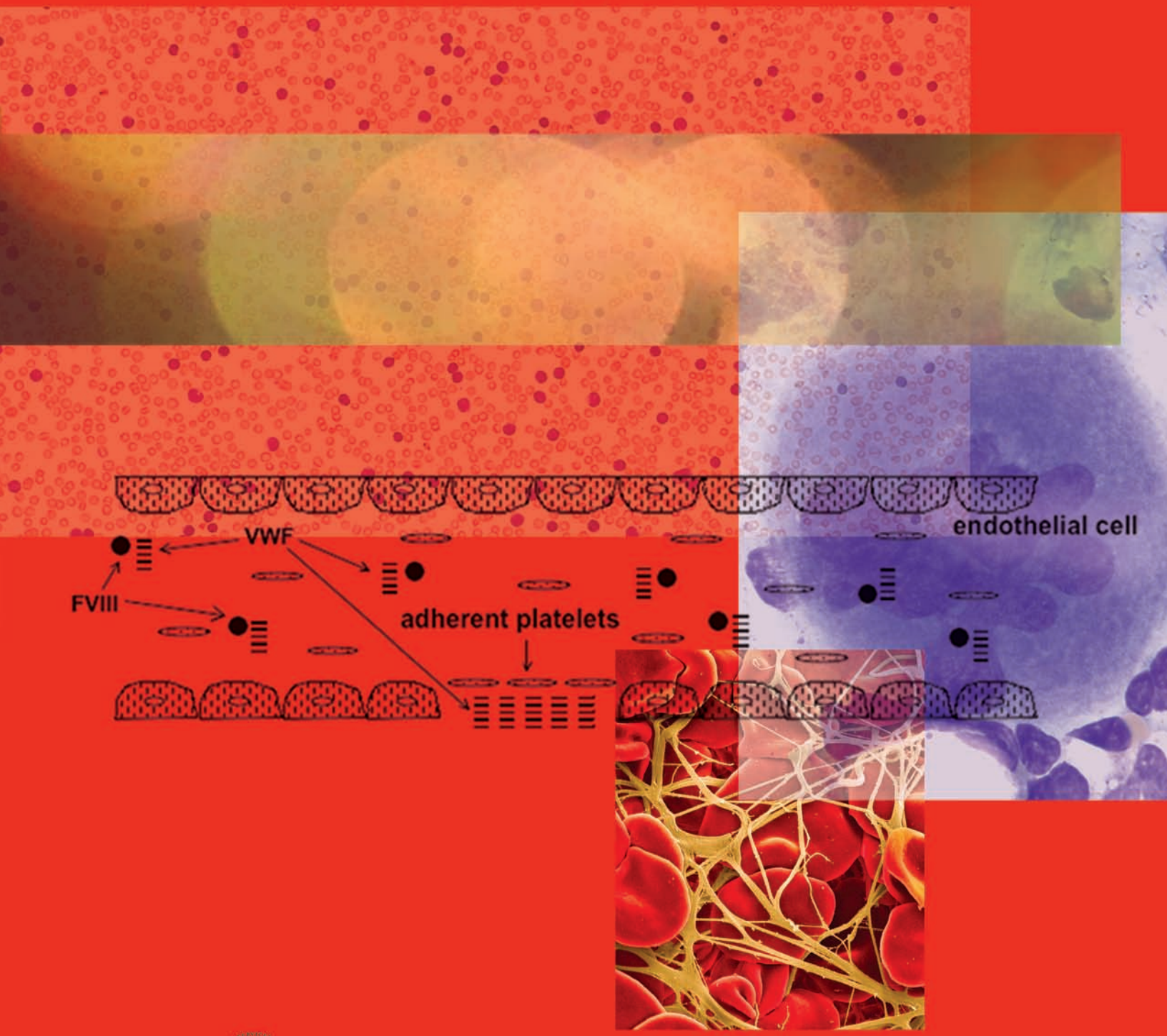
FULL REPORT

The Diagnosis, Evaluation, and Management of

von Willebrand Disease



U.S. Department of Health and Human Services
National Institutes of Health
National Heart, Lung, and Blood Institute

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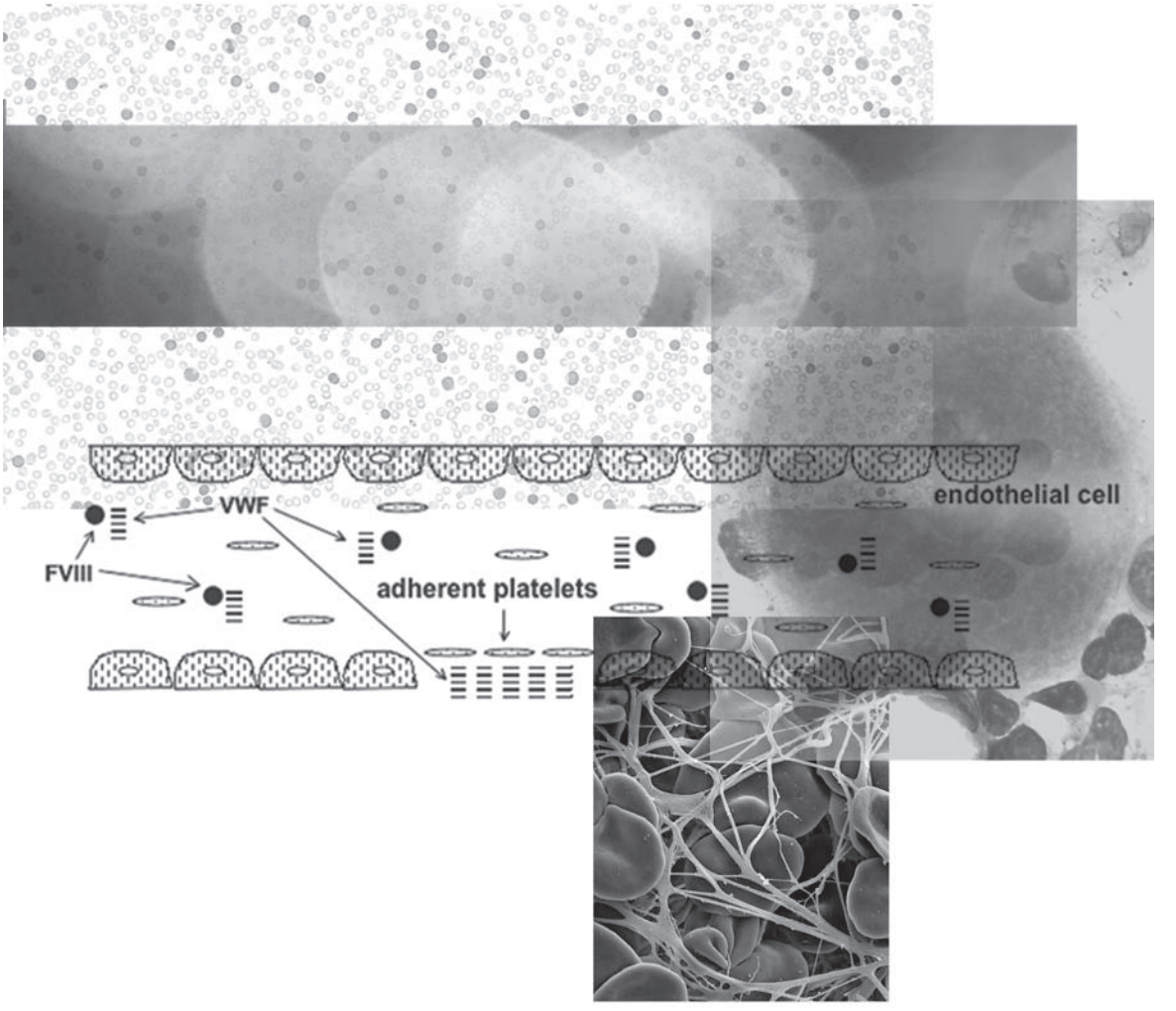

