Review Article

Diagnosis and management of von Willebrand disease in Australia

Emmanuel J. Favaloro[1,2], Leonardo Pasalic[1,2], Jennifer Curnow[2,3]

[1]Laboratory Haematology, Institute of Clinical Pathology and Medical Research (ICPMR), NSW Health Pathology, Westmead Hospital, Westmead, NSW, Australia; [2]Sydney Centres for Thrombosis and Haemostasis, Westmead, NSW, Australia; 3Clinical Haematology, Westmead Hospital, Westmead, NSW, Australia

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Correspondence to: Emmanuel J. Favaloro, PhD, FFSc. Haematology, ICPMR, Westmead, NSW, Australia. Email: emmanuel.favaloro@health.nsw.gov.au.

Abstract: Von Willebrand disease (VWD) is reportedly the most common inherited bleeding disorder, and can also arise as an acquired event where it is termed von Willebrand syndrome. Both arise from deficiency and/or defect of von Willebrand factor (VWF), an adhesive plasma protein that acts primarily to prevent bleeding by anchoring platelets to sites of vascular injury. Factor VIII is also proportionally reduced, due to loss of stabilizing and anti-proteolytic effect normally exerted by VWF on FVIII. Primary VWD management aims to protect against bleeding by replacement of VWF, and sometimes FVIII, using VWF/FVIII concentrates, and/or in some patients, administration of desmopressin (DDAVP) to permit release of endogenous VWF. Adjunct therapies such as anti-fibrinolytics and hormonal therapies in women may also be used, depending on the type and severity of VWD, the type and severity of the bleeding event, and whether therapy is for prophylaxis or treatment. Diagnosis and treatment of VWD involves comprehensive laboratory testing. This review outlines current diagnosis and treatment of VWD in Australia, and is part of an issue of this journal dedicated to diagnosis and treatment of VWD in different geographical localities.

Keywords: Von Willebrand disease (VWD); diagnosis; management, factor concentrates; therapy; monitoring

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Von Willebrand disease (VWD) and von Willebrand factor (VWF)

VWD is typically identified as being the most common inherited bleeding disorder. The exact prevalence of VWD is debated, but has been reported in epidemiological studies to affect up to 1% of the general population, but alternatively the prevalence may be as low as 0.01% (1 in 10,000) based on symptomatic patient presentations to clinics (1).

VWD is caused by deficiencies and/or defects in VWF, a large and complex multimeric protein, which otherwise would facilitate both primary and secondary hemostasis, by binding to platelets, factor VIII (FVIII), and subendothelial matrix components such as collagen (1-4).

Congenital VWD primarily arises due to mutations in VWF. Diagnosis requires evidence of personal or family history of (mainly) mucocutaneous bleeding, together with laboratory findings that demonstrate quantitative or qualitative defects in VWF (1-6).

Current classification of VWD, based on whether VWF quantitative deficiencies (VWD types 1 and 3), or qualitative defects (type 2 VWD) are present, defines 6 types (*Table 1*) (2).

Type 1 VWD is characterized by quantitative deficiency of an otherwise functionally normal VWF. Type 1 VWD is therefore confirmed by detection of reduced levels of VWF protein ('antigen'; VWF:Ag), and similar proportionally decreased levels of functional VWF, which can be identified by various assays, including VWF ristocetin cofactor (VWF:RCo) and collagen binding (VWF:CB) (7-10) (*Table 2*). There is a corresponding fall in plasma levels of FVIII,

Table 1 Classification scheme for von Willebrand disease and summary of phenotypic presentation

VWD type	Description	Phenotypic presentation
1	Partial quantitative deficiency of VWF	Low levels of VWF, with VWF functional concordance (i.e., ratio of functional VWF/VWF:Ag approximates unity)
2A	Decreased VWF-dependent platelet adhesion and a selective deficiency of high-molecular-weight (HMW) VWF multimers	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)
2B	Increased affinity of VWF for platelet glycoprotein 1b	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
2M	Decreased VWF-dependent platelet adhesion without a selective deficiency of high-molecular-weight (HMW) VWF multimers	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
2N	Markedly decreased binding affinity for factor VIII	Identified by VWF:FVIIIB assay, with low FVIIIB/VWF ratios
3	Virtually complete deficiency of VWF	Typically defined by VWF levels <2 U/dL and FVIII <10 U/dL

Classification scheme derived and adapted from Sadler *et al.*, 2006 (2). CB/Ag, collagen binding to antigen ratio; DDAVP, desmopressin; HMW, high molecular weight; FVIII:C, factor VIII coagulant; 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:CB, von Willebrand factor collagen binding; VWF:Ag, von Willebrand factor antigen; VWF:FVIIIB, VWF FVIII binding assay; VWF:RCo, von Willebrand factor ristocetin cofactor.

since VWF acts to protect FVIII from proteolysis.

Representing the most severe phenotype, Type 3 VWD essentially describes an absence of VWF, but in practice can also be identified by very low levels of VWF:Ag (i.e., <2-5 U/dL) should assays suffer from low level sensitivity issues (*Table 2*). Results of functional VWF assays are similarly low, but low limit of VWF detection issues may further affect correct diagnosis, and falsely higher values may be reported.

Type 2 VWD patients exhibit qualitative VWF defects; accordingly, levels of VWF protein (VWF:Ag) might be normal (although it is usually reduced), FVIII levels might also be normal or low, but most importantly, VWF function is somehow impaired. 'Subtypes' of type 2 VWD are identified according to the type of impaired function.

Type 2A VWD is defined by absence or deficiency of high molecular weight (HMW) VWF (2), representing the most biologically active forms, and specifically identified phenotypically by absence of HMW VWF on multimer analysis and/or by low VWF activity/Ag ratios, using various functional assays (e.g., low VWF:RCo/Ag and low VWF:CB/Ag; *Table 2*).

