Treatment of von Willebrand Disease

Jennifer Curnow, MBBS, FRACP, FRCPA, PhD[1] Leonardo Pasalic, MBBS, FRACP, FRCPA[1,2]
Emmanuel J. Favaloro, PhD, FFSc (RCPA)[1,2]

[1] Departments of Clinical and Laboratory Haematology, Institute of Clinical Pathology and Medical Research and Westmead Hospital, Sydney Centres for Thrombosis and Haemostasis, Westmead, NSW Australia
[2] Pathology West, NSW Health Pathology, Westmead, NSW Australia

Address for correspondence Jennifer Curnow, MBBS, FRACP, FRCPA, PhD, Departments of Clinical and Laboratory Haematology, Institute of Clinical Pathology and Medical Research, Sydney Centres for Thrombosis and Haemostasis, Westmead, NSW 2145, Australia (e-mail: Jennifer.curnow@sydney.edu.au).

Semin Thromb Hemost 2016;42:133–146.

Abstract

Congenital von Willebrand disease (VWD) and acquired von Willebrand syndrome (AVWS) reflect conditions caused by von Willebrand factor (VWF) deficiency and/or defects. VWD is the most common inherited bleeding disorder and AVWS arises from a variety of causes. Since VWF stabilizes and protects factor VIII (FVIII) in the circulation, this is also reduced in many patients with VWD. The treatment of VWD and AVWS therefore primarily entails replacement of VWF, and sometimes FVIII, to protect against bleeding. This may entail the use of VWF concentrates (currently plasma-derived) and/or FVIII concentrates (currently plasma-derived or more increasingly recombinant forms), and/or desmopressin to release endogenous VWF in subgroups of patients. For AVWS additional treatment of the underlying condition is also required. Adjunct therapies include antifibrinolytics. Globally, various formulations exist for both VWF and FVIII concentrates and are differentially available based on manufacturer marketing or regulatory approvals/clearances in different geographies. Also, guidelines for treatment of VWD vary for different localities and recombinant VWF is undergoing clinical trials. The current review provides an overview of the treatment of VWD as currently practiced in developed countries, and also provides a glimpse towards the future.

Keywords
- von Willebrand disease
- VWD
- diagnosis
- management
- factor concentrates
- recombinant VWF
- recombinant FVIII

Disorders of von Willebrand Factor

Acquired von Willebrand syndrome (AVWS) and congenital von Willebrand disease (VWD) are both caused by deficiencies and/or defects in the plasma protein von Willebrand factor (VWF).[1–3] Considered the most common inherited bleeding disorder, the true prevalence of VWD is unknown. Epidemiological studies estimate a value up to 1% of the general population[3]; however, based on clinical presentations of symptomatic patients, a more conservative prevalence would be around 1 in 10,000 (0.01%) of the general population. AVWS arises as an acquired disorder from a variety of causes (►**Table 1**),[4–6] but essentially still manifests clinically as bleeding due to "deficiency of VWF." The true prevalence of AVWS is not known; however, large centers report that AVWS can comprise up to 25% of all diagnosed cases of VWD cases.[6]

von Willebrand Factor: Production and Functional Properties

VWF is a large and complex protein with essential roles in both primary and secondary hemostasis ([1,7,8] for extensive reviews). In vivo biosynthesis of VWF is limited to endothelial cells and megakaryocytes.[9,10] VWF is initially "constructed" as a pre-propolypeptide configuration, comprising a 22 amino acid signal peptide (pre), a 741 amino acids propolypeptide and the remaining mature VWF subunit of 2,050 amino acids. After synthesis in the endoplasmic reticulum of endothelial cells, the signal peptide is cleaved, and oligosaccharide chains are added using N-linked glycosylation. Dimerization of pro-VWF molecules then occurs through "tail-to-tail" intersubunit carboxyl termini disulfide bond formation. The N-linked oligosaccharide chains are further modified in the Golgi apparatus by a series of glycosidases and glycosyltransferases to produce complex type

published online
February 2, 2016

Issue Theme At the Crossroads of Transfusion Medicine and Hemostasis; Guest Editors: Glenn Ramsey, MD, and Hau C. Kwaan, MD.

DOI http://dx.doi.org/10.1055/s-0035-1569070.
ISSN 0094-6176.

Table 1 Main diseases associated with acquired von Willebrand syndrome

Underlying Disorder	Approximate incidence (% of total)
Lymphoproliferative	18–48
Monoclonal gammopathy of undetermined significance	14–23
Multiple myeloma	2–9
M. Waldenström	2–4
Non-Hodgkin lymphoma	4–5
Other (hairy cell leukemia/acute lymphocytic leukemia)	1–2
Myeloproliferative	15–34
Essential thrombocythemia	6–21
Polycythemia vera	1–9
Other (chronic myeloid leukemia/myelofibrosis)	3–8
Neoplasia[a]	1–6
Immune disease[b]	2–6
Cardiovascular	12–41
Aortic stenosis	2–23
Other[c]	10–18
Hypothyroidism	2–8
Other/miscellaneous[d]	5–28

Note: Summarized from Federici et al,[5] as taken from various acquired von Willebrand syndrome registries and published literature.
[a]Wilms tumor, carcinomas, and solid tumors, peripheral neuroectodermal tumor.
[b]Systemic lupus erythematosus, autoimmune disease, mixed connective tissue disease, graft-versus-host disease, Ehlers–Danlos syndrome.
[c]Ventricular septal defect, atrial septal defect, mitral valve prolapse, endocarditis, cardiac assist device, angiodysplasia.
[d]Drug related, infectious diseases, other systemic diseases, idiopathic.

carbohydrates, and additional oligosaccharide chains are added to each VWF monomer. Multimerization of pro-VWF dimers then takes place in the post-Golgi, involving another round of disulfide bond formation near the amino-termini of the subunits. Additional modifications in the trans-Golgi network include the proteolytic removal of the large VWF propeptide, which is known to play an essential role in the multimer assembly (since deletion of the propeptide abolishes multimerization), but which is not required for VWF function in plasma.

Mature VWF then enters the plasma as a series of oligomers containing a variable number of subunits, ranging from a minimum of 2 to a maximum of around 40, with the largest (high molecular weight [HMW]) multimers having molecular weights in excess of 20,000 kDa. The VWF is released from endothelium into the plasma through either a direct constitutive secretory pathway, or tubulized and stored in internal organelles known as Weibel–Palade bodies, to be released later as required.

Upon exocytosis, rapid unfolding of VWF into ultra-long strings occurs, with VWF "docking" on the endothelial cells to permit adhesion to platelets. Thus, VWF stored within Weibel–Palade bodies of endothelial cells is composed of the largest multimeric species, ultra-large VWF (UL-VWF), which are usually not observed in normal plasma because of ADAMTS-13 (a disintegrin-like and metalloprotease with thrombospondin type 1 motif, member 13) cleavage at the time of secretion. Regulated secretion of stored VWF from endothelial cells occurs in response to several physiologically relevant agonists, including histamine and thrombin. VWF multimers and the VWF propeptide are secreted together in 1:1 stoichiometric amounts, but subsequently have different fates; the propeptide dissociates from VWF multimers and circulates independently as a noncovalent homodimer with a very short half-life of approximately 2 hours.

The D'–D3 domains of VWF represent the binding site for factor VIII (FVIII), and mutations in this region can lead to type 2N VWD. The D'–D3 domains are also possible binding sites for P-selectin, which has been determined to anchor newly released ultra-large VWF to the surface of activated endothelial cells and thus present the VWF cleavage site to ADAMTS-13. The A1 domain represents the binding site for the platelet glycoprotein Ib (GPIb) receptor, as well as binding sites for heparin, sulfated glycolipids, the snake venom botrocetin, and some forms of collagen, notably type VI. The A2 domain contains the ADAMTS-13 cleavage site. The A3 domain is the binding site for fibrillar collagen types I and III, and the C1 domain comprises the RGD sequence (Arg-Gly-Asp), being the binding site for the platelet integrin αIIbβ3 (►**Fig. 1**).