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Introduction

Von Willebrand disease (VWD) is an inherited bleeding disorder that is caused by deficiency or dysfunction of von Willebrand factor (VWF), a plasma protein that mediates the initial adhesion of platelets at sites of vascular injury and also binds and stabilizes blood clotting factor VIII (FVIII) in the circulation. Therefore, defects in VWF can cause bleeding by impairing platelet adhesion or by reducing the concentration of FVIII.

VWD is a relatively common cause of bleeding, but the prevalence varies considerably among studies and depends strongly on the case definition that is used. VWD prevalence has been estimated in several countries on the basis of the number of symptomatic patients seen at hemostasis centers, and the values range from roughly 23 to 110 per million population (0.0023 to 0.01 percent).[1]

The prevalence of VWD also has been estimated by screening populations to identify persons with bleeding symptoms, low VWF levels, and similarly affected family members. This population-based approach has yielded estimates for VWD prevalence of 0.6 percent,[2] 0.8 percent,[3] and 1.3 percent[4]—more than two orders of magnitude higher than the values arrived at by surveys of hemostasis centers.

The discrepancies between the methods for estimating VWD prevalence illustrate the need for better information concerning the relationship between VWF levels and bleeding. Many bleeding symptoms are exacerbated by defects in VWF, but the magnitude of the effect is not known. For example, approximately 12 percent of women who have menstrual periods have excessive menstrual bleeding.[5] This fraction is much higher among women who have VWD, but it also appears to be increased for women who have VWF levels at the lower end of the normal range. Quantitative data on these issues would allow a more informed approach to the diagnosis and management of VWD and could have significant implications for medical practice and for public health.

Aside from needs for better information about VWD prevalence and the relationship of low VWF levels to bleeding symptoms or risk, there are needs for enhancing knowledge and improving clinical and laboratory diagnostic tools for VWD. Furthermore, there are needs for better knowledge of and treatment options for management of VWD and bleeding or bleeding risk. As documented in this VWD guidelines publication, a relative paucity of published studies is available to support some of the recommendations which, therefore, are mainly based on Expert Panel opinion.

Guidelines for VWD diagnosis and management, based on the evidence from published studies and/or the opinions of experts, have been published for practitioners in Canada,[6] Italy,[7] and the United Kingdom,[8,9] but not in the United States. The VWD guidelines from the U.S. Expert Panel are based on review of published evidence as well as expert opinion. Users of these guidelines should be aware that individual professional judgment is not abrogated by recommendations in these guidelines.

These guidelines for diagnosis and management of VWD were developed for practicing primary care and specialist clinicians—including family physicians, internists, obstetrician-gynecologists, pediatricians, and nurse-practitioners—as well as hematologists and laboratory medicine specialists.

History of This Project

During the spring of 2004, the National Heart, Lung, and Blood Institute (NHLBI) began planning for the development of clinical practice guidelines for VWD in response to the FY 2004 appropriations conference committee report (House Report 108-401) recommendation. In that report, the conferees urged NHLBI to develop a set of treatment guidelines for VWD and to work with medical associations and experts in the field when developing such guidelines.

In consultation with the American Society of Hematology (ASH), the Institute convened an Expert Panel on VWD, chaired by Dr. William Nichols of the Mayo Clinic, Rochester, MN. The Expert Panel members were selected to provide expertise in basic sciences, clinical and laboratory diagnosis, evidence-based medicine, and the clinical management of VWD, including specialists in hematology as well as in family medicine, obstetrics and gynecology, pediatrics, internal medicine, and laboratory sciences. The Expert Panel comprised one basic scientist and nine physicians—including one family physician, one obstetrician and gynecologist, and seven hematologists with expertise in VWD (two were pediatric hematologists). Ad hoc members of the Panel represented the Division of Blood Diseases and Resources of the NHLBI. The Panel was coordinated by the Division for the Application of Research Discoveries (DARD), formerly the Office of Prevention, Education, and Control of the NHLBI. Panel members disclosed, verbally and in writing, any financial conflicts. (See page i for the financial and other disclosure summaries.)

Charge to the Panel

Dr. Barbara Alving, then Acting Director of the NHLBI, gave the charge to the Expert Panel to examine the current science in the area of VWD and to come to consensus regarding clinical recommendations for diagnosis, treatment, and management of this common inherited bleeding disorder. The Panel was also charged to base each recommendation on the current science and to indicate the strength of the relevant literature for each recommendation.

The development of this report was entirely funded by the NHLBI, National Institutes of Health (NIH). Panel members and reviewers participated as volunteers and were reimbursed only for travel expenses related to the three in-person Expert Panel meetings.

Panel Assignments

After the Expert Panel finalized a basic outline for the guidelines, members were assigned to the three sections: (1) Introduction and Background, (2) Diagnosis and Evaluation, and (3) Management of VWD. Three members were assigned lead responsibility for a particular section. The section groups were responsible for developing detailed outlines for the sections, reviewing the pertinent literature, writing the sections, and drafting recommendations with the supporting evidence for the full Panel to review.

Literature Searches

Three section outlines, approved by the Expert Panel chair, were used as the basis for compiling relevant search terms, using the Medical Subject Headings (MeSH terms) of the MEDLINE database. If appropriate terms were not available in MeSH, then relevant non-MeSH keywords were used. In addition to the search terms, inclusion and exclusion criteria were defined based on feedback from the Panel about specific limits to include in the search strategies, specifically:

- Date restriction: 1990–2004
- Language: English
- Study/publication types: randomized-controlled trial; meta-analysis; controlled clinical trial; epidemiologic studies; prospective studies; multicenter study; clinical trial; evaluation studies; practice guideline; review, academic; review, multicase; technical report; validation studies; review of reported cases; case reports; journal article (to exclude letters, editorials, news, etc.)

