels and longer treatment duration will be required for major surgery. Examples of the general bleeding risks associated with a number of relatively common procedures are outlined in Table 1. Furthermore, data suggest that the bleeding risks associated with some surgical procedures (particularly those involving mucosal membranes) may be specifically increased in patients with VWD. For our patient, it is clear that his TKR surgery represents major surgery and thus, will inevitably be associated with a significant bleeding challenge.

**Table 1. Surgical risk stratification**

| Surgical category | Examples |
|---|---|
| Major | Spinal/neurosurgical procedures |
| | Laparotomy |
| | Prostatectomy |
| | Tonsillectomy |
| | Hysterectomy |
| | Prostatectomy |
| | Orthopedic (eg, joint replacement or amputation) |
| | Caesarean section |
| Minor | Biopsy: breast, cervical |
| | Complicated dental extractions |
| | Gingival surgery |
| | Laparoscopic procedures |
| Single treatment if uncomplicated | Cataract surgery |
| | Endoscopy (without biopsy) |
| | Simple dental extractions |

## What treatment options should be considered for this patient?

In patients with VWD, therapeutic plasma VWF and FVIII levels can be achieved either through provoked release of endogenous VWF stores (DDAVP) or via infusion of exogenous VWF (in the form of either plasma-derived von Willebrand factor [pdVWF]-containing concentrates or recombinant von Willebrand factor [rVWF]). Adjunctive hemostatic agents, such as antifibrinolytic agents (eg, TXA or aminocaproic acid), are also often useful in this context.

## What is the role of antifibrinolytic therapy in the perioperative setting?

Antifibrinolytic drugs bind to the lysine sites on fibrinogen and promote clot stabilization, helping to reduce bleeding risk for patients with VWD undergoing procedures, particularly those involving mucosal surfaces.[10] Clinical reluctance to use TXA is often encountered because of longstanding concerns regarding the risk of thromboembolism. Although originally described in case reports, an increased risk of thromboembolism has not been borne out in more recent large randomized clinical trials.[11,12] Indeed, the use of antifibrinolytics even in high-risk settings, including trauma, postpartum hemorrhage, coronary artery, and pelvic and orthopedic surgery, has demonstrated clinical efficacy without a significant increase in thromboembolism.[11-15] The use of antifibrinolytics should be considered in all patients with VWD undergoing surgery, provided that no contraindications (eg, hematuria, renal failure, or previous history of thrombosis) are present.[10] Consequently, in our patient, I would recommend that TXA (1 g every 8 hours [tds] PO/IV) treatment be used for 48 to 72 hours postoperatively to minimize bleeding risk.

## Is there a role for DDAVP in the perioperative setting for patients with type 2M VWD?

DDAVP is a synthetic analog of vasopressin that stimulates release of VWF from the Weibel Palade bodies of endothelial cells into the circulation. In patients with low VWF levels (plasma VWF levels 30-50 IU/dL), DDAVP induces a predictable and sustained response.[7] For patients with type 1 or 2 VWD, responses to DDAVP are higher.[16] Failure to respond is more commonly seen in patients with baseline plasma VWF levels $<10$ IU/dL.[17] For patients with increased plasma VWF clearance owing to specific VWF mutations (type 1C VWD) or enhanced susceptibility to cleavage by ADAMTS13 (some patients with type 2A VWD), an initial adequate response to DDAVP may be short lived, underscoring the importance of a trial

to assess DDAVP response in advance of surgery.[16] The use of DDAVP in type 2B VWD is relatively contraindicated because of concerns of worsening thrombocytopenia.[17] For surgery, DDAVP may be administered via the IV or subcutaneous route (off label in the United States), with similar responses seen.[18] Because of the risk of dilutional hyponatremia, sodium levels should be checked before repeated use, and fluids should be restricted post-DDAVP (1-1.5 L in 24 hours after use). This fluid restriction may preclude its use in surgeries for which fluid boluses are anticipated post-operatively. DDAVP is avoided in infants younger than 2 years of age and those with a history of cardiovascular disease, cerebrovascular disease, peripheral vascular disease, heart failure, or hyponatriemia.[19] With repeated dosing, tachyphylaxis may occur, and therefore, DDAVP is best suited for procedures in patients with milder defects, particularly procedures requiring short duration of hemostatic cover.[19] Our patient has previously received DDAVP therapy to successfully manage episodes of epistaxis. However, based on his DDAVP trial, it is clear that the VWF:RCo correction is of limited duration. Furthermore, our patient is now 70 years of age. Consequently, DDAVP is not considered a reasonable option for his forthcoming TKR procedure. Instead, exogenous VWF replacement with either pdVWF or rVWF will be required.