In summary, the adhesive protein VWF permits adhesion of platelets to each other and to subendothelial matrix (including collagen) after tissue injury.[1,7,8] Moreover, VWF binds FVIII, thereby protecting it from proteolysis and preserving its hemostatic function. VWF therefore delivers and localizes platelets (containing much procoagulant material) plus FVIII to tissue injury sites, contributing to both primary

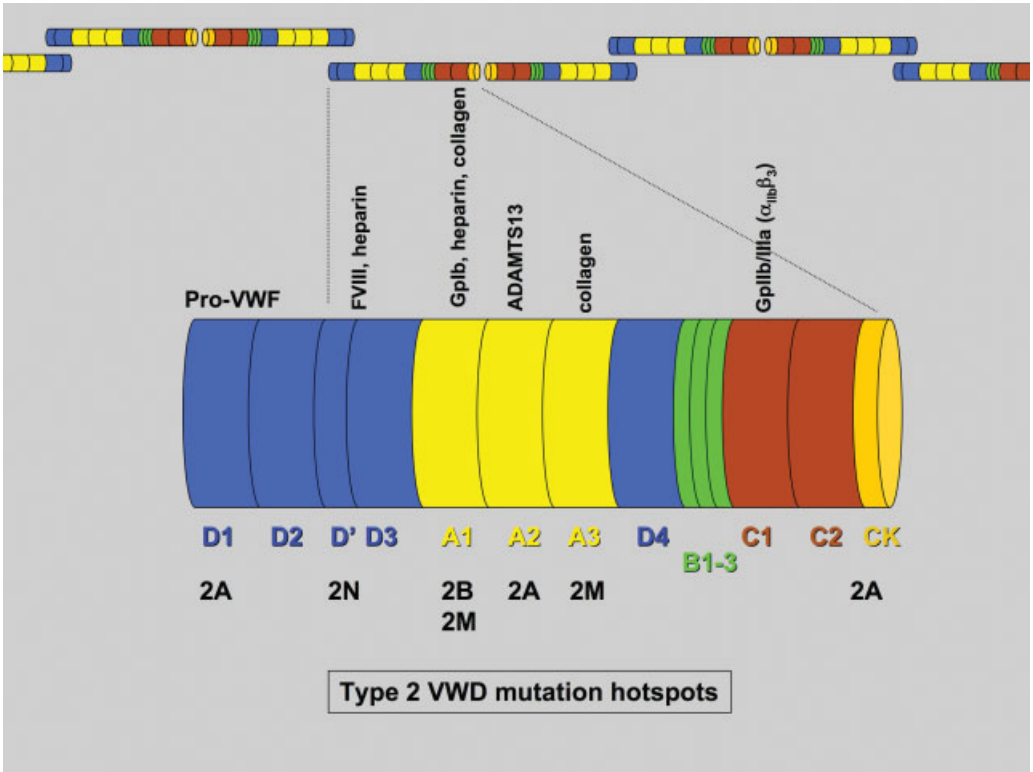

Fig. 1 The structure of von Willebrand factor (VWF). Figure shows the domain structure of VWF, ligand binding sites, plus the ADAMTS-13 cleavage site, as well as formation into dimers and multimers. ADAMTS-13, a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13; VWF, von Willebrand factor.

and secondary hemostasis to promote thrombus formation and facilitate sealing and subsequent repair of the injured site. These functions are achieved because of various ligand-binding sites on VWF, as well as its multimeric structure.

Classification of von Willebrand Disease and Overview of Therapeutic Rationale

A comprehensive review of the differential diagnosis and laboratory testing for VWD and AVWS is beyond the scope of the current review, and has been addressed in considerable detail elsewhere.[1–6,11–17] Nevertheless, an overview is important, since this diagnosis then determines the required and most appropriate therapy. Congenital VWD arises from deficiency and/or defects in VWF, most commonly due to mutation/s in *VWF*, mapped at 12p13.3. VWD diagnosis requires the presence of a personal (typically lifelong) and family history of (primarily) mucocutaneous bleeding, as well as laboratory evidence of absence, deficiency, or defect in VWF.[1–3,13–17] In young patients, historical evidence of "lifelong" bleeding may be limited or absent. Diagnosis of AVWS requires similar evidence of bleeding and lack, deficiency or defect in VWF, but a family history is often absent, and personal history is not typically lifelong.[4–6] AVWS results from a variety of disorders (see ►**Table 1**). Unlike inherited VWD, AVWS is often associated with normal or even increased production of VWF (especially the cardiovascular related disorders). Quantitative deficiencies of VWF are caused by increased clearance of VWF from the circulation, either by immune mechanisms (i.e., autoantibodies) or absorbance onto surfaces of malignant cells or platelets. An exception is hypothyroidism, where VWF production may be compromised. In acquired quantitative deficiencies, the presenting phenotype mimics a type 1 VWD (see below). In other cases, VWS may arise as a qualitative defect, for example, in aortic stenosis (which may induce a selective removal of HMW VWF under high shear stress), and in some plasma cell disorders; these cases phenotypically mimic a type 2A VWD (see below).

According to the current classification scheme,[1] there are six types of VWD (►**Table 2**), characterized on the basis of quantitative deficiencies of VWF (VWD types 1 and 3), or qualitative defects in VWF (type 2 VWD), which may or may not be also associated with a quantitative deficiency of VWF.

Type 1 VWD defines a quantitative deficiency of VWF in which the plasma VWF is otherwise functionally normal, and is the most common form of VWD in developed countries (40–70% of all cases).[3] In normal practice, type 1 VWD is identified by a low level of VWF antigen (VWF:Ag), but with similar levels of functional VWF (usually identified using VWF ristocetin cofactor [VWF:RCo] and collagen binding [VWF:CB]; ►**Table 3**, ►**Fig. 2**). The severity of the bleeding diathesis is directly (although imperfectly) related to the extent of the deficiency. FVIII falls in parallel with VWF, but is normally present at levels higher than VWF. Type 1 VWD may often be effectively treated with desmopressin (1-deamino-8-*d*-arginine vasopressin, DDAVP), which facilitates release of endogenously stored VWF. In cases where DDAVP response

Table 2 Classification scheme for von Willebrand disease, phenotypic presentation, and therapy considerations

VWD type	Description	Incidence	Phenotypic presentation	Therapy considerations
1	Partial quantitative deficiency of VWF	Most common presentation of "VWD" to most laboratories, with most patients presenting with mildly reduced levels of VWF	Low levels of VWF, with VWF functional concordance (i.e., ratio of functional VWF/VWF:Ag approximates unity)	Usually respond well to DDAVP, unless VWF < 10 U/dL. VWF concentrate required for DDAVP nonresponders or for long-term therapy. Need to replace VWF and sometimes also FVIII
2A	Decreased VWF-dependent platelet adhesion and a selective deficiency of HMW VWF multimers	Globally considered to be the most common presentation of type 2 VWD	Loss of HMW VWF. Usually low levels of VWF, with VWF functional discordance (i.e., ratios of RCo/Ag and CB/Ag typically < 0.7)	Variable clinical response to DDAVP. VWF concentrate represents most common therapy. Need to replace (HMW) VWF and sometimes also FVIII
2B	Increased affinity of VWF for platelet glycoprotein 1b	Rare form (generally 10–20%) of type 2 VWD (~1–5 cases per million population). Defined by enhanced responsiveness in a RIPA assay	Low to normal levels of VWF, typically with VWF functional discordance (i.e., ratios of RCo/Ag and CB/Ag generally < 0.7), loss of HMW VWF and (mild) thrombocytopenia. Atypical cases may not show this pattern. Enhanced RIPA responsiveness is characteristic of type 2B VWD	DDAVP use is contentious (believed contraindicated by some; whereas others feel this may represent an effective treatment in a proportion of patients). VWF concentrate represents most common therapy. Need to replace (HMW) VWF and only rarely also FVIII
2M	Decreased VWF-dependent platelet adhesion without a selective deficiency of HMW VWF multimers	Under-recognized form of type 2 VWD. Probably as common as 2A VWD	Low to normal levels of VWF, usually with VWF functional discordance detected by RCo/Ag generally 0.7, but relatively normal CB/Ag ratio. HMW VWF present, but multimers may show other abnormalities	Variable clinical response to DDAVP and VWF concentrate represents most common therapy. Need to replace functional VWF and sometimes also FVIII
2N	Markedly decreased binding affinity for FVIII	Rare form (generally < 10%) of type 2 VWD (~1–5 cases per million population)	Defined by VWF:FVIIIB assay, with low FVIIIB/VWF ratios	Variable clinical response to DDAVP and VWF concentrate represents most common therapy. Need to replace functional VWF and also sometimes FVIII (perhaps at least initially. Once stable infused VWF levels ("steady state") reached, FVIII levels will rise due to stabilization of endogenous FVIII, and FVIII transfusion will no longer be required)
3	Virtually complete deficiency of VWF	Rare form of VWD in developed countries (~1–5 cases per million population), but disproportionately more common in developing countries	Typically defined by VWF levels < 2U/dL and FVIII < 10U/dL	DDAVP ineffective, and VWF concentrate represents only effective therapy. Need to replace VWF and also FVIII, at least initially. Once stable infused VWF levels ("steady state") reached, FVIII levels will rise due to stabilization of endogenous FVIII, and FVIII transfusion will no longer be required

Abbreviations: CB/Ag, collagen binding to antigen ratio; DDAVP, desmopressin; FVIII:C, factor VIII coagulant; HMW, high molecular weight; LOD, limit of detection; RCo/Ag, ristocetin cofactor to antigen ratio; RIPA, ristocetin induced platelet agglutination (/aggregation); VWD, von Willebrand disease; VWF, von Willebrand factor; VWF:Ag, von Willebrand factor antigen; VWF:CB, von Willebrand factor collagen binding; VWF:FVIIIB, VWF FVIII binding assay; VWF:RCo, von Willebrand factor ristocetin cofactor.
Note: Classification scheme derived and adapted from Sadler et al, 2006.[1] Table modified from Favaloro et al, 2012.[12]