Patients with type 2B VWD have a hyper-adhesive form of VWF, which binds platelets with increased avidity and is then removed from circulation more rapidly, often resulting in a selective depletion of HMW VWF, and 'classically' also (mild) thrombocytopenia. A diagnosis of 2B VWD is confirmed by enhanced ristocetin induced platelet aggregation (RIPA) (10,12); patients also typically have reduced HMW VWF, with low ratios for VWF activity/Ag (e.g., low VWF:RCo/Ag and low VWF:CB/Ag; *Table 2*).

Patients with type 2N VWD have VWF defects that prevent it binding to FVIII, leading to more rapid proteolytic degradation and depletion of plasma FVIII. Consequent hemorrhagic manifestations and laboratory test patterns may therefore be mistaken for those of hemophilia A. Type 2N VWD is phenotypically discriminated from hemophilia A using VWF:FVIII binding assays (*Table 2*) (13).

Type 2M VWD characterizes different qualitative VWF defects that are not linked to depletion of HMW VWF (2). Often type 2M VWD is phenotypically identified by low VWF:RCo/Ag ratio without loss of HMW VWF by multimer analysis, although it can alternatively be identified by discordance between VWF:RCo/Ag and VWF:CB/Ag ratios [whereby one is normal (usually VWF:CB/Ag) and the other is low (usually VWF:RCo/Ag); *Table 2*].

Recent advances in VWD diagnostics

Worldwide, the mainly used assays in VWD diagnostics are FVIII, VWF:Ag, VWF:RCo, while VWF:CB is used in some geographies. The main recent advances relate to

Table 2 A practical guide to differential identification of von Willebrand disease (VWD) type

VWD type	VWF: Ag	VWF: RCo*	VWF: CB	FVIII:C	Multimers	RCo/Ag*	CB/Ag*	FVIII/ VWF*	Comments/additional testing**
1	↓to ↓↓	↓to ↓↓	↓to ↓↓	N to ↓↓	Normal pattern but reduced intensity	Normal	Normal	Normal	VWF levels between ~30–50 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' type 1 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 haemophilia 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

*, VWF GPIb binding assays [including the Siemens 'Innovance' VWF Ac assay, recently named VWF:GPIbM (11)] will provide results that will most closely match VWF:RCo. Low assay ratios are generally identified as < (0.5–0.7), with the actual value depending on the locally established cut-off; normal assay ratios are generally identified as > (0.5–0.7), again depending on the locally established cut-off. **, 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 USA tend to use % or U/dL, but some hemophilia centres report FVIII in U/mL. Ag, antigen; CB, collagen binding; FVIII, factor VIII; HMW, high molecular weight (VWF); GPIb, glycoprotein Ib (the platelet VWF receptor); N, normal; NA, not applicable; RCo, ristocetin cofactor; RIPA, ristocetin induced platelet aggregation; VWF, von Willebrand factor; VWD, von Willebrand disease.

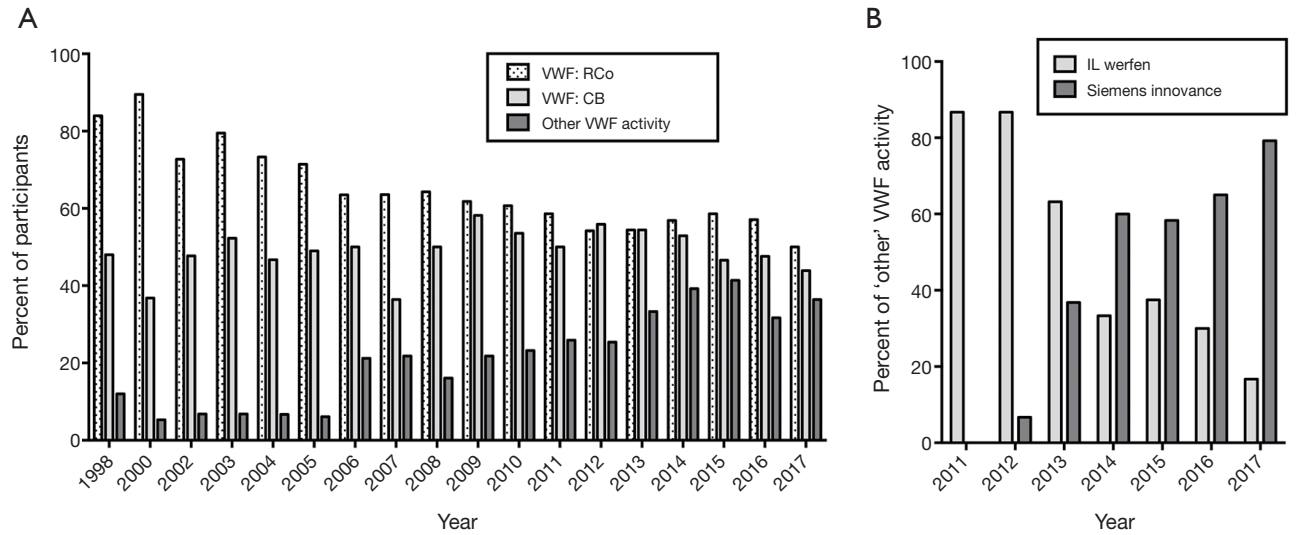

Figure 1 Changes in usage of von Willebrand factor (VWF) 'activity' assays over time in Australasia. Data from Royal College of Pathologists of Australasia (RCPA) Quality Assurance Programs (QAP) Haematology showing changes in percentage of participating laboratories performing a particular VWF test type from 1998 to current [2017]. Over this time, testing for collagen binding (VWF:CB) has been fairly steady at around 50–60% of laboratories. In contrast, ristocetin cofactor (VWF:RCo) testing has fallen from a high of over 90% of laboratories in the year 2000, to current levels at close to 50%, with this test being increasingly replaced with other VWF 'activity' assays. Initial replacement was with an IL Werfen assay, but currently, the Siemens Innovance VWF Ac (or VWF:GPIbM) assay is increasingly taking hold.