## pdVWF-containing concentrates

pdVWF concentrates are heterogenous, differing significantly in their production methods, viral inactivation steps, and multimer distribution (Table 2).[20] All pdVWF concentrates are variably deficient in HMWMs. Nonetheless, clinical studies of the use of pdVWF in surgical settings have demonstrated their hemostatic efficacy.[10] Critically, most pdVWF contain variable amounts of FVIII (Table 2). Patients with VWD retain the ability to synthesize and secrete endogenous FVIII, which will stabilize after administration of exogenous VWF. For some patients with low VWF and type 1 VWD, the stress response associated with surgery may boost endogenous plasma VWF release postoperatively, and VWF replacement requirements may be lower than expected. For patients with type 2 or type 3 VWD undergoing major surgery, however, repeated infusions of VWF will be required. Consequently, repeated dosing of pdVWF in patients undergoing major surgical procedures can, therefore, result in significantly elevated plasma FVIII:C levels during the postoperative period.

## rVWF

The first rVWF product (vonicog alfa, Vonvendi [United States], and Veyvondi [Europe]; Takeda) has recently been licensed. This rVWF is produced in Chinese hamster ovary cells. Because rVWF is not exposed to ADAMTS13 during its manufacture, it contains increased ultralarge multimers and HMWMs compared with pdVWF concentrates.[21] After the initial Food and Drug Administration approval for use in adults with VWD in 2015, the rVWF license was expanded in 2018 to include surgical prophylaxis.[22,23]

## Communication of hemostatic management plan

Whenever possible, major surgery in patients with VWD should be performed in a center with a hematologist with expertise in the management of bleeding disorders and continuous access to laboratory testing (VWF:Ag, VWF:RCo, and FVIII:C levels).[16] A formal written hemostatic management plan should be developed and then communicated to both the patient and the operative team (surgical, anesthetics, and nursing). This plan should clearly outline the planned treatment approach, blood sampling requirements, and monitoring intervals. Nonsteroidal anti-inflammatory drugs, intramuscular injections, and neuraxial/spinal anesthesia should be avoided in patients with type 2 VWD because of the increased bleeding risk.[24] In this patient who has failed to attend for a number of years, plasma VWF assays, renal and liver function, and serology should be evaluated preoperatively.

## Perioperative management

Before surgery, 1 g TXA should be administered IV and then, continued every 8 hours postoperatively. For surgery, pdVWF-FVIII concentrates can generally be administered on the day of the procedure. rVWF and some high-purity pdVWF concentrates (eg, Wilfactin; LFB) do not contain significant amounts of FVIII. Consequently, for VWD patients with reduced plasma FVIII:C levels, rVWF should be administered 12 to 24 hours preoperatively to allow sufficient time for correction in plasma FVIII:C levels. This is achieved, because the infused rVWF can bind and stabilize

**Table 2. VWF-containing concentrates in use globally for the treatment of VWD**

| Product trade name | Type | Availability | Manufacturer | VWF:RCo-to-FVIII ratio | Viral inactivation process |
|---|---|---|---|---|---|
| Vonvendi/ Veyvondi | Recombinant, Chinese hamster ovary cells | North America/ Europe | Takeda, United States | rVWF, negligible FVIII | Not applicable |
| Wilfactin/Willfact/ Willefact | Plasma derived | Europe | LFB, France | 50 | SD, dry heat (80°C, 72 h), nanofiltration (35 nM) |
| Humate P/ Haemate P | Plasma derived | North America/ internationally | CSL Behring, Germany | 2.4 | Pasteurization (60°C for 10 h) |
| Voncento | Plasma derived | Europe | CSL Behring, Germany | 2.4 | SD, dry heat (80°C, 72 h) |
| Biostate | Plasma derived | Australia/Asia | CSL Behring, Australia | 2 | SD, dry heat (80°C,72 h) |
| Wilstart | Plasma derived | France | LFB, France | 2 | SD, dry heat (80°C, 72 h), nanofiltration (35 nM) |
| Immunate | Plasma derived | Internationally | Takeda, Austria | 1.1 | SD, vapor heat, 60°C, 10 h at 190 mbar |
| Wilate | Plasma derived | Internationally | Octapharma, Austria | 0.9 | SD, dry heat (100°C, 2 h) |
| Alphanate/Fandhi | Plasma derived | North America/ internationally | Grifols, United States | 0.91 | SD, dry heat (80°C, 72 h) |
| Factor 8Y | Plasma derived | Limited European countries | BioProducts Laboratory, England | 0.82 | Dry heat (80°C, 72 h) |