Table 3 A practical guide to current identification of VWD and VWD type

VWD type	VWF:Ag	VWF:RCo[a]	VWF:CB	FVIII:C	Multimers	RCo/Ag[a]	CB/Ag[a]	FVIII/VWF[a]	Comments/additional testing[b]
1	↓ to ↓↓	↓ to ↓↓	↓ to ↓↓	N to ↓↓	Normal pattern but reduced intensity	Normal	Normal	Normal	VWF levels between ~30 and 50 U/dL will generally not be associated with *VWF* mutations and may be considered as representing "low" VWF as a risk factor for bleeding. VWF levels below ~30 U/dL will often be associated with *VWF* mutations and can be considered as representing "true" VWD
2A	↓ to ↓↓	↓↓ to ↓↓↓	↓↓ to ↓↓↓	↓ to ↓↓	Loss of HMW VWF	Low	Low	Normal	2A and 2B VWD can only be distinguished by means of RIPA. Platelet type (PT-) VWD phenotypically resembles 2B VWD; these can be distinguished by means of RIPA mixing studies, or by genetic analysis of *VWF* and/or platelet *GPIb*
2B	N to ↓↓	↓ to ↓↓↓	↓ to ↓↓↓	N to ↓↓	Loss of HMW VWF	Low	Low	Normal	
2N	N to ↓↓	N to ↓↓	N to ↓↓	↓↓to ↓↓↓	Normal pattern	normal	normal	low	Phenotypically similar to hemophilia A; distinguish using VWF:FVIII binding assay or genetic analysis of *FVIII* and/or *VWF*
2M	↓ to ↓↓	↓ to ↓↓↓	↓ to ↓↓↓	↓ to ↓↓	No loss of HMW VWF; some multimer defects may be present	Low (platelet binding defect) or normal (collagen binding defect)	Low (collagen binding defect) or normal (platelet binding defect)	Normal	2A and 2M VWD can only be distinguished by comprehensive or composite panel testing, including VWF:Ag, VWF:RCo (or GPIb binding assay), *plus* VWF:CB or multimer analysis
3	↓↓↓ (Absent)	↓↓↓ (Absent)	↓↓↓ (Absent)	↓↓↓	No VWF present	NA	NA	NA	Type 3 VWD can only be identified when VWF tests are performed and these are sensitive to very low levels of VWF

Abbreviations: Ag, antigen; CB, collagen binding; FVIII, factor VIIII; GPIb, glycoprotein Ib (the platelet VWF receptor); HMW, high molecular weight (VWF); N, normal; NA, not applicable; RCo, ristocetin cofactor; RIPA, ristocetin induced platelet aggregation; VWD, von Willebrand disease; VWF, von Willebrand factor.

[a]VWF GPIb binding assays (including the Siemens (Marburg, Germany) "Innovance" VWF Ac assay) will provide results that will most closely match VWF:RCo. Monoclonal antibody-based "activity" assays will also often match, but there will be some significant discrepancies. Low assay ratios are generally identified as $<$ (0.5–0.7), with the actual value depending on the locally established cutoff; normal assay ratios are generally identified as $>$ (0.5–0.7), again depending on the locally established cutoff.

[b]Units: U/mL, U/dL, %, IU/mL, and IU/dL may alternatively be used as units for VWF and FVIII:C in various publications. Australia and the United States tend to use % or U/dL, but some hemophilia centers report FVIII in U/mL.

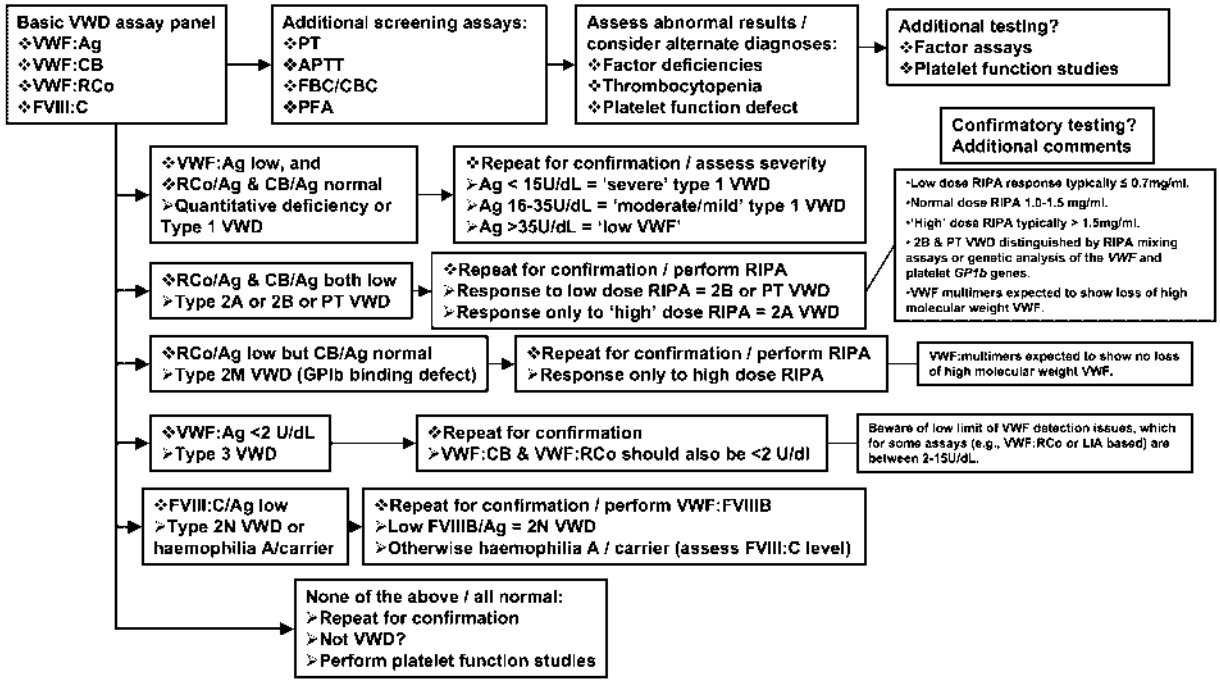

Fig. 2 Current algorithmic approach to diagnosis or exclusion of VWD at our institution. Alternative algorithms and diagnostic approaches with a more North American-based focus exist in the literature (e.g., see Ng et al[14] and Lillicrap[15]). In our institution, the VWF:CB is used as an additional VWF functional assay to VWF:RCo, and also as a surrogate marker for presence/absence of HMW VWF (NB: low CB/Ag plus low RCo/Ag ratio = loss of HMW VWF = 2A, 2B or PT VWD; low RCo/Ag ratio with normal CB/Ag ratio = no loss of HMW VWF but likely VWF dysfunction = 2M VWD). Ag, von Willebrand factor antigen result; APTT, activated partial thromboplastin time; CB/Ag, ratio of VWF:CB to VWF:Ag; FBC/CBC, full/complete blood count; FVIIIB, level of factor VIII bound in a von Willebrand factor–FVIII binding assay; FVIII:C, factor VIII coagulant; PFA, platelet function analyzer (-100, or -200); PT, prothrombin time; PT-VWD, platelet-type VWD; RCo/Ag, ratio of VWF:RCo to VWF:Ag; RIPA, ristocetin-induced platelet agglutination assay; VWD, von Willebrand disease/disorder; VWF, von Willebrand factor; VWF:Ag, von Willebrand factor antigen (assay); VWF:CB, von Willebrand factor collagen binding (assay); VWF:FVIIIB, von Willebrand factor–FVIII binding assay; VWF:RCo, von Willebrand factor ristocetin cofactor (assay).

is inadequate or contraindicated, treatment entails replacing the missing VWF, and if required also the FVIII, aiming to increase levels to normal. This is currently largely achieved using VWF concentrate therapy, typically also containing FVIII (►**Tables 4** and **5**).

Type 3 VWD defines the most severe defect, essentially describing an absence of VWF and representing a rare form of VWD in developed countries (< 5% of all VWD cases). In normal practice, type 3 VWD is identified by a low level of VWF:Ag < 2 to 5U/dL (depending on assay sensitivity limits; ►**Table 3**, ►**Fig. 2**). Treatment is based on replacing the missing VWF, aiming to increase levels to normal, but here there is a need to replace both VWF and also (at least initially) FVIII, although the latter would ideally be tapered off or omitted once the exogenously provided VWF binds to and protects the patient's endogenously produced FVIII. This typically occurs within approximately 24 hours of treatment. Continued infusion of FVIII after this time may produce undesirably high levels and potentially increase the risk of thrombosis (see section "Excess of von Willebrand factor and FVIII is associated with thrombosis"). DDAVP is ineffective in type 3 VWD patients (►**Table 4**).