automation of VWF:CB, and commercialization of new assays that reflect platelet glycoprotein Ib (GPIb) binding but which do not use platelets and in some cases do not use ristocetin (5-16). Extensive descriptions of these assays are outside the remit of the present review, and have otherwise been reviewed or published (5-16). Suffice to say that these assays are likely to increase in usage, and otherwise replace or supplement existing test systems (*Figure 1*). Importantly, the newer GPIb binding assays will likely replace classical VWF:RCo assays in the immediate future, and essentially will be considered interchangeable with VWF:RCo when identifying VWD and defining VWD subtypes. Nevertheless, additional research may be required to further explore similarities and differences between assays before they can be defined to be identical. Such comparative evaluations may be facilitated with some new nomenclature devised by the International Society on Thrombosis and Haemostasis (ISTH) VWF Scientific Standardization Committee (SSC) (5,6,11).

Diagnosis of VWD in Australia

The current review essentially updates a previous analogous review published in 2011 (17). Our own approach to diagnosis/exclusion of VWD is represented in algorithmic form in *Figures 2,3*. In addition to personal and familial bleeding history and physical examination, a battery of laboratory studies may be required, including, but not necessarily limited to VWF and FVIII testing (*Figures 2,3*). For example, in urgent cases where access to VWF tests may be limited, the Platelet Function Analyzer (PFA)-100/200 may be useful in order to exclude VWD (18-21). The PFA-100/200 shows high sensitivity to deficiency of VWF (e.g., types 1 and 3 VWD), and also to selective loss of HMW VWF (i.e., type 2A VWD), and some defects in VWF (e.g., type 2M VWD). PFA-100/200 closure times (CTs) are therefore prolonged in virtually all cases of type 2A, 2M, 2B and 3, and in most cases of type 1 VWD, especially those with levels of VWF below 30U/dL. Thus, normal PFA CTs are generally inconsistent with VWD.

However, where more specific VWF testing is indicated, especially for diagnosis and typing of VWD, then our recommended approach is as per *Figure 3*. For all patients we recommend a minimum four test ('basic') panel of investigations, and namely FVIII, VWF:Ag, VWF:CB and

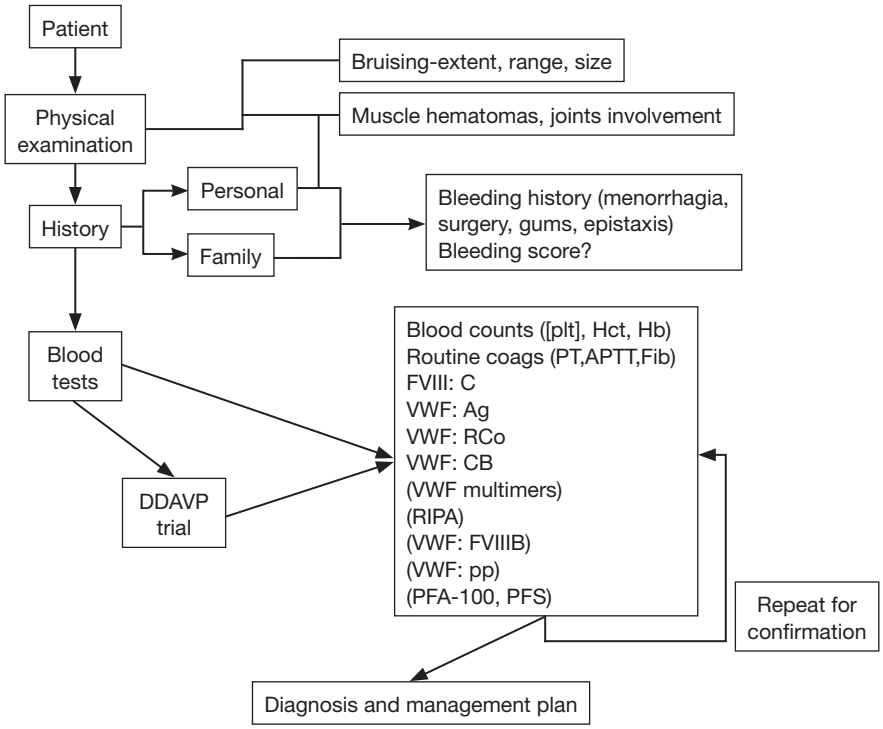

Figure 2 General algorithm for characterization of bleeding disorders including identification of von Willebrand disease (VWD). [plt], platelet count; Hct, hematocrit; Hb, hemoglobin; PT, prothrombin time; APTT, activated partial thromboplastin time; Fib, fibrinogen; FVIII:C, factor VIII coagulant; VWF, von Willebrand factor; Ag, antigen; RCo, ristocetin cofactor; CB, collagen binding; RIPA, ristocetin induced platelet aggregation; FVIIIB, factor VIII binding; pp, propeptide; PFA, platelet function analyzer; PFS, platelet function studies; DDAVP, desmopressin.

a GPIb binding assay—be it classical VWF:RCo or one of the modern 'alternatives' (e.g., VWF:GPIbM). This recommendation is also in line with those of the United Kingdom Haemophilia Centre Doctors Organization (4). Based on the plasma levels identified, further testing may be required. Mandatory repeat testing using a new sample is undertaken before VWD is categorically diagnosed, or even excluded in some cases, due to the possibility of both pre-analytical issues (22) and analytical (5) test limitations. The test levels and test patterns provide clues to the VWD diagnosis and which approach to testing should subsequently be followed to make a final diagnosis and characterize VWD type.