The search strategies were constructed and executed in the MEDLINE database as well as in the Cochrane Database of Systematic Reviews to compile a set of citations and abstracts for each section. Initial searches on specific keyword combinations and date and language limits were further refined by using the publication type limits to produce results that more closely matched the section outlines. Once the section results were compiled, the results were put in priority order by study type as follows:

1. Randomized-controlled trial
2. Meta-analysis (quantitative summary combining results of independent studies)
3. Controlled clinical trial
4. Multicenter study
5. Clinical trial (includes all types and phases of clinical trials)

6. Evaluation studies
7. Practice guideline (for specific health care guidelines)
8. Epidemiological
9. Prospective studies
10. Review, academic (comprehensive, critical, or analytical review)
11. Review, multicase (review with epidemiological applications)
12. Technical report
13. Validation studies
14. Review of reported cases (review of known cases of a disease)
15. Case reports

Upon examination of the yield of the initial literature search, it was determined that important areas in the section outlines were not addressed by the citations, possibly due to the date exclusions. In addition, Panel members identified pertinent references from their own searches and databases, including landmark references predating the 1990 date restriction, and 2005 and 2006 references (to October 2006). Therefore, as a followup, additional database searching was done using the same search strategies from the initial round, but covering dates prior to 1990 and during 2005 and 2006 to double check for key studies appearing in the literature outside the limits of the original range of dates. Also, refined searches in the 1990–2006 date range were conducted to analyze the references used by Panel members that had not appeared in the original search results.

These revised searches helped round out the database search to provide the most comprehensive approach possible. As a result, the references used in the guidelines included those retrieved from the two literature searches combined with the references suggested by the Panel members. These references inform the guidelines and clinical recommendations, based on the best available evidence in combination with the Panel's expertise and consensus.

Clinical Recommendations—Grading and Levels of Evidence

Recommendations made in this document are based on the levels of evidence described in Table 1, with a priority grading system of A, B, or C. Grade A is reserved for recommendations based on evidence levels Ia and Ib. Grade B is given for recommendations having evidence levels of IIa, IIb, and III; and Grade C is for recommendations based on evidence level IV.[8] None of the recommendations merited a Grade of A. Evidence tables are provided at the end of the document for those recommendations that are graded as B and have two or more references (see pages 83–111).

Table 1. Level of Evidence

Level	Type of Evidence
Ia	Evidence obtained from meta-analysis of randomized-controlled trials
Ib	Evidence obtained from at least one randomized-controlled trial
IIa	Evidence obtained from at least one well-designed controlled study without randomization
IIb	Evidence obtained from at least one other type of well-designed quasi-experimental study
III	Evidence obtained from well-designed non-experimental descriptive studies, such as comparative studies, correlation studies, and case-control studies
IV	Evidence obtained from expert committee reports or opinions and/or clinical experiences of respected authorities

Source: Acute pain management: operative or medical procedures and trauma. (Clinical practice guideline). Publication No. AHCPR 92–0032. Rockville, MD: Agency for Health Care Policy and Research, Public Health Service, U.S. Department of Health and Human Services, February 1992.

External and Internal Review

The NHLBI sought outside review of the guidelines through a two-fold process. The following Government agencies and professional organizations were invited to review the draft document and submit comments: Centers for Disease Control and Prevention, Food and Drug Administration, American Academy of Family Physicians, American College of Obstetricians and Gynecologists, American College of Physicians, American Society of Hematology, American Society of Pediatric Hematology/Oncology, College of American Pathologists, Hemophilia & Thrombosis Research Society, National Hemophilia Foundation Medical and Scientific Advisory Committee, and the North American Specialized Coagulation Laboratory Association. In addition, the guidelines were posted on the NHLBI Web site for public review and comment during a 30-day period ending September 22, 2006. Comments from the external review were compiled and given to the full Panel for review and consensus. Revisions to the document were then made as appropriate. The final draft, after Panel approval, was sent through review within the NIH and finally approved for publication by the NHLBI Director.

Scientific Overview

Discovery and Identification of VWD/VWF

The patient who led to the discovery of a hereditary bleeding disorder that we now call VWD was a 5-year-old girl who lived on the Åland Islands and was brought to Deaconess Hospital in Helsinki, Finland, in 1924 to be seen by Dr. Erik von Willebrand.[10] He ultimately assessed 66 members of her family and reported in 1926 that this was a previously undescribed bleeding disorder that differed from hemophilia and exhibited (1) mucocutaneous bleeding, (2) autosomal inheritance rather than being linked to the X chromosome, (3) prolonged bleeding times by the Duke method (ear lobe bleeding time), and (4) normal clotting time. Not only did he recognize the autosomal inheritance pattern, but he recognized that bleeding symptoms were greater in children and in women of childbearing age. He subsequently found that blood transfusions were useful not only to correct the anemia but also to control bleeding.

In the 1950s, it became clear that a "plasma factor," antihemophilic factor (FVIII), was decreased in these persons and that Cohn fraction I-0 could correct both the plasma deficiency of FVIII and the prolonged bleeding time. For the first time, the factor causing the long bleeding time was called "von Willebrand factor." As cryoprecipitate and commercial FVIII concentrates were developed, it was recognized that both VWF and "antihemophilic factor" (FVIII) purified together.

When immunoassays were developed, persons who had VWD (in contrast to those who had hemophilia A) were found to have reduced "factor VIII-related antigen" (FVIIIR:Ag), which we now refer to as VWF:Ag. Characterization of the proteins revealed that FVIII was the clotting protein deficient in hemophilia A, and VWF was a separate "FVIII carrier protein" that resulted in the cofractionation of both proteins in commercial concentrates. Furthermore, a deficiency of VWF resulted in increased FVIII clearance because of the reduced carrier protein, VWF.

Since the 1980s, molecular and cellular studies have defined hemophilia A and VWD more precisely. Persons who had VWD had a normal FVIII gene on the X chromosome, and some were found to have an abnormal VWF gene on chromosome 12. Variant forms of VWF were recognized in the 1970s, and we now recognize that these variations are the result of synthesis of an abnormal protein. Gene sequencing identified many of these persons as having a VWF gene mutation. The genetic causes of milder forms of low VWF are still under investigation, and these forms may not always be caused by an abnormal VWF gene. In addition, there are acquired disorders that may result in reduced or dysfunctional VWF (see section on "Acquired von Willebrand Syndrome" [AVWS]). Table 2 contains a synopsis of VWF designations, functions, and assays. Table 3 contains abbreviations used throughout this document.

The VWF Protein and Its Functions In Vivo

VWF is synthesized in two cell types. In the vascular endothelium, VWF is synthesized and subsequently stored in secretory granules (Weibel-Palade bodies) from which it can be released by stress or drugs such as desmopressin (DDAVP, 1-desamino-8-D-arginine vasopressin), a synthetic analog of vasopressin. VWF is also synthesized in bone marrow megakaryocytes where it is stored in platelet alpha-granules from which it is released following platelet activation. DDAVP does not release platelet VWF.