In type 2 VWD patients, characterized by various qualitative defects of VWF, the level of VWF protein may be normal or reduced, and FVIII levels may also be low or normal. Type 2A VWD describes an absence or deficiency in HMW VWF,[1] the form of VWF that is most biologically active. Type 2A VWD is classically considered the most common form of type 2 VWD, although type 2M VWD may be as common.[3] Type 2A VWD is identified by loss of HMW VWF on multimer analysis or by low RCo/Ag and CB/Ag ratios (►**Table 3**, ►**Fig. 2**). Replacement therapy ("treatment") aims to provide functionally normal VWF. In cases where FVIII is deficient, this will need to be replaced also. DDAVP is only effective in a proportion of type 2 VWD patients (►**Table 4**).

Type 2B VWD describes patients in which VWF is hyperadhesive,[1] which is then cleared from the circulation with "spontaneously" bound platelets, leading to a loss of HMW VWF, and also sometimes (mild) thrombocytopenia. Type 2B VWD is identified by elevated response to ristocetin in a ristocetin-induced platelet aggregation (RIPA) assay, and in general these patients also present with reduced HMW VWF and thus low RCo/Ag and CB/Ag ratios (►**Table 3**, ►**Fig. 2**). Type 2B VWD is a relatively rare form of type 2 VWD, affecting < 5% of all VWD patients.[3] Replacement therapy aims to provide functionally normal VWF. FVIII levels in type 2B VWD are often normal, although they can be low in some patients, so selective FVIII replacement may be required in only a minority of patients. DDAVP is considered contraindicated in these patients by many clinicians, although others suggest this is a safe treatment for some patients (►**Table 4**).[18,19]

Table 4 A summary of major current therapies for congenital VWD and AVWS

Congenital VWD	Main therapies	Additional therapies
Type 1	DDAVP; VWF(/FVIII) concentrate	Antifibrinolytic therapy (e.g., tranexamic acid and aminocaproic acid; used for less severe forms of mucosal bleeding, menorrhagia, epistaxis, dental procedures), hormonal treatments (effectively helps manage menorrhagia in some cases)
Type 2A	VWF(/FVIII) concentrate; DDAVP	
Type 2B	VWF(/FVIII) concentrate; (DDAVP)	
Type 2M	VWF(/FVIII) concentrate; DDAVP	
Type 2N	VWF(/FVIII) concentrate; DDAVP	
Type 3	VWF(/FVIII) concentrate	
AVWS	As per congenital VWD, plus:	Intravenous immunoglobulins (may be effective in AVWS associated with lymphoproliferative disorders and IgG monoclonal gammopathies)
	Treatment for primary disorder	
	Eradication of inhibitors if present	

Abbreviations: AVWS, acquired von Willebrand syndrome; DDAVP, desmopressin; FVIII, factor VIII; VWF, von Willebrand factor.
Notes: Table modified from Favaloro et al, 2012.[12]
VWD: DDAVP is favored as main therapy for type 1 VWD, with factor concentrate used where DDAVP is ineffective or insufficiently effective for need on a case-by-case basis. DDAVP can also be trialed for types 2A, 2M, and 2N VWD; however, DDAVP will likely be insufficiently effective for most cases, and hence VWF (/FVIII) concentrates will usually be required. VWF (/FVIII) concentrates provide the main form of therapy in type 2B VWD; some experts consider DDAVP to be contraindicated whereas others consider this to provide an efficacious therapy in some cases. VWF (/FVIII) concentrates provide the main form of therapy in type 3 VWD; DDAVP is ineffective.
AVWS: Therapy for bleeding issues is similar to that of VWD. Thus, for (a) type 1 VWD-like cases, DDAVP is favored as main therapy with factor concentrate used where DDAVP is ineffective or insufficiently effective for need; (b) type 2A VWD-like cases, DDAVP can be trialed, but will likely be insufficiently effective for most cases, and hence factor concentrates will usually be required. In AVWS, there is a requirement also to treat the underlying primary disorder, and to eliminate inhibitors if these are present.
General: Additional therapies for either VWD or AVWS may be applied in distinct geographies (e.g., developing countries), based on nonavailability of main treatments such as DDAVP and/or VWF (/FVIII) concentrates.

Table 5 A summary of some currently available VWF/FVIII concentrates—some similarities and some differences

Concentrate	Biostate[a]	Haemate P/humate-P[b]	Alphanate[c]	Fanhdi[d]	Immunate[e]	Wilate[f]	Wilfactin[g]	Factor 8Y[h]	Range
HMWM VWF (% of NHP)	86	93.6	29.3	31.7	3.9	N/A	N/A	32.1	4–94
VWF:RCo/ VWF:Ag	0.73–0.99	0.91	0.43	0.69	0.38	0.9–1.0	0.95	0.6	0.4–1.0
VWF:CB/ VWF:Ag	0.72–0.95	0.89	0.49	0.47	0.21	N/A	N/A	N/A	0.2–1.0
VWF:RCo/ FVIII:C	2.00	2.88	0.82	1.29	0.67	1.0	> 10	1.8	0.7–> 10
VWF:CB/ FVIII:C	2.53	2.28	0.68	0.80	0.16	N/A	N/A	N/A	0.2–2.5

Abbreviations: FVIII:C, factor VIII coagulant activity: HMW, high molecular weight; N/A, not available; NHP, normal human plasma; VWF, von Willebrand factor; VWF:Ag, von Willebrand factor antigen; VWF:CB, von Willebrand factor collagen binding assay; VWF:RCo, von Willebrand factor ristocetin cofactor assay.
Note: Data collated from various references.[36–45]
[a]CSL Behring, Melbourne, Australia.
[b]CSL Behring, King of Prussia, PA.
[c]Grifols, Los Angeles, CA.
[d]Grifols, Cambridgeshire, United Kingdom.
[e]Baxter AG, Vienna, Austria.
[f]Octapharma, Hoboken, NJ.
[g]LFB, Les Ulis, France.
[h]BioProducts Laboratory, Hertfordshire, United Kingdom.

Type 2N VWD reflects a defect in VWF that does not permit proper binding to FVIII[1] and is a relatively rare form of type 2 VWD, anticipated to affect $< 5\%$ of all VWD cases.[3] Like type 3 VWD, this leads to early proteolysis and loss of plasma FVIII, with consequent bleeding symptoms similar to those of hemophilia A. In normal practice, 2N VWD is identified using a VWF:FVIII binding assay or by genetic analysis of *VWF*, although these patients may be identified earlier because of reduced FVIII:C/VWF:Ag ratios (►**Table 3**, ►**Fig. 2**). Replacement therapy ("treatment") still aims to replace VWF (rather

than FVIII), because therapy with FVIII only provides short-term benefit (the replaced FVIII is rapidly degraded), whereas the replaced VWF binds to and protects the patient's endogenously produced (normal) FVIII. FVIII therapy may be needed initially in some patients, where low levels of FVIII are expressed; but could be omitted in subsequent infusions as exogenously provided VWF stabilizes endogenously produced FVIII and plasma FVIII levels become normal. DDAVP is only effective in some of these patients (►**Table 4**).

Type 2M VWD describes various qualitative defects not associated with loss of HMW VWF.[1] Although classically considered a rare form of VWD, many cases of type 2M have been inappropriately misidentified as type 1 or 2A VWD,[3] and so type 2M VWD is often misdiagnosed and may be as common as type 2A VWD. In normal practice, 2M VWD is generally identified by the combination of low RCo/Ag ratios but normal CB/Ag ratios, or low RCo/Ag but no loss of HMW VWF on multimer gels (►**Table 3**, ►**Fig. 2**). Treatment in 2M VWD aims to replace the dysfunctional VWF. Since FVIII levels may be low or normal its replacement needs to be individualized. DDAVP is only effective in a proportion of these patients (►**Table 4**). In practice, the current therapy applied to 2A and 2M VWD is virtually identical.

Platelet type (PT-) VWD is not considered a true VWD, since the defect lies in platelet GPIb, which is the platelet VWF receptor. While the laboratory phenotype of PT-VWD essentially mimics 2B VWD, including enhanced binding in a RIPA assay, in PT-VWD the enhanced binding is due to the hyperadhesive GPIb receptor, whereas for 2B VWD it due to hyperadhesive VWF. Distinguishing between these disorders may be possible with a RIPA mixing assay but a definitive diagnosis of PT-VWD requires demonstration of a mutation within the platelet *GP1BA* gene.[20,21] PT-VWD is a rare disorder that occurs at the rate of approximately 10% that of type 2B VWD.[3] Importantly, PT-VWD requires a different therapeutic management, based on platelet replacement rather than replacing VWF, which is already normal in these patients.[20,21]

Why do Patients with von Willebrand Disease/ Acquired von Willebrand Syndrome Bleed?