SD, solvent detergent.

endogenously secreted FVIII. Consequently, the rise in plasma FVIII:C levels post-rVWF administration is gradual, with a mean hourly rise of 8.44 IU/dL (range, 4.43-11.57 IU/dL; n = 16).[22] If rVWF concentrate is used for surgery, plasma VWF:Ag, VWF:RCo, and FVIII:C levels would be checked 2 hours preoperatively to ensure full correction before theater, with additional treatment if required. In the event of urgent surgery or where patients cannot attend before surgery, coadministration of rVWF with a single dose of rFVIII will be required on the day of surgery to ensure that immediate hemostatic plasma VWF and FVIII:C levels are achieved.

Dosing of VWF replacement is based on body weight and in vivo recovery (IR) of VWF:RCo and FVIII, with 1 IU/kg VWF:RCo or FVIII raising plasma VWF and FVIII levels ~2 IU/dL.[25] Despite the increased prevalence of obesity, the impact of elevated body mass index on IR in VWD remains uncertain, and dosing is based on actual body weight. Where the IR for a patient is unknown, it is assumed to be 2, with the dose required calculated as ([desired plasma VWF rise (international units)/IR] × body weight [kilograms]) for both rVWF and pdVWF.[25] Based on the most recent VWF:RCo level for our patient (10 IU/dL), to correct his plasma VWF level to 100 IU/dL, a dose of 45 IU/kg body weight of pdVWF concentrate would be administered 2 hours preoperatively. After infusion, VWF:Ag, VWF:RCo, and FVIII:C levels would be repeated to ensure that all are corrected before theater. In addition, repeat blood sampling postoperatively should be performed to determine plasma VWF:Ag, VWF:RCo, and FVIII:C levels and guide additional replacement therapy if required.

## Perioperative therapeutic targets and treatment duration

Perioperative therapeutic strategies aim to minimize bleeding, maintaining hemostatic plasma VWF levels throughout the postoperative period until bleeding risk abates and healing is complete. Earlier publications observed hemostatic efficacy in patients for whom only FVIII:C levels were monitored postoperatively, leading to suggestion that plasma FVIII was the main determinant of bleeding in people with VWD.[26,27] In these studies by Biggs and Matthews[26] (n = 4) and Larrieu et al[27] (n = 3), bleeding time was assessed after preoperative administration of plasma-fractionated FVIIII. Recent guidelines advise monitoring of both VWF:RCo and FVIII levels in the postoperative period. However, there remains a lack of evidence to define optimal plasma VWF:Ag, VWF:RCo, and/or FVIII:C levels (Table 3).[10,16,24,28] Consequently, clinical practice varies significantly with respect to assay(s) used and how laboratory findings are used to guide further VWF replacement therapy. In general terms, for minor surgery, treatment is usually continued for 1 to 5 days, with 7 to 14 days of hemostatic treatment for major surgery (Table 3).[10,16,24,28] In our practice, plasma VWF:Ag, VWF:RCo, and FVIII:C levels are determined by the administration of VWF concentrate preoperatively to ensure adequacy of levels before surgery. Levels are repeated postoperatively, with additional VWF concentrate administered that day if required to maintain plasma VWF:Ag and VWF:RCo trough >50 IU/dL. Thereafter, daily VWF:Ag, VWF:RCo, and FVIII:C levels are performed for all patients with VWD after major surgery. On the basis of these daily results, additional VWF concentrate is administered daily as required to maintain trough VWF:RCo levels >50 IU/dL for at least 7 to 10 days.