VWF is a protein that is assembled from identical subunits into linear strings of varying size referred to as multimers. These multimers can be >20 million daltons in mass and >2 micrometers in length. The complex cellular processing consists of dimerization in the endoplasmic reticulum (ER), glycosylation in the ER and Golgi, multimerization in the Golgi, and packaging into storage granules. The latter two

Table 2. Synopsis of VWF Designations, Properties, and Assays

Designation	Property	Assay
von Willebrand factor (VWF)	Multimeric glycoprotein that promotes platelet adhesion and aggregation and is a carrier for FVIII in plasma	See specific VWF assays below
von Willebrand factor ristocetin cofactor activity (VWF:RCo)	Binding activity of VWF that causes binding of VWF to platelets in the presence of ristocetin with consequent agglutination	Ristocetin cofactor activity: quantitates platelet agglutination after addition of ristocetin and VWF
von Willebrand factor antigen (VWF:Ag)	VWF protein as measured by protein assays; does not imply functional ability	Immunologic assays such as ELISA*, LIA*, RIA*, Laurell electroimmunoassay
von Willebrand factor collagen-binding activity (VWF:CB)	Ability of VWF to bind to collagen	Collagen-binding activity: quantitates binding of VWF to collagen-coated ELISA* plates
von Willebrand factor multimers	Size distribution of VWF multimers as assessed by agarose gel electrophoresis	VWF multimer assay: electrophoresis in agarose gel and visualization by monospecific antibody to VWF
Factor VIII (FVIII)	Circulating coagulation protein that is protected from clearance by VWF and is important in thrombin generation	FVIII activity: plasma clotting test based on PTT* assay using FVIII-deficient substrate; quantitates activity
Ristocetin-induced Platelet Aggregation (RIPA)	Test that measures the ability of a person's VWF to bind to platelets in the presence of various concentrations of ristocetin	RIPA: aggregation of a person's PRP* to various concentrations of ristocetin

*See Table 3. Nomenclature and Abbreviations.

processes are under the control of the VWF propeptide (VWFpp), which is cleaved from VWF at the time of storage. VWF that is released acutely into the circulation is accompanied by a parallel rise in FVIII, but it is still not entirely clear whether this protein–protein association first occurs within the endothelial cell.[11,12]

In plasma, the FVIII–VWF complex circulates as a loosely coiled protein complex that does not interact strongly with platelets or endothelial cells under basal conditions. When vascular injury occurs, VWF becomes tethered to the exposed subendothelium (collagen, etc.). The high fluid shear rates that occur in the microcirculation appear to induce a conformational change in multimeric VWF that causes platelets to adhere, become activated, and then aggregate so as to present an activated platelet phospholipid surface. This facilitates clotting that is, in part, regulated by FVIII. Because of the specific characteristics of hemostasis and fibrinolysis on mucosal surfaces, symptoms in VWD are often greater in these tissues.

Plasma VWF is primarily derived from endothelial synthesis. Platelet and endothelial cell VWF are released locally following cellular activation where this VWF participates in the developing hemostatic plug or thrombus (see Figure 1 on page 10).

Plasma VWF has a half-life of approximately 12 hours (range 9–15 hours). VWF is present as very large multimers that are subjected to physiologic degradation by the metalloprotease ADAMTS13 (A Disintegrin-like And Metalloprotease domain [reprolysin type] with Thrombospondin type I motifs). Deficiency of ADAMTS13 is associated with the pathologic microangiopathy of thrombotic thrombocytopenic purpura (TTP). The most common variant forms of type 2A VWD are characterized by increased VWF susceptibility to ADAMTS13.

Table 3. Nomenclature and Abbreviations

Designation	Definition
ADAMTS13	A Disintegrin-like And Metalloprotease domain (reprolysin type) with ThromboSpondin type 1 motifs, a plasma metalloprotease that cleaves multimeric VWF
ASH	American Society of Hematology
AVWS	acquired von Willebrand syndrome
BT	bleeding time
CAP	College of American Pathologists
CBC	complete blood count
CDC	Centers for Disease Control and Prevention
CFC	clotting factor concentrate
CI	confidence interval
C.I.	continuous infusion
CLSI	Clinical Laboratory Standards Institute (formerly National Committee for Clinical Laboratory Standards: NCCLS)
CNS	central nervous system
CV	coefficient of variation
Cyclic AMP	adenosine 3'5'cyclic phosphate
CK	cystine knot
D & C	dilation and curettage
DARD	Division for the Application of Research Discoveries
DDAVP	1-desamino-8-D-arginine vasopressin (desmopressin, a synthetic analog of vasopressin)
DIC	disseminated intravascular coagulation
DNA	deoxyribonucleic acid
DVT	deep vein thrombosis
ELISA	enzyme-linked immunosorbent assay
ER	endoplasmic reticulum
FDA	Food and Drug Administration
FFP	fresh frozen plasma
FVIII*	[blood clotting] factor VIII
FVIIIR:Ag*	factor VIII-related antigen (see VWF:Ag)
FVIII:C*	factor VIII coagulant activity
FVIII gene	factor VIII gene
GI	gastrointestinal

Table 3. Nomenclature and Abbreviations (continued)

Designation	Definition
GPIb	glycoprotein Ib (platelet)
GPIIb/IIIa	glycoprotein IIb/IIIa complex (platelet)
HRT	hormone replacement therapy
IgG	immunoglobulin G
IGIV	immune globulin intravenous (also known as IVIG)
ISTH	International Society on Thrombosis and Haemostasis
IU/dL	international units per deciliter
LIA	latex immunoassay (automated)
MAB	monoclonal antibody
MeSH	medical subject headings (in MEDLINE)
MGUS	monoclonal gammopathy of uncertain significance
NCCLS	National Committee for Clinical Laboratory Standards
NHF, MASAC	National Hemophilia Foundation, Medical and Scientific Advisory Committee
NHLBI	National Heart, Lung, and Blood Institute
NIH	National Institutes of Health
N.R.	not reported
NSAIDs	nonsteroidal anti-inflammatory drugs
OCP	oral contraceptive pill
PAI-1	plasminogen activator inhibitor type 1
PCR	polymerase chain reaction
PFA-100®	platelet function analyzer
PLT-VWD	platelet-type von Willebrand disease
PRP	platelet-rich plasma
PT	prothrombin time
PTT	partial thromboplastin time (activated partial thromboplastin time)
RIA	radioimmunoassay
RIPA	ristocetin-induced platelet aggregation
SDS	sodium dodecyl sulfate
TTP	thrombotic thrombocytopenic purpura
tPA	tissue plasminogen activator
TT	thrombin time
Tx	treatment

Table 3. Nomenclature and Abbreviations (continued)

Designation	Definition
VWD	von Willebrand disease
VWF*	von Willebrand factor (FVIII carrier protein)
VWF:Ac	von Willebrand factor activity
VWF:Ag*	von Willebrand factor antigen
VWF:CB*	von Willebrand factor collagen-binding activity
VWF:FVIIIB*	von Willebrand factor: factor VIII binding assay
VWF gene	von Willebrand factor gene
VWF:PB assay	von Willebrand factor platelet-binding assay
VWFpp	von Willebrand factor propeptide
VWF:RCo*	von Willebrand factor ristocetin cofactor activity
WHO	World Health Organization

*These abbreviations (for FVIII and VWF and all their properties) are defined in Marder VJ, Mannucci PM, Firkin BG, Hoyer LW, Meyer D. Standard nomenclature for factor VIII and von Willebrand factor: a recommendation by the International Committee on Thrombosis and Haemostasis. *Thromb Haemost* 1985 Dec;54(4):871–872; Mazurier C, Rodeghiero F. Recommended abbreviations for von Willebrand Factor and its activities. *Thromb Haemost 2001* Aug;86(2):712.