As overview, the presenting hemorrhagic diathesis of VWF disorders is related to the degree of VWF deficiency, the type of VWF defect, and/or the severity of the VWF defect. For example, in the most severe case of deficiency (i.e., type 3 VWD), there is a complete absence of VWF.[1,2] In terms of primary hemostasis, bleeding in VWD is typically of mucocutaneous type (i.e., menorrhagia, epistaxis, oral cavity or gastrointestinal bleeding, etc.), reflecting VWF's adhesive functions (platelets, subendothelial matrix) discussed above. However, because VWF is missing, the normally produced plasma FVIII cannot be protected against proteolysis and is also largely absent. Thus, the coassociated deficiency of FVIII will also contribute to bleeding events that are more typical of a secondary hemostatic defect such as hemophilia A (i.e., muscular hematomas, hemarthroses, postsurgical bleeding from large wounds, etc.). Treatment would therefore intend to replace both missing components (VWF and FVIII).

Type 1 VWD, which is characterized by a quantitative loss of VWF, may lead to a relative reduction in FVIII, although some patients will have normal levels of FVIII. In other cases of VWD, abnormalities in VWF may be localized within discrete sections of the molecule and cause more specific problems.[1,2,22] A specific defect may, for example, affect the ability of VWF to bind to platelets, whereas other abnormalities may impair the ability of VWF to bind to subendothelial matrix components such as collagen. These cases are mostly represented by types 2A and 2M VWD. In both cases, there is a failure or reduction in the ability of platelets to effectively bind to injured tissue, and thus thrombus formation is compromised to varying extents. In many of these patients, the level of FVIII is normal, and thus therapy should in general aim to only correct the missing functional VWF. Another form of VWD is type 2N VWD, which describes a specific VWF defect where binding to FVIII is impaired. In these patients, like type 3 VWD, plasma FVIII remains "unprotected" and vulnerable to early proteolysis, so that the bleeding symptoms actually mimic those of hemophilia A. However, VWF levels and other VWF functions are often preserved in type 2N VWD, hence mucocutaneous bleeding is less common, and the therapy should mainly address the missing FVIII, due to the VWF defect.

Therefore, the variability in clinical bleeding phenotype is influenced by the type of VWD.

Limitations of Current Treatment Options

Currently available biological therapies contain both plasma-derived VWF and FVIII concentrates (albeit with variable proportion of VWF/FVIII) and thus represent a "one-size fits all" approach to VWD treatment. Thus, although VWD/AVWS may present in different ways, as deficiency and/or (specific) defect in VWF, sometimes with and at other times without FVIII deficiency, standard treatment would currently still entail use of the same VWF(FVIII) concentrate for all presentations, and use of different concentrates in different geographic locations. This is explored in greater detail in the section "Current Biological VWF Concentrate Therapies for von Willebrand Disease."

Excess of von Willebrand Factor and Factor VIII is Associated with Thrombosis

The other side of the hemostasis coin in VWD (deficiency of VWF) is the potential for thrombosis when excess VWF and/or FVIII are present. In normal individuals, the levels of plasma VWF and FVIII are regulated to within a tight physiological range. When levels fall below this range there is a risk of bleeding (e.g., VWD or hemophilia A), and when levels are above this range there is a risk of thrombosis. The risk of thrombosis can occur when FVIII or VWF levels are high, or when there is specific excess of HMW VWF forms; the latter is represented by congenital (Upshaw–Schulman syndrome) or acquired forms of thrombotic thrombocytopenic purpura,

caused by a deficiency of, or antibodies to, ADAMTS-13.[23–27] As noted in the previous section "von Willebrand factor: production and functional properties," ADAMTS-13 cleaves HWW VWF during secretion or at sites of vascular attachment, and this normally prevents downstream accumulation of the very adhesive (ultra-large) UL-VWF multimers. Thrombosis may alternatively occur due to overaccumulation of VWF or FVIII, and this may occur in normal individuals or in VWD/AVWS treatment as a consequence of VWF/FVIII replacement therapy.[28,29] However, only two venous thrombotic events and five episodes of superficial thrombophlebitis were reported in a systematic review of prospective studies involving over 8,000 concentrate infusions in 361 VWD patients, suggesting the absolute thrombotic risk to an individual requiring replacement therapy is low.[30]

Current Therapies for von Willebrand Disease

Desmopressin Therapy

DDAVP is most commonly administered intravenously, although a subcutaneous preparation is available outside the United States.[2] Intranasal preparations vary in concentration and not all are available widely. Stimate (CSL Behring LLC, Kiel, Germany) (1.5 mg/mL solution) is available in the United States and Europe and contains 150 µg DDAVP per puff. An individual who is responsive to intravenously administered DDAVP should be tested for response to the nasal preparation before using it. A lower dose preparation (10 µg DDAVP per puff) is used for enuresis and patients should ensure they have the more concentrated preparation for VWD treatment).[2]

Administration of DDAVP triggers release of VWF and FVIII from endothelial cells.[31,32] Cellular VWF is usually normal in type 1 VWD and thus the majority of these patients demonstrate an increase in VWF levels of sufficient magnitude and duration to recommend DDAVP as first-line therapy for minor surgery and bleeding.[31,32] Furthermore, the response pattern is consistent within families, so that a parent's response may be used to predict that of an affected child. In type 2 VWD, responses to DDAVP are highly variable but generally better in type 2M than 2A.[33] Type 2N patients may show a short-lived response to DDAVP, and DDAVP is generally considered contraindicated in type 2B VWD since release of additional abnormal VWF with enhanced affinity for the GPIb receptor leads to thrombocytopenia and there is concern this may increase the bleeding risk.[32]

To determine an individual's pattern of response to DDAVP, an infusion of a test dose of 0.3 µg/kg in 50 mL normal saline administered intravenously over 30 minutes is assessed by performing preinfusion testing of FVIII:C, VWF:Ag, and VWF:RCo (and in our laboratory also VWF:CB and if indicated PFA-100 closure time) and repeat testing at 1 , 2 and/or 4 hours, and finally 24 hours postinfusion. "Responders" (patients who are classified as having a sufficient response to DDAVP) show a two to fivefold increase from baseline and have VWF and FVIII:C levels above 50 U/dL at 1 hour. Levels remain above 30 U/dL by 4 hours postinfusion unless VWF and/or FVIII clearance is significantly increased, but by 24 hours levels generally return to baseline.[2,31] Doses may be repeated for up to 72 hours but responses diminish due to depletion of VWF stores, described as tachyphylaxis. In our laboratory, a DDAVP response profile can also have diagnostic and VWD typing utility, by firming up a diagnosis/VWD type in a patient with otherwise unclear diagnosis.[34,35]

Adverse effects of DDAVP infusion include facial flushing, hypertension or hypotension, tachycardia, headache, gastrointestinal upset, and hyponatremia, rarely complicated by seizures. Myocardial infarction has rarely been reported and thus DDAVP should be avoided in patients with increased risk for cardiovascular and cerebrovascular disease.[2] Fluid restriction and monitoring of electrolytes is recommended when repeat doses are used.

In women with menorrhagia, DDAVP may be self-administered by subcutaneous injection at the onset of menses or via an intranasal spray; however, large doses of the intranasal formulations may be necessary to achieve a response.[31] In women with type 1 VWD there is a two to threefold rise in FVIII and VWF levels during the second and third trimesters of pregnancy. If levels are above 50 U/dL, then no antenatal intervention is required and spinal or epidural anesthesia is considered safe.[31] Levels return to baseline by 7 to 21 days postpartum but may fall more rapidly in some cases and consequently the risk of postpartum hemorrhage (PPH), including delayed PPH, is 30% (sixfold higher than the general population). DDAVP may be administered at parturition after section of the umbilical cord and for up to 2 days postpartum to reduce this risk but its use during pregnancy, although not absolutely contraindicated, is often avoided due to limited safety data.[2]

While DDAVP is an affordable therapeutic option and should be utilized, VWF concentrates are required in circumstances where DDAVP is ineffective, response is inadequate, or its use is contraindicated.

Current Biological von Willebrand Factor Concentrate Therapies for von Willebrand Disease

A wide range of VWF concentrates are currently available worldwide (summarized in ►**Table 5**).[36–45] There are several expert and national guidelines or recommendations for VWD treatment (►**Table 6**).[2,12,46–49] There are additional differential global features worth noting.[12] First, most plasma-derived concentrates contain *both* VWF and FVIII, although they differ in terms of relative proportions (►**Table 5**); this has important implications for therapeutic management. Some concentrates have relatively high, and others relatively low, proportional levels of FVIII, and few concentrates are essentially FVIII deficient, or only contain VWF. Second, production techniques for VWF concentrates vary, so that the retention or loss of HMW VWF also varies. As HMW VWF forms are the most adhesive or functional forms of VWF, a concentrate containing HMW VWF would provide greater adhesive hemostatic efficacy than one relatively devoid of HMW VWF. Surrogate markers are used for laboratory testing of concentrates such as VWF ristocetin cofactor and/or collagen binding to antigen (RCo/Ag or CB/Ag) ratios, to provide an

Table 6 Recommendations/guidelines for treatment of VWD with VWF/FVIII concentrates

Table 6A Guidelines from the United States (NHLBI expert panel)[2]

	Loading dose[a]	Maintenance dose	Monitoring	Therapeutic goal	Safety parameter	Comments
Major surgery/ bleeding	40–60 U/kg	20–40 U/kg every 8–24 h	VWF:RCo and FVIII trough and peak, at least daily	Trough VWF: RCo and FVIII > 50 IU/dL for 7–14 d	Do not exceed VWF:RCo 200 IU/dL or FVIII 250–300 IU/dL	May alternate with DDAVP for latter part of treatment
Minor surgery/ bleeding	30–60 U/kg	20–40 U/kg every 12–48 h	VWF:RCo and FVIII trough and peak, at least once	Trough VWF: RCo and FVIII > 50 IU/dL for 3–5 d		

Abbreviations: FVIII, factor VIII; VWF:RCo, von Willebrand factor ristocetin cofactor activity.
[a]Loading dose is in VWF:RCo IU/dL.