Patients with type 2 VWD will typically require repeated dosing of VWF concentrates after major surgery. Preliminary data suggest that the half-life of rVWF may be longer than that of pdVWF concentrates.[21] This may be related to the altered glycosylation profile of rVWF.[29,30] Similarly, enhanced stabilization of endogenous FVIII in patients with VWD has also been reported after treatment with rVWF compared with pdVWF concentrates.[21,31] Additional studies will be required to define the clinical importance of these findings and elucidate the underlying biological mechanisms involved.

In the case of our patient, he was treated with 45 IU/kg of pdVWF concentrate preoperatively with preoperative plasma VWF levels of VWF:Ag 128 IU/dL, VWF:RCo 102 IU/dL, and FVIII:C 125 IU/dL. Postoperative levels at 6 hours after dose showed a VWF:Ag of 96 IU/dL, a VWF:RCo of 73 IU/dL, and FVIII:C of 102 IU/dL. An additional dose of 25 IU/kg of VWF concentrate was administered at 12 hours postoperation, and thereafter, trough plasma VWF:RCo levels >50 IU/dL were maintained with once daily blood sampling and dosing for 10 days.

## Should thromboprophylaxis be used, and if so, when should it be introduced?

A number of reports have described episodes of venous thromboembolism (VTE) developing in patients with VWD receiving VWF replacement.[32,33] The limited data available suggest that the overall rates of thrombotic events in this context are low (estimated 0.048% of all VWF replacement infusions or 1.9% of all treated VWD patients).[32] Moreover, these thrombotic episodes were more common in patients with additional risk factors (eg, obesity, elderly, or estrogen use).[33] These thrombotic complications have led some authors to propose that elevated plasma FVIII:C levels in VWD patients after prolonged VWF replacement may be important in VTE etiology. Although increased plasma FVIII:C levels constitute a dose-dependent risk factor for VTE in the general population, the importance of elevated FVIII:C levels in the perioperative setting has not yet been clearly elucidated.[32] Nevertheless, current US VWD treatment guidelines recommend avoiding plasma FVIII:C >250 IU/dL and VWF:RCo >200 IU/dL in the postoperative period.[16] European guidance is more restrictive, favoring maintaining plasma FVIII levels <150 IU/dL (Table 3).[28] Additional studies will also be necessary to define whether thrombotic risk is lower for VWF concentrates lacking significant amounts of FVIII. Published experience of perioperative use of rVWF is limited to 10 patients, with 1 episode of deep vein thrombosis reported in a patient with additional thrombotic risk factors; additional postlicensing surveillance will be essential.[22]

For VWD patients undergoing surgery who are considered at risk of thrombosis, standard thromboprophylaxis should be considered after adequate hemostatic replacement has been achieved postoperatively and continued until VWF replacement is discontinued.[28] In addition, thromboembolic deterrent stockings should be fitted for patients where suitable, and early mobilization is encouraged.

## Could pharmacokinetic guided dosing of VWF concentrate optimize perioperative management?

Previous studies have demonstrated marked interindividual variations in the half-life of infused pdVWF or rVWF concentrates.[21,31,34] In addition, as discussed earlier, current evidence suggests that there are also significant pharmacokinetic (PK) differences between VWF concentrates.[34] Taken together, these data suggest that there may be a role to improve the management of perioperative hemostasis in patients with VWD by developing individualized PK-tailored treatment regimens. The clinical utility of steady-state VWF PK

Table 3. Recommendations on the perioperative therapeutic targets for patients with VWD undergoing surgery

| Source | Major surgery | | Minor surgery | |
|---|---|---|---|---|
| | Preoperative target plasma levels | Postoperative target plasma levels | Preoperative target plasma levels | Postoperative target plasma levels |
| Nichols et al[16] | VWF:RCo and FVIII:C > 100 | VWF:RCo and FVIII:C > 50 for ≥7-10 d; avoid VWF:RCo > 200 and FVIII:C > 250 | VWF:RCo and FVIII:C > 30; preferable >50 | VWF:RCo and FVIII:C > 30; preferable >50 for 3-5 d |
| Laffan et al[24] | VWF:RCo and FVIII:C > 100 | FVIII:C > 50; duration not specified; "postoperative period" | VWF:RCo and FVIII:C > 50 | Not specified |
| Castaman et al[28] | VWF:RCo and FVIII:C = 80-100 | VWF:RCo and FVIII:C = 80-100 for 36 h; then, >50 for 5-10 d; avoid FVIII:C > 150 | Trough FVIII:C > 30 | FVIII:C > 30 for 2-4 d |
| Windyga et al[10] | VWF:RCo > 50; FVIII:C > 80-100 | Day of surgery: VWF:RCo > 50; FVIII:C > 80-100; days 1-7: VWF: RCo > 30; FVIII:C > 50; days 8-14: VWF:RCo and FVIII:C > 30; avoid FVIII:C > 250 | VWF:RCo > 50; FVIII:C > 80-100 | Trough VWF:RCo > 30 and FVIII:C > 50 for 3-5 d |