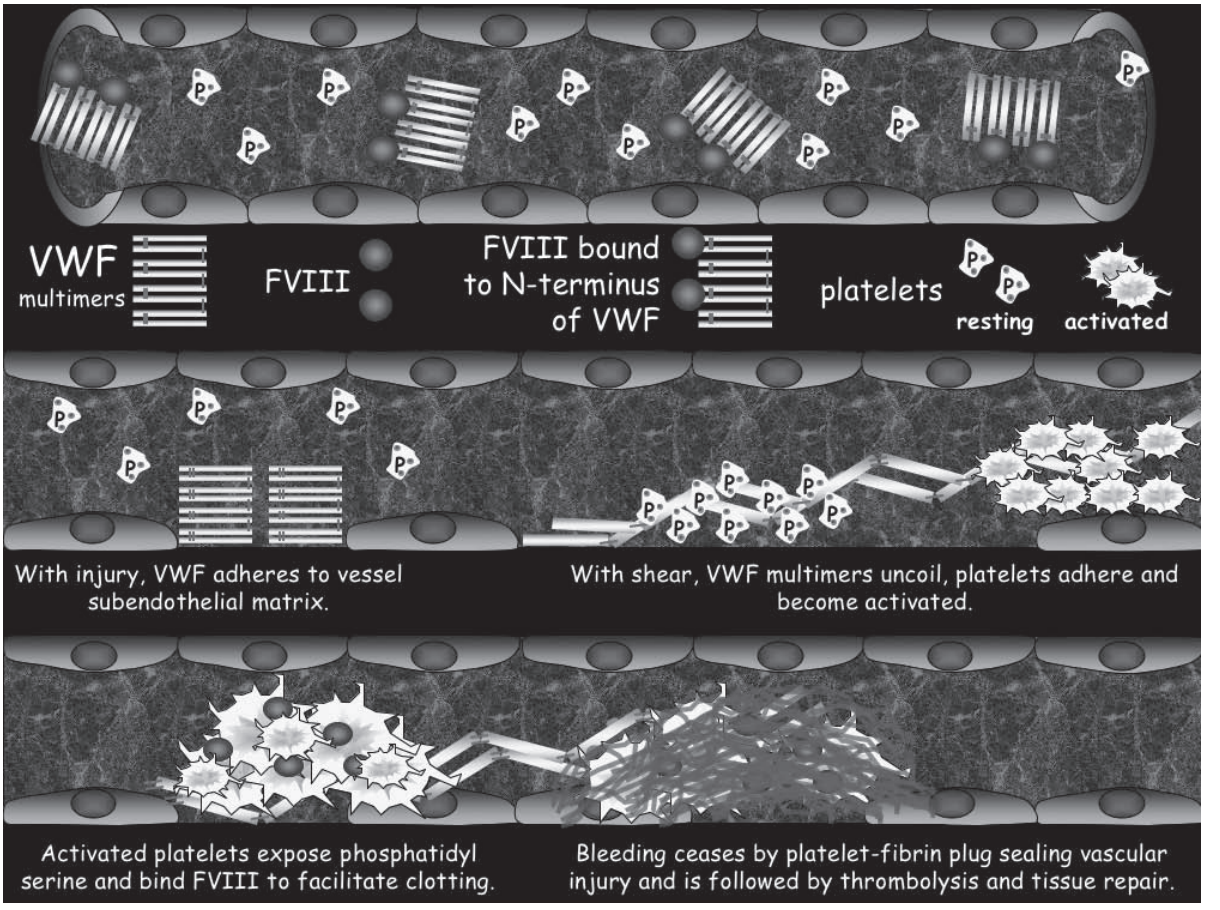
Factors that affect levels of plasma VWF include age, race, ABO and Lewis blood groups, epinephrine, inflammatory mediators, and endocrine hormones (particularly those associated with the menstrual cycle and pregnancy). VWF is increased during pregnancy (a three- to fivefold elevation over the woman's baseline by the third trimester), with aging, and with acute stress or inflammation. Africans and African Americans have higher average levels of VWF than the Caucasian population.[13,14] VWF is reduced by hypothyroidism and rarely by autoantibodies to VWF. The rate of VWF synthesis probably is not affected by blood group; however, the survival of VWF appears to be reduced in individuals who have type O blood. In fact, ABO blood group substance has been identified on VWF.

The Genetics of VWD

Since the 1980s, molecular and cellular studies have defined hemophilia A and VWD more precisely. Persons who have severe VWD have a normal FVIII gene on the X chromosome, and some are found to have an abnormal VWF gene on chromosome 12. The VWF gene is located near the tip of the short arm of chromosome 12, at 12p13.3.[15] It spans approximately 178 kb of DNA and contains 52 exons.[16] Intron–exon boundaries tend to delimit structural domains in the protein, and introns often occur at similar positions within the gene segments that encode homologous domains. Thus, the structure of the VWF gene reflects the mosaic nature of the protein (Figure 2).

A partial, unprocessed VWF pseudogene is located at chromosome 22q11.2.[17] This pseudogene spans approximately 25 kb of DNA and corresponds to exons 23–34 and part of the adjacent introns of the VWF gene.[18] This segment of the gene encodes domains A1A2A3, which contain binding sites for platelet glycoprotein Ib (GPIb) and collagen, as well as the site cleaved by ADAMTS13. The VWF pseudogene and gene have diverged 3.1 percent in DNA sequence, consistent with a relatively recent origin of the pseudogene by partial gene duplication.[18] This pseudogene is found in humans and great apes (bonobo, chimpanzee,