Based on national statistics and a locally maintained database, the breakdown of VWD types is as shown in *Tables 3*,*4*. Patients identified to have low VWF (as a risk factor for bleeding) or type 1 VWD predominate in Australia, as per all other geographies. Type 3 VWD is relatively rare. Type 2 is less common than type 1, but these patients still comprise a significant proportion of VWD cases, and typically represent the category of patients most likely to be misdiagnosed (either as another type of VWD, or as not suffering from VWD) (23-25).

Therapeutic rationale in VWD

Primary treatment of VWD involves restoring the depleted or dysfunctional VWF, and also in some circumstances the lost FVIII (26,27). Additional therapeutic measures might also be necessary in a proportion of patients. Type 1 VWD is usually effectively managed using desmopressin (1-deamino-8-d-arginine vasopressin, DDAVP); this facilitates release of endogenous VWF, stored in endothelial cells (*Table 5*) (27). Prior to use, it is recommended to first trial DDAVP and assess both responsiveness and tolerance, either in the patient or a close family member suffering the same disorder (27-29). DDAVP may also be effective in a subset of patients with type 2 VWD, but is not useful in

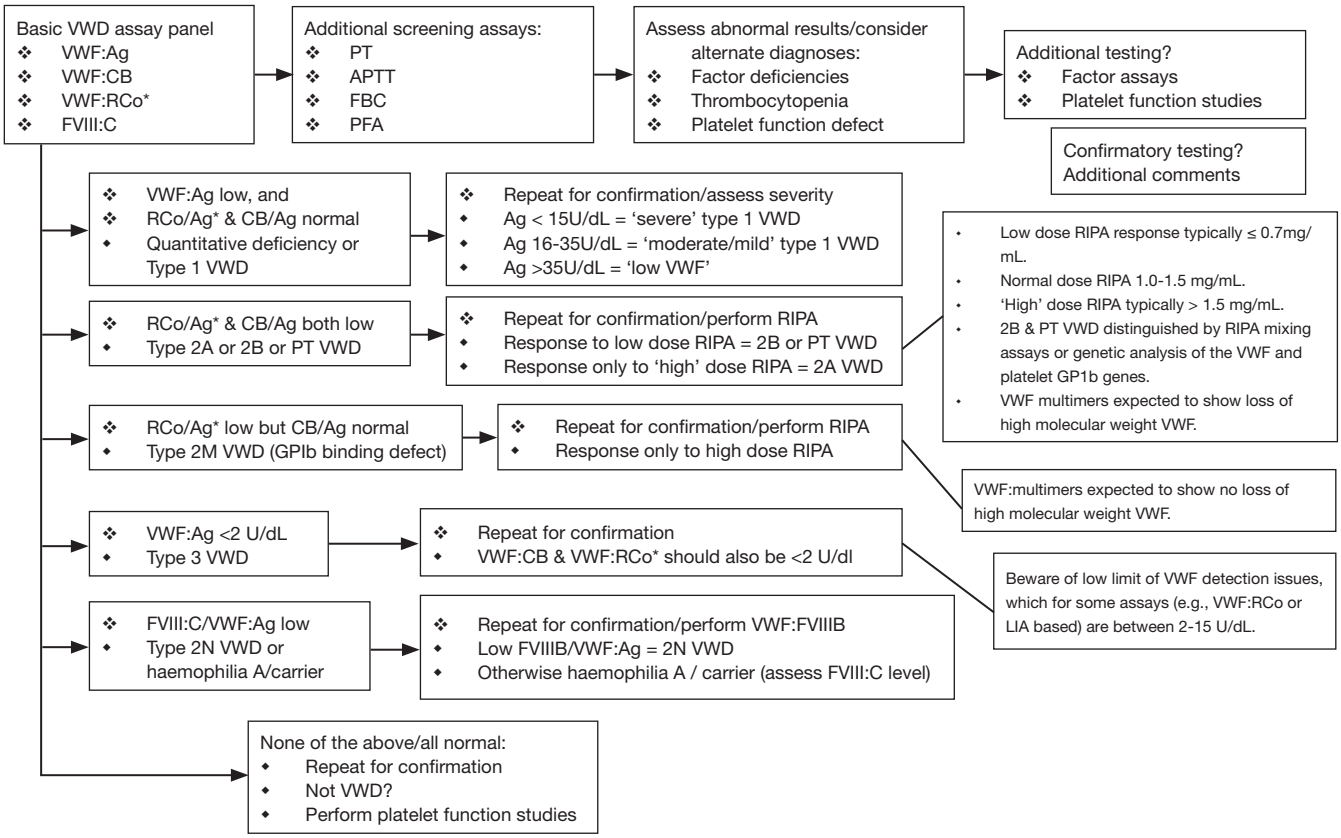

Figure 3 Our current algorithmic approach to diagnosis or exclusion of VWD using locally available tests as a test panel approach. *, Testing by the Innovance VWF Ac ('VWF:GPIbM') assay will provide results that closely match those of VWF:RCo. Also, there are no published differences between results of platelet ('VWF:RCo') vs latex ('VWF:GPIbR') based VWF:RCo assays. 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).

type 3 VWD, and may only be partially useful in any VWD patient with limited DDAVP responsiveness or requiring longer duration of therapy, for instance after major surgery.