Table 6B Some recommendations from the Netherlands[47]

Indication	Dose in IU FVIII/kg[a]	Frequency of infusions	Target plasma levels
Mild mucocutaneous bleeding (epistaxis/oral cavity)	20	Usually single dose	
Spontaneous or traumatic bleeding	20–40	Usually single dose	
Dental extraction	20–40	Single dose plus tranexamic acid	FVIII:C and VWF:RCo > 50 IU/dL
Surgery			Before surgery and 36 hours postsurgery FVIII:C and VWF:RCo > 80 IU/dL
Major surgery	50	Twice daily 25 IU FVIII/kg, based on FVIII:C levels	FVIII:C 50 IU/dL for 7–10 d
Minor surgery	30–50	Twice daily 15–25 IU FVIII/kg, based on FVIII:C levels	FVIII:C > 50 IU/dL for 3 d and 30 IU/dL for additional 4–7 d

Abbreviations: FVIII, factor VIII; FVIII:C, factor VIII coagulant; VWF:RCo, von Willebrand factor ristocetin cofactor activity.
[a]Dose is irrespective of patients' own FVIII:C levels and based on usage of haemate-P. Note that dosage based on FVIII will differ according to the concentration used.

Table 6C Some recommendations from Italy[48]

Indication	Dose[a] of VWF: RCo (IU/kg)	Number of infusions	Target plasma VWF: RCo level
Major surgery	40–60	Daily until healing is complete	50–100 U/dL; maintain levels for 5–10 d
Minor surgery	30–50	Daily until healing is complete	> 30 U/dL; maintain levels for 2–4 d
Dental extraction	20–30	Single dose before procedure	> 30 U/dL for > 12 h
Spontaneous bleeding	20–60	Daily until bleeding stops (usually 2–4 d)	> 30 U/dL
Delivery	40–50	Daily before delivery and in the postpartum period	> 50 U/dL; maintain levels for 3–4 d

Abbreviations: VWD, von Willebrand disease; VWF:RCo, von Willebrand factor ristocetin cofactor activity.
[a]These dosages are indicated for VWD patients with severely reduced VWF:RCo levels (less than 10 U/dL).

Table 6D Our local practice based on a phase II/III Australian and New Zealand study[49]

Indication	Dose[a] of VWF:RCo (IU/kg)	Number of infusions	Target plasma VWF:RCo level
Type 1 VWD major surgery or hemorrhage	Loading dose 40, then 40–50	Every 8–12 h for 3 d then daily for up to 7 d	> 50 U/dL; maintain levels for 7–10 d
Type 1 VWD minor surgery or hemorrhage	40–50	1 or 2 doses	> 30 U/dL; maintain levels for 2–4 d
Type 2 or 3 VWD major surgery or hemorrhage	Loading dose 50–60 then 40–60	Every 8–12 h for 3 d then daily for up to 7 d	> 50 U/dL; maintain levels for 7–10 d
Type 2 or 3 VWD minor surgery or hemorrhage	40–50	1 or 2 doses	> 30 U/dL; maintain levels for 2–4 d

Abbreviations: FVIII, factor VIII; VWF, von Willebrand factor; VWF:RCo, von Willebrand factor ristocetin cofactor activity.
[a]Units: U/mL, U/dL, %, IU/mL, and IU/dL may alternatively be used as units for VWF and FVIII:C in various publications. Australia and the United States tend to use % or U/dL, but some hemophilia centers report FVIII in U/mL.

estimate of the level of "specific" VWF activity (►**Table 5**). Third, the type and extent of postproduction concentrate treatment for removal and destruction of potentially infectious agents such as human immunodeficiency virus or hepatitis viruses, also differs.[37] Fourth, although VWF concentrates are used for VWF replacement and treatment of VWD/AVWS, some are only labeled with FVIII levels, and/or dosed according to the level of FVIII and/or monitored by FVIII:C testing, perhaps reflecting regulatory restrictions preventing labeling of products with newer VWF activity levels.[12] Nevertheless, as different concentrates vary widely in terms of relative VWF and FVIII level, dosing VWD patients by concentrate FVIII level is not ideal, and potentially hazardous if applied inappropriately (►**Table 5**).[12]

Concentrates are given intravenously, to treat or prevent bleeds, and efficacy is monitored clinically and by laboratory testing using the same tests as used for VWD diagnosis.[1–3] Importantly, current therapy would entail the use of the same locally available VWF concentrate, most usually containing FVIII, for *all* forms of VWD/AVWS, irrespective of the type of disorder, the underlying VWF defect or VWF/FVIII deficiency, and the period of treatment.

Our own treatment protocol is identified in ►**Table 6**, in comparison with several guidelines. Our treatment protocol is based on a phase II/III open-label multicenter study conducted in Australia and New Zealand utilizing Biostate (CSL Behring, Melbourne, Australia), a double virus inactivated plasma-derived product in which HMW VWF multimers are retained and the FVIII:C to VWF:RCo ratio is 1:2.[49] The product and regimen selected was safe and efficacious for achieving hemostasis in patients with acute bleeds and undergoing surgical procedures. Both FVIII:C and VWF:RCo levels were measured to assess the adequacy of replacement therapy.

Pharmacokinetic studies may be used to fine tune individual therapy. Laboratory tests for VWF:RCo and VWF:CB may be more meaningful measures of the efficacy of replacement therapies but are not always as readily available as FVIII:C levels.[13] In fact, not all plasma-derived products are labeled with VWF activity due to local regulatory restrictions, even though they may be used for VWD.

Newer Biological Therapies

The development of recombinant human VWF (rVWF) may overcome limitations of plasma-derived products including the availability of plasma donors, potential for viral transmission, variable product composition (including deficiency of HMW VWF multimers in some), and allergic reactions associated with extraneous plasma proteins. Vonicog alfa is a rVWF product synthesized in a Chinese hamster ovary cell line and has recently been tested in two clinical trials in patients with severe VWD.[50,51] Mannucci et al conducted a phase I study dose escalation study including a pharmacokinetics (PK) cohort in which a blinded dual crossover design was utilized to compare a single 50 IU/kg dose of rVWF–rFVIII in a 1.3:1 ratio with a plasma-derived concentrate containing both VWF and FVIII (Humate P/Haemate P (CSL Behring, King of Prussia, PA)).[50] The rVWF appeared safe with no anaphylaxis, no thrombotic events and no inhibitor development. Endogenous ADAMTS-13 was able to proteolyse the UL-VWF multimers of rVWF. Minor adverse events of tremor, pruritus, psychomotor hyperactivity, hypertension, nausea, dizziness, and variable sP-selectin values were noted. The PK profiles for the comparator products were similar although rVWF appeared to show enhanced stabilization of endogenous FVIII and a longer terminal half-life. Gill et al[51] have recently reported results of a phase III study of the safety, efficacy and PK of rVWF with or without rFVIII for the treatment of clinical bleeding. All bleeding episodes were successfully treated and a single infusion was sufficient in 81.8% of the cases. Safety findings were similar to the phase I study. There was no difference in PK results for 50 or 80 IU/kg doses. The mean terminal half-lives of rVWF alone (21.9 hours) or with rFVIII (19.6 hours) were longer than published half-lives for plasma-derived products (12–16 hours).[37] Endogenous FVIII was stabilized for a prolonged period indicating that rFVIII infusions may not be required after a first dose. These data support the hypothesis that it may be possible to titrate rVWF and rFVIII infusions separately and thus individualize therapy.