Figure 1. VWF and Normal Hemostasis



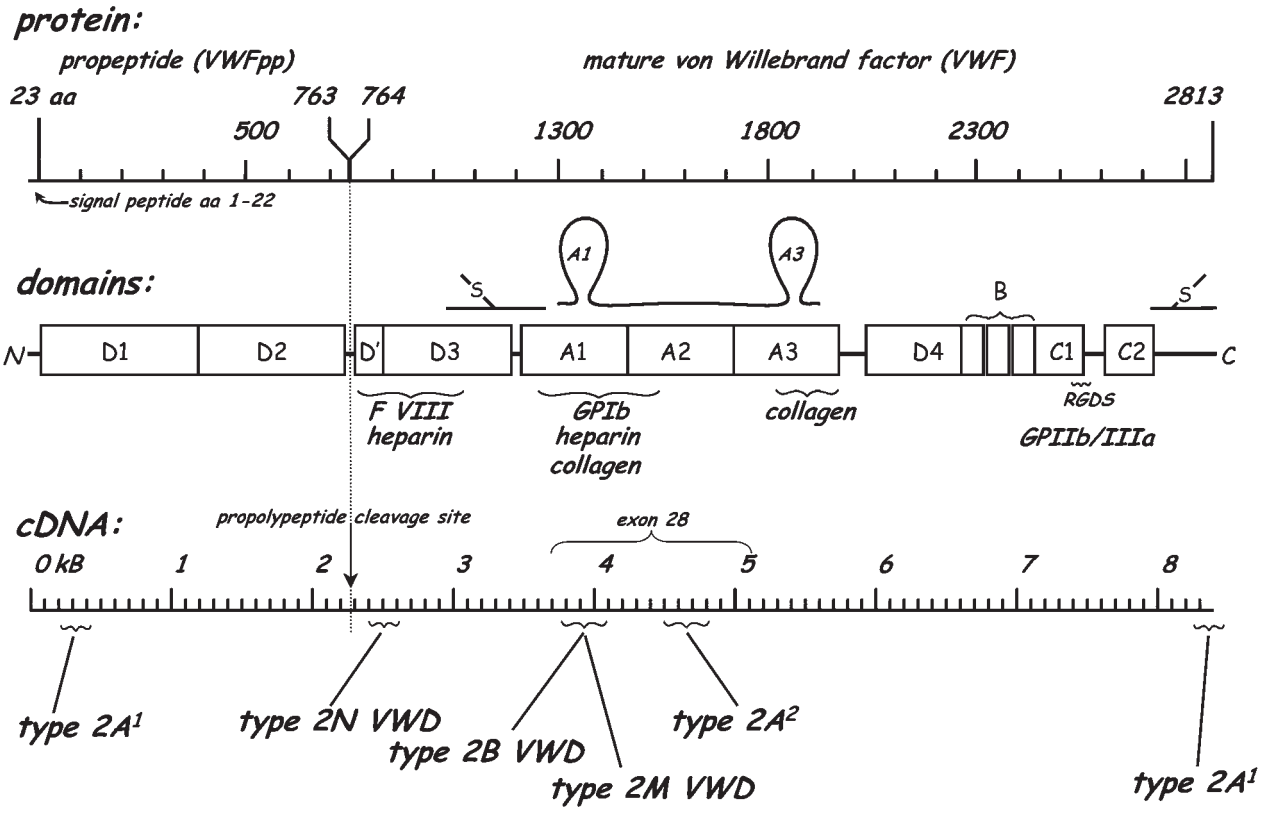
A cross-sectioned blood vessel shows stages of hemostasis. Top, VWF is the carrier protein for blood clotting factor VIII (FVIII). Under normal conditions VWF does not interact with platelets or the blood vessel wall that is covered with endothelial cells. Middle left, following vascular injury, VWF adheres to the exposed subendothelial matrix. Middle right, after VWF is uncoiled by local shear forces, platelets adhere to the altered VWF and these platelets undergo activation and recruit other platelets to this injury site. Bottom left, the activated and aggregated platelets alter their membrane phospholipids exposing phosphatidylserine, and this activated platelet surface binds clotting factors from circulating blood and initiates blood clotting on this surface where fibrin is locally deposited. Bottom right, the combination of clotting and platelet aggregation and adhesion forms a platelet-fibrin plug, which results in the cessation of bleeding. The extent of the clotting is carefully regulated by natural anticoagulants. Subsequently, thrombolysis initiates tissue repair and ultimately the vessel may be re-endothelialized and blood flow maintained.
Note: Used by permission of R.R. Montgomery.

gorilla, orangutan) but not in more distantly related primates.[19] The VWF pseudogene complicates the detection of VWF gene mutations because polymerase chain reactions (PCRs) can inadvertently amplify segments from either or both loci, but this difficulty can be overcome by careful design of gene-specific PCR primers.[18]

The VWF pseudogene may occasionally serve as a reservoir of mutations that can be introduced into the VWF locus. For example, some silent and some potentially pathogenic mutations have been identified in exons 27 and 28 of the VWF gene of persons who have VWD. These same sequence variations occur consecutively in the VWF pseudogene and might have been transferred to the VWF by gene conversion.[20–22] The segments involved in the potential gene conversion events are relatively short, from a minimum of 7 nucleotides[20] to a maximum of 385 nucleotides.[22] The frequency of these potential interchromosomal exchanges is unknown.

The spectrum of VWF gene mutations that cause VWD is similar to that of many other human genetic diseases and includes large deletions, frameshifts from small insertions or deletions, splice-site mutations, nonsense mutations causing premature termination of translation, and missense mutations affecting

Figure 2. | Structure and Domains of VWF



The von Willebrand factor (VWF) protein sequence (amino acid 1–2813) is aligned with the cDNA sequence (nucleic acid 1–8439). The VWF signal peptide is the first 22 aa, the propeptide (VWFpp) aa 23–763, and mature VWF aa 764–2800. Type 2 mutations are primarily located in specific domains (regions) along the VWF protein. Types 2A, 2B, and 2M VWF mutations are primarily located within exon 28 that encodes for the A1 and A2 domains of VWF. The two different types of 2A are those that have increased proteolysis ($2A^2$) and those with abnormal multimer synthesis ($2A^1$). Type 2N mutations are located within the D' and D3 domains. Ligands that bind to certain VWF domains are identified, including FVIII, heparin, GPIb (platelet glycoprotein Ib complex), collagen, and GPIIb/IIIa (platelet glycoprotein IIb/IIIa complex that binds to the RGD [arginine-glycine-aspartate] amino acid sequence in VWF).
Note: Used by permission of R.R. Montgomery.

single amino acid residues. A database of VWF mutations and polymorphisms has been compiled for the International Society on Thrombosis and Haemostasis (ISTH)[23,24] and is maintained for online access at the University of Sheffield (http://www.shef.ac.uk/vwf/index.html). Mutations causing VWD have been identified throughout the VWF gene. In contrast to hemophilia A, in which a single major gene rearrangement causes a large fraction of severe disease, no such recurring mutation is common in VWD. There is a good correlation between the location of mutations in the VWF gene and the subtype of VWD, as discussed in more detail in "Classification of VWD Subtypes." In selected families, this information can facilitate the search for VWF mutations by DNA sequencing.

Classification of VWD Subtypes

VWD is classified on the basis of criteria developed by the VWF Subcommittee of the ISTH, first published in 1994 and revised in 2006 (Table 4).[25,26]

The classification was intended to be clinically relevant to the treatment of VWD. Diagnostic categories were defined that encompassed distinct pathophysiologic mechanisms and correlated with the response to treatment with DDAVP or blood products. The classification was designed to be conceptually independent of specific laboratory testing procedures, although most of the VWD subtypes could be assigned by using tests that were widely available. The 1994 classification reserved the designation of VWD for disorders caused by mutations within the VWF gene,[25] but this criterion

Table 4. Classification of VWD

Type	Description
1	Partial quantitative deficiency of VWF
2	Qualitative VWF defect
2A	Decreased VWF-dependent platelet adhesion with selective deficiency of high-molecular-weight multimers
2B	Increased affinity for platelet GPIb
2M	Decreased VWF-dependent platelet adhesion without selective deficiency of high-molecular-weight multimers
2N	Markedly decreased binding affinity for FVIII
3	Virtually complete deficiency of VWF

Note: VWD types are defined as described in Sadler JE, Budde U, Eikenboom JC, Favaloro EJ, Hill FG, Holmberg L, Ingerslev J, Lee CA, Lillicrap D, Mannucci PM, et al. Update on the pathophysiology and classification of von Willebrand disease: a report of the Subcommittee on von Willebrand Factor. *J Thromb Haemost* 2006 Oct;4(10):2103–2114.

has been dropped from the 2006 classification[26] because in practice it is verifiable for only a small fraction of patients.