DDAVP has a number of potential adverse effects including facial flushing, tachycardia, headache, hypotension or hypertension, gastrointestinal upset and hyponatremia, which if severe can rarely lead seizures (3). The risk of hyponatremia is significant after repeat doses; therefore, fluid restriction and monitoring of electrolytes is recommended in this setting. DDAVP should also be avoided in patients with symptomatic cardiovascular and cerebrovascular disease (3).

Where DDAVP is contraindicated or in patients with a DDAVP response that is sub-therapeutic or short-lived, exogenous replacement of VWF (/FVIII) is used (2,3,27). Our treatment protocol is identified in *Table 6*, and is based on a phase II/III open-label multicenter study conducted in Australia and New Zealand, as using the only Australian available concentrate (named Biostate; CSL Limited; a double virus inactivated plasma-derived product which has retained HMW VWF multimers and where the FVIII:C to VWF:RCo ratio is at least 1:2) (30). Pharmacokinetic studies may be used to personalize individual therapy if required (e.g., if patients show increased clearance of VWF).

Table 3 Von Willebrand disease (VWD)—statistics from Australia—Australia-wide data*

VWD type	2011 data					2015–2016 data				
	Female	Male	Total	% of total VWD	% of type 2 VWD	Female	Male	Total	% of total VWD	% of type 2 VWD
VWD type 1	420	601	1,021	75.4		851	477	1,328	63.5	
VWD type 2A	28	34	62	4.6	21.2	62	56	118	5.6	23.5
VWD type 2B	26	17	43	3.2	14.7	31	31	62	3.0	12.4
VWD type 2M	36	33	69	5.1	23.5	103	80	183	8.7	36.5
VWD type 2N	11	7	18	1.3	6.1	20	10	30	1.4	6.0
VWD type 3	16	25	41	3.0	–	22	21	43	2.1	–
VWD type 2—uncharacterized	49	52	101	7.5	34.5	61	48	109	5.2	21.7
VWD type 2 total	150	143	293	16.0	100					100
VWD—uncharacterized	272	189	461	25.2		125	94	219	10.5	
Totals	1,047	780	1,827	100.0	100.0	1275	817	2,092	100.0	–

*, From Australian Bleeding Disorders Registry (ABDR). 2011 data as per previously published (17). 2015–2016 source data kindly provided by Australian Bleeding Disorders Registry (ABDR) Annual Report 2015–16, as published by the National Blood Authority and available at: https://www.blood.gov.au/data-analysis-reporting. Note the increase in number of patients identified on the database, as well as the relative proportion of type 2M VWD within the type 2 VWD group. The population of Australia in 2016 approximated 24 million people. Thus, this data reflects a prevalence of only ~0.01%. It is suspected that most people with VWD in Australia are not captured in these statistics.

Since FVIII levels may rise excessively when administering concentrates containing both VWF and FVIII for longer duration treatment, monitoring of therapy is critical, and ideally, concentrates devoid of FVIII may be preferred for some treatment applications (2,3,27,31), although these are not currently available in Australia. Similarly, although recombinant VWF has recently been cleared for use in the USA, this is also not yet available in Australia.

Monitoring of therapy in VWD

The tests used to diagnose VWD can also be used to monitor therapy or treatment of VWD (*Table 7*) (28,32). We have recently published an extensive review on this topic (28). In brief, as mentioned, DDAVP administration triggers release of endogenous VWF. As cellular stored VWF is usually normal in type 1 VWD, most of these patients achieve sufficient increases in VWF to allow use of DDAVP as first-line therapy for bleeding or minor surgery and procedures. Further, as the response pattern is consistent within families, a parent's response can predict that of an affected child. Responses to DDAVP are highly variable in type 2 VWD, although usually better in type 2M than 2A. DDAVP response may be short-lived in type 2N VWD, and DDAVP is usually considered contraindicated in type 2B VWD, because increasing the level of 'abnormal' VWF with enhanced affinity for platelet GPIb may result in thrombocytopenia, potentially increasing the risk of bleeding.

In addition to determining potential therapeutic utility, a DDAVP response profile, which is often characteristic for a given VWD type (examples shown in *Figure 4*) (28,29) can assist diagnosis for some patients with otherwise unclear diagnosis.

Efficacy of VWF concentrates is judged clinically by assessing whether treatments have achieved normal haemostasis during surgery and halted or reduced active bleeding, and is also monitored using the same suite of laboratory tests as for diagnosis (*Table 2*) (1-5,27,28).

As reported, the PFA-100/200 is also used, both to exclude severe VWD in urgent cases, as well as to help assess the efficacy of therapy. Prolonged CTs in type 1

Table 4 Von Willebrand disease (VWD)—statistics from Australia—local Westmead database data*

VWD Type	Description/Comments	Number in database	% of total	% of subtotals
Main categories				
1	Quantitative deficiency of VWF	1,254	82.4	
2	Qualitative defects in VWF	241	15.8	
3	Absence of VWF	23	1.5	
PT-VWD	Platelet GPIBA defect	3	0.2	
Totals	(excludes undefined VWD; n=311)	1,521	100	
Subcategories				% of type 1
'1p'	'plausible' Type 1 VWD (VWF 'low' or borderline normal group) (VWF =36–64 U/dL)	1069	70.3	85.2
'1m'	Moderate/mild type 1 VWD (VWF =16–35 U/dL)	136	8.9	10.8
'1s'	Severe type 1 VWD (VWF =2–15 U/dL)	49	3.2	3.9
Totals	(for type 1 VWD)	1,254	82.4	100
Type 2 VWD				% of type 2
2A	Loss of HMW VWF (e.g., CB/Ag and RCo/Ag <0.7)	55	3.6	22.8
2M	Loss of VWF function not due to loss of HMW VWF (e.g., CB/Ag ≥0.7 but RCo/Ag <0.7)	51	3.4	21.2
2B	Enhanced RIPA (low dose ristocetin response)	20	1.3	8.3
2N	Defective VWF-FVIII binding (low FVIIIB/VWF ratio)	31	2.0	12.9
2U	Undefined—VWD/qualitative defects as yet not completely characterized	84	5.5	34.9
Totals	(for type 2 VWD)	241	15.8	100

*, As per 2011 data as previously published (17). The database is currently being analyzed for a separate update publication.