Prophylaxis in von Willebrand Disease

Although prophylaxis with recombinant products is the standard of care for severe hemophilia in countries without

resource limitations, prophylaxis is used relatively infrequently in severe VWD. It is routinely used short-term in the postpartum period for women with severe VWD.[2] Long-term secondary prophylaxis may be commenced in patients with recurrent spontaneous bleeding, in particular haemarthroses.[52] A retrospective study from the VWD prophylaxis network demonstrated its efficacy with reduced annualized bleeding rates but cost-effectiveness has not been established and prospective studies are required.[52]

Antifibrinolytics and Other Adjunctive Therapies

Antifibrinolytic agents impair fibrinolysis by inhibition of plasmin generation and are useful adjunctive therapies in VWD, particularly for mucocutaneous bleeding.[2] Tranexamic acid (10–15 mg/kg) or aminocaproic acid (50–60 mg/kg) may be given orally or intravenously, every 8 hours for up to 7 days. Dose adjustment is necessary for significant renal impairment. Adverse effects include nausea, vomiting, and rarely thrombotic events. These antifibrinolytic agents are relatively contraindicated in disseminated intravascular coagulation and bleeding from the renal tract due to the respective risks of renovascular thrombi and renal tract obstruction by clots.[2]

In women with excessive menstrual bleeding other beneficial adjunctive therapies include use of an oral contraceptive agent or the Mirena (Bayer Healthcare Pharmaceuticals Inc., Whippany, NJ), a levonorgestrel-releasing intrauterine device.[53] Iron therapy may be necessary to optimize iron stores in the setting of chronic menorrhagia and to prevent onset of iron deficiency anemia. Aspirin and nonsteroidal anti-inflammatory agents should not be used for dysmenorrhea often associated with increased blood loss and should be avoided in all patients with VWD since these agents impair platelet function worsening the defect in primary hemostasis.

Occasionally the transfusion of platelets from a donor with normal platelet content of VWF may be beneficial if bleeding persists despite adequate VWF replacement therapy.[54] Topical thrombin (usually available as a bovine source) may be of benefit for minor wound bleeding and fibrin sealants have been used as an adjunct for dental therapies.[2] In case reports, inhibition of angiogenesis by thalidomide has been reported to reduce refractory angiodysplasia-related bleeding and thus may have a role when these conditions are associated with AVWS.[55] Most patients required a dose of at least 100 mg daily over a minimum of 4 months.

Additional Treatment of Acquired von Willebrand Syndrome

Treatment of AVWS requires management of bleeding and therapy directed toward the underlying disease. The therapies discussed above may be utilized for bleeding; however, if the mechanism of AVWS is increased VWF clearance, then the half-life of replacement therapies may be very short.[6] Both the doses of VWF concentrate administered and the dosing interval will need to be adjusted according to individual clinical response and measured VWF activity. An international registry has reported that some patients benefit from intravenous immunoglobulin (1 g/kg for 2 days), plasmapheresis, corticosteroids, or immunosuppression.[56] If bleeding remains uncontrolled, then consideration should be given to the use of recombinant FVIIa (90 µg/kg IV) which has shown efficacy in patients with alloantibodies.[57]

Once the underlying cause of AVWS is established, then specific therapy may be effective and induce remission. For example, hypothyroidism may be simply managed with replacement therapy; however, malignant diseases including myeloproliferative neoplasms and lymphoproliferative disorders usually require chemotherapy. Autoimmune conditions may require specific immunosuppression and cardiovascular diseases may require surgery or percutaneous procedures to address the cause of turbulent blood flow and associated shear stress (reviewed in detail[6] by Budde et al).

Future Treatments

There are some emerging therapies in addition to rVWF that may become part of future clinical management of VWD. Phase II studies have demonstrated the safety and efficacy of recombinant interleukin-11 to induce endogenous VWF expression in patients for whom DDAVP was contraindicated or showed inadequate response.[58–60] The product was administered subcutaneously for 4 days with only minor adverse effects such as fluid retention, flushing, and conjunctival erythema. It appears to act independently of the mechanisms of DDAVP and thus may have a future adjunctive role in combination with DDAVP.

Finally, preliminary *VWF* gene therapy studies have been undertaken in animal models.[61–63] After gene transfer to the liver, ectopic expression of transgene encoded plasma VWF was demonstrated. However, much higher levels of transgenic VWF are required in VWD than for FVIII to treat hemophilia A and the biosynthesis of VWF is complex with both intracellular and extracellular processing required for the VWF protein to be fully functional. Consequently, human trials have not been possible to date.

Conclusions and Future Perspectives

Most developed countries currently use "standard" therapy to manage bleeding, employing DDAVP wherever possible, VWF/FVIII concentrates in other situations, and additional (e.g., antifibrinolytic) therapy when required. There are differences in content between available concentrates, for example, in relation to comparative levels of VWF and FVIII, or in the composition of VWF and relative retention or loss of the HMW forms, as well as the labeling of product content (FVIII only vs. FVIII and VWF:RCo), and only selective concentrates are available in different localities according to regulatory clearances and marketing. Although dosing in FVIII:C units for surgical hemostasis is recommended by some, there may be more justification for using VWF:RCo–based dosing to treat or prevent mucocutaneous bleeding. This is particularly important given that FVIII:C/VWF ratios differ substantially between products, and thus dosing using FVIII:C will deliver different amounts of VWF according to the concentrate used, and thus recommendations are not interchangeable according to product used.

These reflect important but often overlooked issues when using replacement therapy, and also mean that true global "standardization" of biological therapy in VWD is currently not feasible. rVWF has been developed and is undergoing clinical trials, and this promising therapy may change the VWD management landscape in the near future. Finally, further refinement to patient management, within the concept of personalized medicine is likely to evolve. Thus, differential therapy may in the future be applied to different people depending on the type and extent of the VWF abnormality/deficiency as well as the duration of treatment. There generally is a need to provide VWF, but only sometimes is FVIII required. VWF may be required in all its molecular weight forms, but in some cases, it may be preferential to provide only HMW VWF, and in other cases, even low-molecular-weight VWF may be preferred. Whether rVWF, rFVIII, and perhaps other recombinant proteins such as interleukin-11, become an arsenal of recombinants for management of VWD in the future also waits to be determined, as does the as yet unmet promise of gene therapy.

References

1 Sadler JE, Budde U, Eikenboom JC, et al; Working Party on von Willebrand Disease Classification. Update on the pathophysiology and classification of von Willebrand disease: a report of the Subcommittee on von Willebrand Factor. J Thromb Haemost 2006;4(10):2103–2114

2 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

3 Favaloro EJ. Von Willebrand disease: local diagnosis and management of a globally distributed bleeding disorder. Semin Thromb Hemost 2011;37(5):440–455

4 Franchini M, Lippi G, Favaloro EJ. Advances in hematology. Etiology and diagnosis of acquired von Willebrand syndrome. Clin Adv Hematol Oncol 2010;8(1):20–24

5 Federici AB, Budde U, Castaman G, Rand JH, Tiede A. Current diagnostic and therapeutic approaches to patients with acquired von Willebrand syndrome: a 2013 update. Semin Thromb Hemost 2013;39(2):191–201

6 Budde U, Bergmann F, Michiels JJ. Acquired von Willebrand syndrome: experience from 2 years in a single laboratory compared with data from the literature and an international registry. Semin Thromb Hemost 2002;28(2):227–238

7 Yee A, Kretz CA. Von Willebrand factor: form for function. Semin Thromb Hemost 2014;40(1):17–27

8 Peyvandi F, Garagiola I, Baronciani L. Role of von Willebrand factor in the haemostasis. Blood Transfus 2011;9(Suppl 2):s3–s8

9 Jaffe EA, Hoyer LW, Nachman RL. Synthesis of von Willebrand factor by cultured human endothelial cells. Proc Natl Acad Sci U S A 1974;71(5):1906–1909

10 Sporn LA, Chavin SI, Marder VJ, Wagner DD. Biosynthesis of von Willebrand protein by human megakaryocytes. J Clin Invest 1985;76(3):1102–1106

11 Favaloro EJ. Recent advances in laboratory-aided diagnosis of von Willebrand disease. Expert Opinion on Orphan Drugs 2015;3(9):975–995

12 Favaloro EJ, Franchini M, Lippi G. Biological therapies for von Willebrand disease. Expert Opin Biol Ther 2012;12(5):551–564

13 Favaloro EJ. Diagnosing von Willebrand disease: a short history of laboratory milestones and innovations, plus current status, challenges, and solutions. Semin Thromb Hemost 2014;40(5):551–570

14 Ng C, Motto DG, Di Paola J. Diagnostic approach to von Willebrand disease. Blood 2015;125(13):2029–2037

15 Lillicrap D. von Willebrand disease: advances in pathogenetic understanding, diagnosis, and therapy. Hematology Am Soc Hematol Educ Program 2013;2013:254–260

16 Favaloro EJ, Bodó I, Israels SJ, Brown SA. von Willebrand disease and platelet disorders. Haemophilia 2014;20(Suppl 4):59–64

17 Flood VH. Perils, problems, and progress in laboratory diagnosis of von Willebrand disease. Semin Thromb Hemost 2014;40(1):41–48

18 Casonato A, Gallinaro L, Cattini MG, et al. Reduced survival of type 2B von Willebrand factor, irrespective of large multimer representation or thrombocytopenia. Haematologica 2010;95(8):1366–1372