All target plasma levels are expressed as international units per deciliter.

has previously been assessed.[34] However, steady-state PK profiles have failed to accurately predict postoperative plasma FVIII:C and VWF:RCo levels, likely related to the altered consumption of VWF and the surgery-induced stress response, provoking endogenous VWF release.[34] Even with adherence to current clinical guidelines, postoperative plasma levels may be suboptimal, with supratherapeutic FVIII:C levels seen in all patients of a type 1 VWD cohort treated with pdVWF at 36 hours (median 180 IU/dL; n = 54).[25] In this study, patients with type 2 and 3 VWD (n = 49) also experienced elevated plasma FVIII:C levels, with FVIII:C trough levels >270 IU/dL in 8% of patients.[25] Despite these excessive FVIII:C levels, no thrombotic episodes were reported, with thromboprophylaxis used in 61% of patients.[25] There clearly remains an ongoing, unmet need for improved and personalized VWF treatment approaches, particularly for surgical management. The current OPTI-CLOT To-WIN study is addressing these issues by using Bayesian analysis to develop VWF population PK models to try to optimize perioperative management protocols.[35]

## What if bleeding postoperatively occurs despite adequate replacement?

Although postoperative hemorrhage is often attributed to the underlying bleeding disorder, if plasma VWF and FVIII:C levels are confirmed as hemostatic, surgical causes of bleeding should be considered, particularly if bleeding is identified at a single drain site with all other sites dry. Up to 10% to 20% of the total amount of VWF present in normal platelet (plt)-rich plasma whole blood is actually contained within the plt α-granules.[36] Previous in vitro and in vivo studies have demonstrated the importance of plt-VWF in maintenance of normal hemostasis, with plt-VWF released in high local concentrations at sites of vascular injury.[36] Interestingly, because of differences in posttranslational modifications, this plt-VWF is also partially resistant to ADAMTS13 proteolysis.[37] Although infusion of exogenous VWF will normalize plasma VWF levels, it is important to recognize that the plt-VWF deficit will not be corrected. Consequently, in the event of ongoing bleeding despite adequate plasma VWF replacement, platelet transfusion may be beneficial in restoring hemostasis.[38]

## What was the outcome in our patient?

Our patient was treated with a combination of TXA and VWF replacement preoperatively and had no bleeding complications in the postoperative period. TXA was discontinued at 48 hours post-TKR, with VWF replacement administered daily until day 10 post-TKR. After satisfactory assessment from both the physiotherapists and orthopedic surgeons, the patient was discharged on day 11 from hospital.

## Conclusions

The perioperative management of patients with VWD is complex, requiring an understanding of the products available and their impact on plasma VWF and FVIII levels. A personalized approach is essential, taking into account the baseline VWF level, bleeding phenotype, previous responses to treatment, nature of surgery, and relevant comorbidities. Close monitoring and hematologist-guided dosing of replacement therapy during the postoperative period are warranted to ensure adequacy of plasma VWF levels and initiation of thromboprophylaxis if indicated.

## Correspondence

Michelle Lavin, Irish Centre for Vascular Biology, Royal College of Surgeons in Ireland, Ardilaun House, 111 St. Stephen's Green, Dublin 2, Ireland; e-mail: michellelavin@rcsi.ie.