VWD tend to normalize following DDAVP, effects that parallel rising VWF, particularly HMW VWF, or VWF forms otherwise identified by testing with VWF:CB and VWF:RCo (26,27,29). However, while DDAVP might restore VWF:Ag in type 2A VWD, it may not correct VWF:CB or VWF:RCo, nor PFA CTs. Thus, performance of PFA CTs, especially during DDAVP trials, can be a useful and quick measure of treatment 'efficacy', with CT normalization reflecting a reasonable surrogate of adequate treatment response, often also associated with correction of VWF:CB and VWF:RCo, as well as typically normalization of RC/Ag and CB/Ag. PFA CT data does not appear to be useful to monitor VWF concentrate therapy, at least reflective of our clinical experience with Biostate in either type 1 or 2A VWD. The normalization of CTs with DDAVP, but not with VWF concentrate, at least in type 1 VWD, may be related to the higher levels of HMW VWF released by DDAVP compared to HMW VWF composition of Biostate. Consequently, the change in CTs may vary with different VWF/FVIII concentrates. Conversely, DDAVP typically fails to normalize CTs in type 2A VWD, since it does not yield release of HMW VWF. In summary, although CT normalization might reflect evidence of efficacious treatment, failure to normalize CTs may not indicate lack of clinical treatment efficacy.

Clinical monitoring in VWD

Clinical monitoring should be individualized according to bleeding phenotype (28). Clinically, effectiveness of bleeding management may be monitored by visual inspection (e.g., cessation in visible hemorrhage such as epistaxis or gingival bleeding), maintenance of adequate haemoglobin levels without iron supplementation

Table 5 Major current therapies for congenital von Willebrand disease (VWD)

VWD type	Summary of main therapies	Therapy—general considerations	Additional therapies
Type 1	DDAVP; VWF(/FVIII) concentrate	Usually respond well to DDAVP, unless VWF <10 U/dL. VWF concentrate required for DDAVP non-responders or for long-term therapy. Need to replace VWF and sometimes also FVIII	Anti-fibrinolytic therapy (e.g., tranexamic acid & aminocaproic acid) may be 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	Variable clinical response to DDAVP. VWF concentrate represents most common therapy. Need to replace (HMW) VWF and sometimes also FVIII	
Type 2B	VWF(/FVIII) concentrate; (DDAVP)	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	
Type 2M	VWF(/FVIII) concentrate; DDAVP	Variable clinical response to DDAVP and VWF concentrate represents most common therapy. Need to replace functional VWF and sometimes also FVIII	
Type 2N	VWF(/FVIII) concentrate; DDAVP	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)	
Type 3	VWF(/FVIII) concentrate	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	

Additional/alternate therapies for VWD may be applied in distinct geographies, based on relative availability of main treatments, including DDAVP and/or VWF(/FVIII) concentrates. Summarized from references (27,28).

Table 6 Recommendations/guidelines for treatment of von Willebrand disease with Biostate*

Indication	Dose* of VWF:RCo (IU/kg)	Number of infusions	Target plasma VWF:RCo level
Type 1 VWD Major surgery or haemorrhage	Loading dose 40, then 40–50	Every 8–12 hours for 3 days then daily for up to 7 days	> 50 U/dL; maintain levels for 7–10 days
Type 1 VWD Minor surgery or haemorrhage	40–50	1 or 2 doses	>30 U/dL; maintain levels for 2–4 days
Type 2 or 3 VWD Major surgery or haemorrhage	Loading dose 50–60 then 40–60	Every 8–12 hours for 3 days then daily for up to 7 days	> 50 U/dL; maintain levels for 7–10 days
Type 2 or 3 VWD Minor surgery or haemorrhage	40–50	1 or 2 doses	>30 U/dL; maintain levels for 2–4 days

*, Our local practice based on a phase II/III Australian and New Zealand study (30). FVIII, factor VIII; VWF, von Willebrand factor; VWF:RCo, von Willebrand factor ristocetin cofactor activity. U/mL, U/dL, %, IU/mL and IU/dL may alternatively be used as units for VWF and FVIII:C in various countries/publications. For example, Australia and the USA tend to use % or U/dL, but some hemophilia centres report FVIII in U/mL.

or transfusion support in cases presenting with gastrointestinal or uterine bleeding or reduced pain/swelling for muskuloskeletal bleeding for severe VWD. For most VWD patients, therapy will only be required at the time of surgery or procedures, when clinical monitoring entails assessment of adequacy of haemostasis achieved by perioperative therapy. Special considerations may apply to women, and situations involving menorrhagia, pregnancy and delivery (28). Other notable special situations include gastrointestinal bleeding/angiodysplasia (especially relevant in type 2 VWD) and prophylaxis (especially relevant in type 3 VWD) (28,33).