VWD is classified into three major categories: partial quantitative deficiency (type 1), qualitative deficiency (type 2), and total deficiency (type 3). Type 2 VWD is divided further into four variants (2A, 2B, 2M, 2N) on the basis of details of the phenotype. Before the publication of the 1994 revised classification of VWD,[25] VWD subtypes were classified using Roman numerals (types I, II, and III), generally corresponding to types 1, 2, and 3 in the 1994 classification, and within type II several subtypes existed (designated by adding sequential letters of the alphabet; i.e., II-A through II-I). Most of the latter VWD variants were amalgamated as type 2A in the 1994 classification, with the exception of type 2B (formerly II-B) for which a separate new classification was created. In addition, a new subtype (2M) was created to include variants with decreased platelet dependent function (VWF:RCo) but no significant decrease of higher molecular weight VWF multimers (which may or may not have other aberrant structure), with "M" representing "multimer." Subtype 2N VWD was defined, with "N" representing "Normandy" where the first individuals were identified, with decreased FVIII due to VWF defects of FVIII binding.

Type 1 VWD affects approximately 75 percent of symptomatic persons who have VWD (see Castaman et al., 2003 for a review).[27] Almost all of the remaining persons are divided among the four

Table 5. Inheritance, Prevalence, and Bleeding Propensity in Patients Who Have VWD

Type	Inheritance	Prevalence	Bleeding Propensity
Type 1	Autosomal dominant	Up to 1%	Mild to moderate
Type 2A	Autosomal dominant (or recessive)	Uncommon	Variable—usually moderate
Type 2B	Autosomal dominant	Uncommon	Variable—usually moderate
Type 2M	Autosomal dominant (or recessive)	Uncommon	Variable—usually moderate
Type 2N	Autosomal recessive	Uncommon	Variable—usually moderate
Type 3 (Severe)	Autosomal recessive	Rare (1:250,000 to 1:1,000,000)	High (severe bleeding)

type 2 variants, and the partitioning among them varies considerably among centers. In France, for example, patients' distribution was reported to be 30 percent type 2A, 28 percent type 2B, 8 percent type 2M (or unclassified), and 34 percent type 2N.[28] In Bonn, Germany, the distribution was reported to be 74 percent type 2A, 10 percent type 2B, 13 percent type 2M, and 3.5 percent type 2N.[29] Table 5 summarizes information about inheritance, prevalence, and bleeding propensity in persons who have different types of VWD.

The prevalence of type 3 VWD in the population is not known precisely but has been estimated (per million population) as: 0.55 for Italy,[30] 1.38 for North America,[31] 3.12 for Sweden,[30] and 3.2 for Israel.[32] The prevalence may be as high as 6 per million where consanguinity is common.[1]

Type 1 VWD

Type 1 VWD is found in persons who have partial quantitative deficiency of VWF. The level of VWF in plasma is low, and the remaining VWF mediates platelet adhesion normally and binds FVIII normally. Laboratory evaluation shows concordant decreases in VWF protein concentration (VWF:Ag) and assays of VWF function (VWF:RCo). Levels of blood clotting FVIII usually parallel VWF and may be reduced secondary to reduced VWF. Usually, in type 1 VWD, the FVIII/VWF:Ag ratio is 1.5–2.0. In most persons who have type 1 VWD, this results in FVIII being normal, or mildly decreased, and not reduced as much as the VWF. VWF multimer gels show no significant decrease in large VWF multimers.[25] The laboratory evaluation of VWD is discussed in the "Diagnosis and Evaluation" section.

The spectrum of mutations occurring in VWD type 1 has been described extensively in two major studies.[33,34] Particularly severe, highly penetrant forms of type 1 VWD may be caused by dominant VWF mutations that interfere with the intracellular transport of dimeric proVWF[35-39] or that promote the rapid clearance of VWF from the circulation.[38,40,41] Persons who have such mutations usually have VWF levels <20 IU/dL.[33,34] Most of the mutations characterized to date cause single amino acid substitutions in domain D3.[35–37,39,42] One mutation associated with rapid clearance has been reported in domain D4.[38]

Increased clearance of VWF from the circulation in type 1 VWD may account for the exaggerated but unexpectedly brief responses to DDAVP observed in some patients. Consequently, better data on the prevalence of increased clearance could affect the approach to diagnosing type 1 VWD and the choice of treatment for bleeding.

A diagnosis of type 1 VWD is harder to establish when the VWF level is not markedly low but instead is near the lower end of the normal range. Type 1 VWD lacks a qualitative criterion by which it can be recognized and instead relies only on quantitative decrements of protein concentration and function. VWF levels in the healthy population span a wide range of values. The mean level of plasma VWF is 100 IU/dL, and approximately 95 percent of plasma VWF levels lie between 50 and 200 IU/dL.[43,44] Because mild bleeding symptoms are very common in the healthy population, the association of bleeding symptoms with a moderately low VWF level may be coincidental.[45] The conceptual and practical issues associated with the evaluation of moderately low VWF levels are discussed more completely later in this section. (See "Type 1 VWD Versus Low VWF: VWF Level as a Risk Factor for Bleeding.")

Type 2 VWD

The clinical features of several type 2 VWD variants are distinct from those of type 1 VWD, and they can have strikingly distinct and specific therapeutic needs. As a consequence, the medical care of patients who have type 2 VWD benefits from the participation of a hematologist who has expertise in hemostasis. Bleeding symptoms in type 2 VWD are often thought to be more severe than in type 1 VWD, although this impression needs to be evaluated in suitable clinical studies.

Type 2A VWD refers to qualitative variants in which VWF-dependent platelet adhesion is decreased because the proportion of large VWF multimers is decreased. Levels of VWF:Ag and FVIII may be normal or modestly decreased, but VWF function is abnormal as shown by markedly decreased VWF:RCo.[46] Type 2A VWD may be caused by mutations that interfere with the assembly or secretion of large multimers or by mutations that increase the susceptibility of VWF multimers to proteolytic degradation in the circulation.[47–49] The deficit of large multimers predisposes persons to bleed.