## References

1. Rydz N, James PD. The evolution and value of bleeding assessment tools. *J Thromb Haemost*. 2012;10(11):2223-2229.
2. Federici AB, Bucciarelli P, Castaman G, et al. The bleeding score predicts clinical outcomes and replacement therapy in adults with von Willebrand disease. *Blood*. 2014;123(26):4037-4044.
3. Tosetto A, Rodeghiero F, Castaman G, et al. A quantitative analysis of bleeding symptoms in type 1 von Willebrand disease: results from a multicenter European study (MCMDM-1 VWD). *J Thromb Haemost*. 2006;4(4):766-773.
4. Elbatarny M, Mollah S, Grabell J, et al; Zimmerman Program Investigators. Normal range of bleeding scores for the ISTH-BAT: adult and pediatric data from the merging project. *Haemophilia*. 2014;20(6): 831-835.
5. Bowman M, Mundell G, Grabell J, et al. Generation and validation of the Condensed MCMDM-1VWD Bleeding Questionnaire for von Willebrand disease. *J Thromb Haemost*. 2008;6(12):2062-2066.
6. Albánez S, Ogiwara K, Michels A, et al. Aging and ABO blood type influence von Willebrand factor and factor VIII levels through interrelated mechanisms. *J Thromb Haemost*. 2016;14(5):953-963.