Table 7 Monitoring of therapy in VWD—a summary of our practice

Therapy	Clinical monitoring	Laboratory monitoring	Notes
DDAVP Trial	Facial flushing, hypertension or hypotension, tachycardia, headache, gastrointestinal upset and hyponatremia (rarely complicated by seizures)	Minimum: pre and post DDAVP testing of FVIII:C and VWF:RCo Recommended: pre and post DDAVP testing of FVIII:C, VWF:Ag, VWF:RCo and VWF:CB (and if indicated PFA-100/200 closure time). Assessment of functional VWF/Ag (e.g., RCo/Ag and CB/Ag) ratios Timepoints: pre-dose plus repeat testing performed at 1 hour, 2 and/or 4 hours, and finally 24 hours post infusion Other: pre- and post-DDAVP assessment of standard blood counts, especially platelet count, may be useful (e.g., 2B VWD). Pre- and post-DDAVP monitoring of electrolytes (especially sodium) may be useful in select patients (up to 24h post)	PFA-100/200 closure times tend to correct if functional VWF levels normalize, and/or if functional VWF/Ag ratios are normal (select type 1 VWD and type 2 VWD patients)
DDAVP therapy	Efficacy of bleeding treatment (has bleeding stopped or slowed?)	Minimum: pre and post DDAVP testing of FVIII:C and VWF:RCo Recommended: pre and post DDAVP testing of FVIII:C, VWF:Ag, VWF:RCo and VWF:CB (and if indicated PFA-100/200 closure time). Assessment of functional VWF/Ag (e.g., RCo/Ag and CB/Ag) ratios Timepoints: pre-dose plus repeat testing performed at 1 hour	Be aware of tachyphylaxis
VWF/FVIII concentrate—pharmacokinetic assessment	–	Minimum: pre and post concentrate testing of FVIII:C and VWF:RCo Recommended: pre and post concentrate dose testing of FVIII:C, VWF:Ag, VWF:RCo and VWF:CB. Assessment of functional VWF/Ag (e.g., RCo/Ag and CB/Ag) ratios Timepoints: pre-dose plus repeat testing performed at 1 hour, 2 and/or 4 hours, and finally 24 hours post infusion	In our experience, PFA-100/200 closure times do not tend to correct when VWF concentrates are used, and so this testing can be omitted
VWF/FVIII concentrate	Efficacy of bleeding treatment (has bleeding stopped or slowed?)	Minimum: pre and post concentrate testing of FVIII:C and VWF:RCo Recommended: pre and post concentrate testing of FVIII:C, VWF:Ag, VWF:RCo and VWF:CB. Assessment of functional VWF/Ag (e.g., RCo/Ag and CB/Ag) ratios. Timepoints: pre-dose plus repeat testing performed at 1 hour.	In our experience, PFA-100/200 closure times do not tend to correct when VWF concentrates are used, and so this testing can be omitted
Antifibrinolytic agents	Efficacy of bleeding treatment (has bleeding stopped or slowed?)	No specific laboratory monitoring when applied to VWD	Monitor for any potential adverse events: nausea, vomiting, diarrhea and rarely thrombotic events
Oral contraceptive agents	Efficacy of bleeding treatment (has bleeding stopped or slowed?)	No specific laboratory monitoring when applied to VWD.	Consider the use of the PBAC
Iron therapy		Assessment of pre-, and post-, iron related parameters may be useful?	–
Normal platelets	Efficacy of bleeding treatment (has bleeding stopped or slowed?)	Assessment of VWD patient platelet VWF level (VWF:Ag and VWF:RCo; also VWF:CB if available) may be useful	FVIII:C can be omitted, as not present in platelets
Topical thrombin	Efficacy of bleeding treatment (has bleeding stopped or slowed?)	No specific laboratory monitoring when applied to VWD	Beware of the rare risk of development of anti-factor V antibodies if using bovine thrombin

Summarized from references (27,28).