19 Casonato A, Steffan A, Pontara E, et al. Post-DDAVP thrombocytopenia in type 2B von Willebrand disease is not associated with platelet consumption: failure to demonstrate glycocalicin increase or platelet activation. Thromb Haemost 1999;81(2):224–228

20 Othman M. Platelet-type von Willebrand disease: a rare, often misdiagnosed and underdiagnosed bleeding disorder. Semin Thromb Hemost 2011;37(5):464–469

21 Othman M, Kaur H, Emsley J. Platelet-type von Willebrand disease: new insights into the molecular pathophysiology of a unique platelet defect. Semin Thromb Hemost 2013;39(6):663–673

22 Hampshire DJ, Goodeve AC. The international society on thrombosis and haematosis von Willebrand disease database: an update. Semin Thromb Hemost 2011;37(5):470–479

23 Hassenpflug WA, Budde U, Schneppenheim S, Schneppenheim R. Inherited thrombotic thrombocytopenic purpura in children. Semin Thromb Hemost 2014;40(4):487–492

24 Knöbl P. Inherited and acquired thrombotic thrombocytopenic purpura (TTP) in adults. Semin Thromb Hemost 2014;40(4):493–502

25 Wada H, Matsumoto T, Yamashita Y. Natural history of thrombotic thrombocytopenic purpura and hemolytic uremic syndrome. Semin Thromb Hemost 2014;40(8):866–873

26 Eerenberg ES, Levi M. The potential therapeutic benefit of targeting ADAMTS13 activity. Semin Thromb Hemost 2014;40(1):28–33

27 Chapman K, Yuen S. Therapy for thrombotic thrombocytopenia purpura: past, present, and future. Semin Thromb Hemost 2014;40(1):34–40

28 Lenting PJ, Denis CV, Wohner N. Von Willebrand factor and thrombosis: risk factor, actor and pharmacological target. Curr Vasc Pharmacol 2013;11(4):448–456

29 Mannucci PM. Venous thromboembolism in von Willebrand disease. Thromb Haemost 2002;88(3):378–379

30 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

31 Rodeghiero F. Von Willebrand disease: pathogenesis and management. Thromb Res 2013;131(Suppl 1):S47–S50

32 Tosetto A, Castaman G. How I treat type 2 variant forms of von Willebrand disease. Blood 2015;125(6):907–914

33 Federici AB, Mazurier C, Berntorp E, et al. Biologic response to desmopressin in patients with severe type 1 and type 2 von Willebrand disease: results of a multicenter European study. Blood 2004;103(6):2032–2038

34 Favaloro EJ, Kershaw G, Bukuya M, Hertzberg M, Koutts J. Laboratory diagnosis of von Willebrand disorder (vWD) and monitoring of DDAVP therapy: efficacy of the PFA-100 and vWF:CBA as combined diagnostic strategies. Haemophilia 2001;7(2):180–189

35 Favaloro EJ. Rethinking the diagnosis of von Willebrand disease. Thromb Res 2011;127(Suppl 2):S17–S21
36 Brooker M. Registry of clotting factor concentrates. 9th ed. World Federation of Hemophilia (WFH); 2012. Available at: http://www1.wfh.org/publications/files/pdf-1227.pdf. Accessed November 17, 2015
37 Batlle J, López-Fernández MF, Fraga EL, Trillo AR, Pérez-Rodríguez MA. Von Willebrand factor/factor VIII concentrates in the treatment of von Willebrand disease. Blood Coagul Fibrinolysis 2009;20(2):89–100
38 Budde U, Metzner HJ, Müller HG. Comparative analysis and classification of von Willebrand factor/factor VIII concentrates: impact on treatment of patients with von Willebrand disease. Semin Thromb Hemost 2006;32(6):626–635
39 Favaloro EJ, Bukuya M, Martinelli T, et al. A comparative multilaboratory assessment of three factor VIII/von Willebrand factor concentrates. Thromb Haemost 2002;87(3):466–476
40 Goudemand J, Scharrer I, Berntorp E, et al. Pharmacokinetic studies on Wilfactin, a von Willebrand factor concentrate with a low factor VIII content treated with three virus-inactivation/removal methods. J Thromb Haemost 2005;3(10):2219–2227
41 Stadler M, Gruber G, Kannicht C, et al. Characterisation of a novel high-purity, double virus inactivated von Willebrand Factor and Factor VIII concentrate (Wilate). Biologicals 2006;34(4):281–288
42 Lethagen S, Carlson M, Hillarp A. A comparative in vitro evaluation of six von Willebrand factor concentrates. Haemophilia 2004;10(3):243–249
43 Lawrie AS, Harrison P, Armstrong AL, Wilbourn BR, Dalton RG, Savidge GF. Comparison of the in vitro characteristics of von Willebrand factor in British and commercial factor VIII concentrates. Br J Haematol 1989;73(1):100–104
44 Mannucci PM, Chediak J, Hanna W, et al; Alphanate Study Group. Treatment of von Willebrand disease with a high-purity factor VIII/von Willebrand factor concentrate: a prospective, multicenter study. Blood 2002;99(2):450–456
45 Federici AB, Baudo F, Caracciolo C, et al. Clinical efficacy of highly purified, doubly virus-inactivated factor VIII/von Willebrand factor concentrate (Fanhdi) in the treatment of von Willebrand disease: a retrospective clinical study. Haemophilia 2002;8(6):761–767
46 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
47 de Wee EM, Leebeek FWG, Eikenboom JCJ. Diagnosis and management of von Willebrand disease in The Netherlands. Semin Thromb Hemost 2011;37(5):480–487
48 Mannucci PM, Franchini M. The use of plasma-derived concentrates. In: Federici AB, Lee CA, Berntorp EE, Lillicrap D, Montgomery RR eds. Von Willebrand Disease. 2nd ed. West Sussex, UK: Blackwell Publishing Ltd; 2010
49 Dunkley S, Baker RI, Pidcock M, et al. Clinical efficacy and safety of the factor VIII/von Willebrand factor concentrate BIOSTATE in patients with von Willebrand's disease: a prospective multicentre study. Haemophilia 2010;16(4):615–624
50 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
51 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
52 Abshire TC, Federici AB, Alvárez MT, et al; VWD PN. Prophylaxis in severe forms of von Willebrand's disease: results from the von Willebrand Disease Prophylaxis Network (VWD PN). Haemophilia 2013;19(1):76–81
53 Kingman CE, Kadir RA, Lee CA, Economides DL. The use of levonorgestrel-releasing intrauterine system for treatment of menorrhagia in women with inherited bleeding disorders. BJOG 2004;111(12):1425–1428
54 Castillo R, Monteagudo J, Escolar G, Ordinas A, Magallón M, Martín Villar J. Hemostatic effect of normal platelet transfusion in severe von Willebrand disease patients. Blood 1991;77(9):1901–1905
55 Boey JP, Hahn U, Sagheer S, McRae SJ. Thalidomide in angiodysplasia-related bleeding. Intern Med J 2015;45(9):972–976
56 Federici AB, Rand JH, Bucciarelli P, et al; Subcommittee on von Willebrand Factor. Acquired von Willebrand syndrome: data from an international registry. Thromb Haemost 2000;84(2):345–349
57 Friederich PW, Wever PC, Briët E, Doorenbos CJ, Levi M. Successful treatment with recombinant factor VIIa of therapy-resistant severe bleeding in a patient with acquired von Willebrand disease. Am J Hematol 2001;66(4):292–294
58 Ragni MV, Jankowitz RC, Chapman HL, et al. A phase II prospective open-label escalating dose trial of recombinant interleukin-11 in mild von Willebrand disease. Haemophilia 2008;14(5):968–977
59 Ragni MV, Jankowitz RC, Jaworski K, Merricks EP, Kloos MT, Nichols TC. Phase II prospective open-label trial of recombinant interleukin-11 in women with mild von Willebrand disease and refractory menorrhagia. Thromb Haemost 2011;106(4):641–645
60 Ragni MV, Novelli EM, Murshed A, Merricks EP, Kloos MT, Nichols TC. Phase II prospective open-label trial of recombinant interleukin-11 in desmopressin-unresponsive von Willebrand disease and mild or moderate haemophilia A. Thromb Haemost 2013;109(2):248–254
61 Pergolizzi RG, Jin G, Chan D, et al. Correction of a murine model of von Willebrand disease by gene transfer. Blood 2006;108(3):862–869
62 De Meyer SF, Vandeputte N, Pareyn I, et al. Restoration of plasma von Willebrand factor deficiency is sufficient to correct thrombus formation after gene therapy for severe von Willebrand disease. Arterioscler Thromb Vasc Biol 2008;28(9):1621–1626
63 Marx I, Lenting PJ, Adler T, Pendu R, Christophe OD, Denis CV. Correction of bleeding symptoms in von Willebrand factor-deficient mice by liver-expressed von Willebrand factor mutants. Arterioscler Thromb Vasc Biol 2008;28(3):419–424