7. Lavin M, Aguila S, Schneppenheim S, et al. Novel insights into the clinical phenotype and pathophysiology underlying low VWF levels. *Blood*. 2017;130(21):2344-2353.
8. Rydz N, Grabell J, Lillicrap D, James PD. Changes in von Willebrand factor level and von Willebrand activity with age in type 1 von Willebrand disease. *Haemophilia*. 2015;21(5):636-641.
9. Sanders YV, Giezenaar MA, Laros-van Gorkom BA, et al; WiN study group. von Willebrand disease and aging: an evolving phenotype. *J Thromb Haemost*. 2014;12(7):1066-1075.
10. Windyga J, Dolan G, Altisent C, Katsarou O, López Fernández MF, Zülfikar B; EHTSB. Practical aspects of factor concentrate use in patients with von Willebrand disease undergoing invasive procedures: a European survey. *Haemophilia*. 2016;22(5):739-751.
11. Roberts I, Shakur H, Coats T, et al. The CRASH-2 trial: a randomised controlled trial and economic evaluation of the effects of tranexamic acid on death, vascular occlusive events and transfusion requirement in bleeding trauma patients. *Health Technol Assess*. 2013;17(10):1-79.
12. WOMAN Trial Collaborators. Effect of early tranexamic acid administration on mortality, hysterectomy, and other morbidities in women with post-partum haemorrhage (WOMAN): an international, randomised, double-blind, placebo-controlled trial. *Lancet*. 2017;389(10084): 2105-2116.
13. Poeran J, Rasul R, Suzuki S, et al. Tranexamic acid use and postoperative outcomes in patients undergoing total hip or knee arthroplasty in the United States: retrospective analysis of effectiveness and safety. *BMJ*. 2014;349:g4829.
14. Breau RH, Kokolo MB, Punjani N, et al. The effects of lysine analogs during pelvic surgery: a systematic review and meta-analysis. *Transfus Med Rev*. 2014;28(3):145-155.
15. Myles PS, Smith JA, Forbes A, et al; ATACAS Investigators of the ANZCA Clinical Trials Network. Tranexamic Acid in Patients Undergoing Coronary-Artery Surgery. *N Engl J Med*. 2017;376(2):136-148.
16. Nichols WL, Hultin MB, James AH, et al. von Willebrand disease (VWD): evidence-based diagnosis and management guidelines, the National Heart, Lung, and Blood Institute (NHLBI) Expert Panel report (USA). *Haemophilia*. 2008;14(2):171-232.
17. Federici AB. The use of desmopressin in von Willebrand disease: the experience of the first 30 years (1977-2007). *Haemophilia*. 2008; 14(suppl 1):5-14.
18. Mannucci PM, Vicente V, Alberca I, et al. Intravenous and subcutaneous administration of desmopressin (DDAVP) to hemophiliacs: pharmacokinetics and factor VIII responses. *Thromb Haemost*. 1987;58(04): 1037-1039.
19. Windyga J, Dolan G, Altisent C, Katsarou O, López Fernández MF, Zülfikar B; EHTSB. Practical aspects of DDAVP use in patients with von Willebrand Disease undergoing invasive procedures: a European survey. *Haemophilia*. 2016;22(1):110-120.
20. Lavin M, O'Donnell JS. New treatment approaches to von Willebrand disease. *Hematology (Am Soc Hematol Educ Program)*. 2016;2016(1): 683-689.
21. Mannucci PM, Kempton C, Millar C, et al; rVWF Ad Hoc Study Group. Pharmacokinetics and safety of a novel recombinant human von Willebrand factor manufactured with a plasma-free method: a prospective clinical trial. *Blood*. 2013;122(5):648-657.
22. Peyvandi F, Mamaev A, Wang JD, et al. Phase 3 study of recombinant von Willebrand factor in patients with severe von Willebrand disease who are undergoing elective surgery. *J Thromb Haemost*. 2019;17(1): 52-62.
23. FDA. Summary of Product Characteristics VONVENDI [von Willebrand Factor (Recombinant)]. Bethesda, MD: FDA; 2015.
24. Laffan MA, Lester W, O'Donnell JS, et al. The diagnosis and management of von Willebrand disease: a United Kingdom Haemophilia Centre Doctors Organization guideline approved by the British Committee for Standards in Haematology. *Br J Haematol*. 2014;167(4): 453-465.
25. Hazendonk HCAM, Heijdra JM, de Jager NCB, et al; "OPTI-CLOT" and "WIN" study group. Analysis of current perioperative management with Haemate® P/Humate P® in von Willebrand disease: identifying the need for personalized treatment. *Haemophilia*. 2018;24(3):460-470.
26. Biggs R, Matthews JM. The treatment of haemorrhage in von Willebrand's disease and the blood level of factor VIII (AHG). *Br J Haematol*. 1963;9(2):203-214.
27. Larrieu MJ, Caen JP, Meyer DO, Vainer H, Sultan Y, Bernard J. Congenital bleeding disorders with long bleeding time and normal platelet count. II. Von Willebrand's disease (report of thirty-seven patients). *Am J Med*. 1968;45(3):354-372.
28. Castaman G, Goodeve A, Eikenboom J; European Group on von Willebrand Disease. Principles of care for the diagnosis and treatment of von Willebrand disease. *Haematologica*. 2013;98(5):667-674.
29. McKinnon TA, Chion AC, Millington AJ, Lane DA, Laffan MA. N-linked glycosylation of VWF modulates its interaction with ADAMTS13. *Blood*. 2008;111(6):3042-3049.
30. Aguila S, Lavin M, Dalton N, et al. Increased galactose expression and enhanced clearance in patients with low von Willebrand factor. *Blood*. 2019;133(14):1585-1596.
31. Gill JC, Castaman G, Windyga J, et al. Hemostatic efficacy, safety, and pharmacokinetics of a recombinant von Willebrand factor in severe von Willebrand disease. *Blood*. 2015;126(17):2038-2046.
32. Coppola A, Franchini M, Makris M, Santagostino E, Di Minno G, Mannucci PM. Thrombotic adverse events to coagulation factor concentrates for treatment of patients with haemophilia and von Willebrand disease: a systematic review of prospective studies. *Haemophilia*. 2012; 18(3):e173-e187.
33. Makris M, Colvin B, Gupta V, Shields ML, Smith MP. Venous thrombosis following the use of intermediate purity FVIII concentrate to treat patients with von Willebrand's disease. *Thromb Haemost*. 2002; 88(3):387-388.
34. Di Paola J, Lethagen S, Gill J, et al. Presurgical pharmacokinetic analysis of a von Willebrand factor/factor VIII (VWF/FVIII) concentrate in patients with von Willebrand's disease (VWD) has limited value in dosing for surgery. *Haemophilia*. 2011;17(5):752-758.
35. Hazendonk HCAM, van Moort I, Fijnvandraat K, et al. The "OPTI-CLOT" trial. A randomised controlled trial on periOperative PharmacokineTIc-guided dosing of CLOTting factor concentrate in haemophilia A. *Thromb Haemost*. 2015;114(3):639-644.
36. McGrath RT, McRae E, Smith OP, O'Donnell JS. Platelet von Willebrand factor–structure, function and biological importance. *Br J Haematol*. 2010; 148(6):834-843.
37. McGrath RT, van den Biggelaar M, Byrne B, et al. Altered glycosylation of platelet-derived von Willebrand factor confers resistance to ADAMTS13 proteolysis. *Blood*. 2013;122(25):4107-4110.
38. Castillo R, Escolar G, Monteagudo J, Aznar-Salatti J, Reverter JC, Ordinas A. Hemostasis in patients with severe von Willebrand disease improves after normal platelet transfusion and normalizes with further correction of the plasma defect. *Transfusion*. 1997;37(8):785-790.