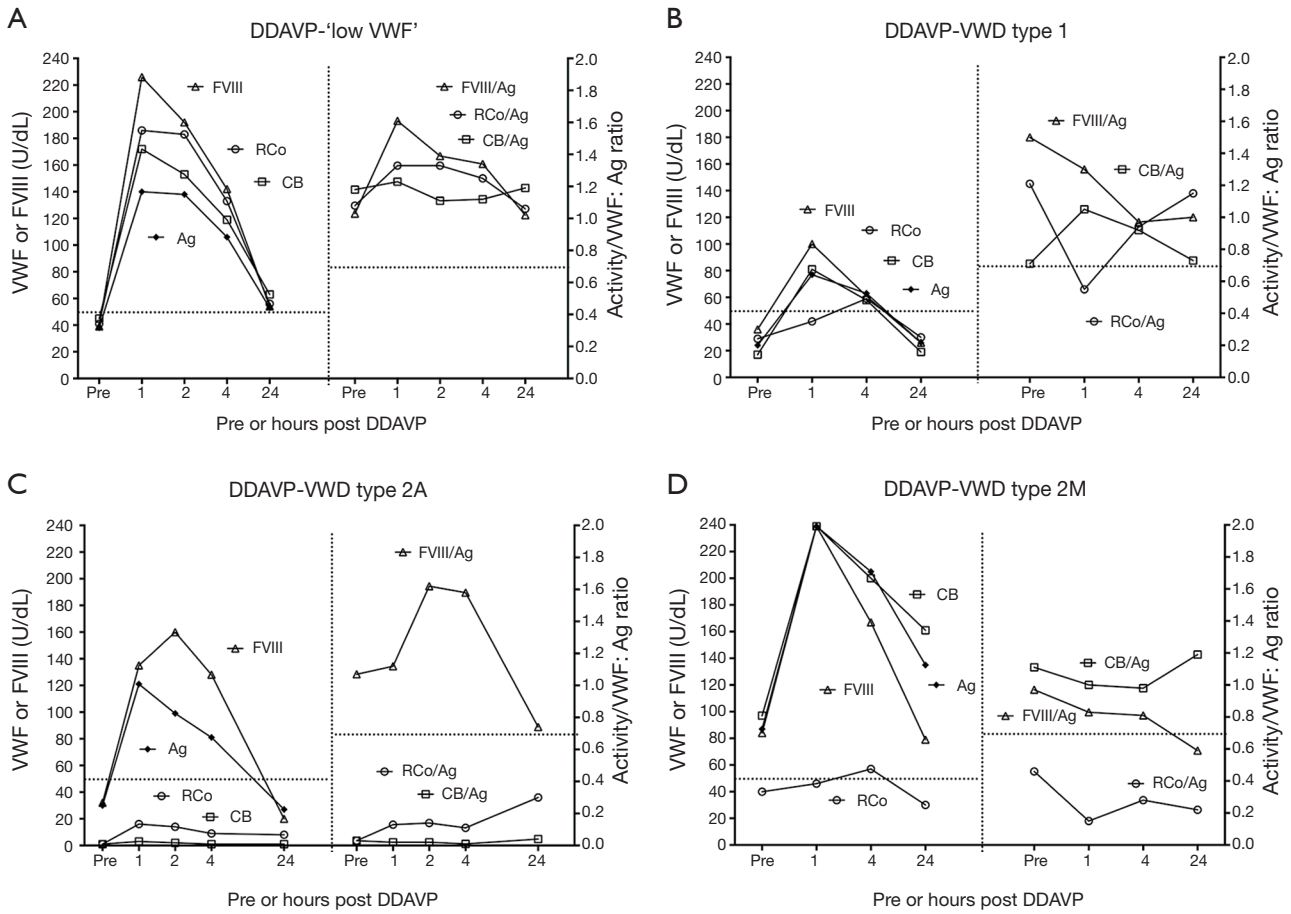

Figure 4 Results of desmopressin (DDAVP) trials in select patients with von Willebrand disease (VWD). A: 'Low VWF' case; B: type 1 VWD; C: type 2A VWD; D: type 2M VWD. Substantial increments in VWF:Ag and FVIII:C may occur in response to DDAVP in most patients with VWD. DDAVP 'responders' show a two to five-fold increase from baseline and their VWF (usually measured using VWF:RCo) and FVIII:C levels are above 50 U/dL at 1 hour. Levels should remain above 30 U/dL by four hours post-infusion unless VWF and/or FVIII clearance is significantly increased, but by 24 hours levels generally return to baseline. DDAVP usually causes all VWF and FVIII parameters rise in low VWF and type 1 VWD, with functional VWF/Ag ratios (including RCo/Ag and CB/Ag) remaining normal and above 0.7 at all time-points (A,B). In type 2A VWD, both VWF:Ag and FVIII typically increment, but functional VWF test parameters may not, and VWF/Ag ratios (both RCo/Ag and CB/Ag) often tend to remain abnormal and below 0.7 at all time-points (C). In type 2M VWD, both VWF:Ag and FVIII again increment, but functional VWF test parameters may or may not increment, and functional VWF/Ag ratios may or may not be normal, depending on the VWF defect present in the patient. In platelet binding defect 2M VWD, VWF:CB tends to increment, but VWF:RCo does not, and so CB/Ag may be normal, whereas RCo/Ag may remain abnormal and below 0.7 at all time-points (C). Left y-axis in each figure shows VWF or FVIII:C level (U/dL) and right y-axis shows activity/VWF:Ag ratios. Data from our laboratory. VWD, von Willebrand disease; VWF, von Willebrand factor; Ag, antigen; CB, collagen binding; RCo, ristocetin cofactor.

Other adjunctive therapies

Antifibrinolytic agents, such as tranexamic acid, are useful for management of mucocutaneous bleeding and in the periprocedural setting, particularly for dental procedures. Occasionally, transfusion of normal platelets containing normal VWF content may help bleeding patients despite 'adequate' VWF replacement therapy (34). Topical thrombin may help minor wound bleeding and fibrin sealants may be useful in dental procedures (3).

Conclusions and future perspectives

In line with the United Kingdom Haemophilia Centre Doctors Organization guideline (4), we believe that diagnosis of VWD requires a minimum four test panel covering FVIII, VWF:Ag, GPIb binding (e.g., VWF:RCo or VWF:GPIbM), and collagen binding (VWF:CB). Additional testing may be required to provide VWD typing, or differential diagnoses, including exclusion of VWD. Such testing can be described by means of an algorithm, such as per *Figure 3*. 'Standard' therapy to manage VWD, in most developed countries, including Australia, utilizes DDAVP wherever possible, otherwise VWF/FVIII concentrates, and adjunct therapy (e.g., antifibrinolytic) as needed (27). Monitoring of therapy typically involves laboratory measurement of baseline and post therapy levels of various VWF parameters and FVIII:C at select intervals, and using the same four test panel used for initial VWD diagnosis (28). We integrate PFA-100/200 testing in select patients, both in diagnosis/exclusion of VWD, as well as in DDAVP therapy (27-29,32).

Genetic testing also has a role in diagnosis of VWD, although (outside of a research setting) we use this selectively in our own practice (35,36). However, given the great strides being made by next generation sequencing (37), we will be rethinking this practice over the next few years.

Our recommendations here as related to our own therapeutic use and monitoring of VWF concentrate might need modification to suit local needs, particularly where different laboratory test panels are in use or concentrates differ substantially from Biostate with respect to VWF:FVIII content (or Humate P, which is structurally similar to Biostate) (38). These differences are sometimes overlooked, but represent a major obstacle to international 'standardization' of diagnosis or biological therapy for VWD. Although recombinant VWF has been successfully developed, and recently approved for use in the USA (31), this is not yet available in Australia and many other jurisdictions. When eventually available more globally than the USA, recombinant VWF use may also impose on us refinements to 'standard' monitoring of therapy, as well as further refinement of patient management alongside concepts of personalized medicine (31).

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Footnote

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