The location of type 2A VWD mutations sometimes can be inferred from high-resolution VWF multimer gels. For example, mutations that primarily reduce multimer assembly lead to the secretion of multimers that are too small to engage platelets effectively and therefore are relatively resistant to proteolysis by ADAMTS13. Homozygous mutations in the propeptide impair multimer assembly in the Golgi and give rise to a characteristic "clean" pattern of small multimers that lack the satellite bands usually associated with proteolysis (see "Diagnosis and Evaluation"); this pattern was initially described as "type IIC" VWD.[50–52] Heterozygous mutations in the cystine knot (CK) domain can impair dimerization of proVWF in the ER and cause a recognizable multimer pattern originally referred to as "type IID."[53,54] A mixture of monomers and dimers arrives in the Golgi, where the incorporation of monomers at the end of a multimer prevents further elongation. As a result, the secreted small multimers contain minor species with an odd number of subunits that appear as faint bands between the usual species that contain an even number of subunits. Heterozygous mutations in cysteine residues of the D3 domain also can impair multimer assembly, but these mutations often also produce an indistinct or "smeary" multimer pattern referred to as "type IIE."[55,56]

In contrast to mutations that primarily affect multimer assembly, mutations within or near the A2 domain of VWF cause type 2A VWD that is associated with markedly increased proteolysis of the VWF subunits[56] (see Figure 2, on page 11). These mutations apparently interfere with the folding of the A2 domain and make the Tyr1605–Met1606 bond accessible to ADAMTS13 even in the absence of increased fluid shear stress. Two subgroups of this pattern have been distinguished: group I mutations enhance proteolysis by ADAMTS13 and also impair multimer assembly, whereas group II mutations enhance proteolysis without decreasing the assembly of large VWF multimers.[49] Computer modeling of domain A2 suggests that group I mutations affect both assembly and proteolysis, because group I mutations have a more disruptive effect on the folding of domain A2 than do group II mutations.[57]

Type 2B VWD is caused by mutations that pathologically increase platelet–VWF binding, which leads to the proteolytic degradation and depletion of large, functional VWF multimers.[56,58] Circulating platelets also are coated with mutant VWF, which may prevent the platelets from adhering at sites of injury.[59]

Although laboratory results for type 2B VWD may be similar to those in type 2A or type 2M VWD, patients who have type 2B VWD typically have thrombocytopenia that is exacerbated by surgery, pregnancy, or other stress.[60–62] The thrombocytopenia probably is caused by reversible sequestration of VWF–platelet aggregates in the microcirculation. These aggregates are dissolved by the action of ADAMTS13 on VWF, causing the characteristic decrease of large VWF multimers and the prominent satellite banding pattern that indicates increased proteolytic degradation.[63,64] The diagnosis of type 2B VWD depends on finding abnormally increased ristocetin induced platelet aggregation (RIPA) at low concentrations of ristocetin.

Type 2B VWD mutations occur within or adjacent to VWF domain A1,[23,55,65–68] which changes conformation when it binds to platelet GPIb.[69] The mutations appear to enhance platelet binding by stabilizing the bound conformation of domain A1.

Type 2M VWD includes variants with decreased VWF-dependent platelet adhesion that is not caused by the absence of high-molecular-weight VWF multimers. Instead, type 2M VWD mutations reduce the interaction of VWF with platelet GPIb or with connective tissue and do not substantially impair multimer assembly. Screening laboratory results in type 2M VWD and type 2A VWD are similar, and the distinction between them depends on multimer gel electrophoresis.[67]

Mutations in type 2M VWD have been identified in domain A1 (see Figure 2 on page 11), where they interfere with binding to platelet GPIb.[23,55,67,70–72] One family has been reported in which a mutation in VWF domain A3 reduces VWF binding to collagen, thereby reducing platelet adhesion and possibly causing type 2M VWD.[73]

Type 2N VWD is caused by VWF mutations that impair binding to FVIII, lowering FVIII levels so that type 2N VWD masquerades as an autosomal recessive form of hemophilia A.[74–76] In typical cases, the FVIII level is less than 10 percent, with a normal VWF:Ag and VWF:RCo. Discrimination from hemophilia A may require assays of FVIII–VWF binding.[77,78]

Most mutations that cause type 2N VWD occur within the FVIII binding site of VWF (see Figure 2

on page 11), which lies between residues Ser764 and Arg1035 and spans domain D' and part of domain D3.[23,79,80] The most common mutation, Arg854Gln, has a relatively mild effect on FVIII binding and tends to cause a less severe type 2N VWD phenotype.[77] Some mutations in the D3 domain C-terminal of Arg1035 can reduce FVIII binding,[81–83] presumably through an indirect effect on the structure or accessibility of the binding site.

Type 3 VWD

Type 3 VWD is characterized by undetectable VWF protein and activity, and FVIII levels usually are very low (1–9 IU/dL).[84–86] Nonsense and frameshift mutations commonly cause type 3 VWD, although large deletions, splice-site mutations, and missense mutations also can do so. Mutations are distributed throughout the VWF gene, and most are unique to the family in which they were first identified.[23,87,88]

A small fraction of patients who have type 3 VWD develop alloantibodies to VWF in response to the transfusion of plasma products. These antibodies have been reported in 2.6–9.5 percent of patients who have type 3 VWD, as determined by physician surveys or screening.[85,89] The true incidence is uncertain, however, because of unavoidable selection bias in these studies. Anti-VWF alloantibodies can inhibit the hemostatic effect of blood-product therapy and also may cause life-threatening allergic reactions.[85,90] Large deletions in the VWF gene may predispose patients to this complication.[89]

VWD Classification, General Issues

The principal difficulties in using the current VWD classification concern how to define the boundaries between the various subtypes through laboratory testing. In addition, some mutations have pleiotropic effects on VWF structure and function, and some persons are compound heterozygous for mutations that cause VWD by different mechanisms. This heterogeneity can produce complex phenotypes that are difficult to categorize. Clinical studies of the relationship between VWD genotype and clinical phenotype would be helpful to improve the management of patients with the different subtypes of VWD.

The distinction between quantitative (type 1) and qualitative (type 2) defects depends on the ability to recognize discrepancies among VWF assay results,[80,91] as discussed in "Diagnosis and Evaluation." Similarly, distinguishing between type 2A and type 2M VWD requires multimer gel analysis. Standards need to be established for using laboratory tests to make these important distinctions.

The example of Vicenza VWD illustrates some of these problems. Vicenza VWD was first described as a variant of VWD in which the level of plasma VWF is usually <15 IU/dL and the VWF multimers are even larger than normal, like the ultralarge multimers characteristic of platelet VWF.[92] The low level of VWF in plasma in Vicenza VWD appears to be explained by the effect of a specific mutation, Arg1205His, that promotes clearance of VWF from the circulation about fivefold more rapidly than normal.[41] Because the newly synthesized multimers have less opportunity to be cleaved by ADAMTS13 before they are cleared, accelerated clearance alone may account for the increased multimer size in Vicenza VWD.[93] Whether Vicenza VWD is classified under type 1 VWD or type 2M VWD depends on the interpretation of laboratory test results. The abnormally large multimers and very low RIPA values have led some investigators to prefer the designation of type 2M VWD.[94] However, the VWF:RCo/VWF: Ag ratio typically is normal, and large VWF multimers are not decreased relative to smaller multimers, so that other investigators have classified Vicenza VWD under type 1 VWD.[41] Regardless of how this variant is classified, the markedly shortened half-life of plasma VWF in Vicenza VWD is a key fact that, depending on the clinical circumstance, may dictate whether the patient should receive treatment with DDAVP or FVIII/VWF concentrates.

Type 1 VWD Versus Low VWF: VWF Level as a Risk Factor for Bleeding

Persons who have very low VWF levels, <20 IU/dL, are likely to have VWF gene mutations, significant bleeding symptoms, and a strongly positive family history.[33,34,37,95–99] Diagnosing such persons as having type 1 VWD seems appropriate because they may benefit from changes in lifestyle and from specific treatments to prevent or control bleeding. Identification of affected family members also may be useful, and genetic counseling is simplified when the pattern of inheritance is straightforward.

On the other hand, VWF levels of 30–50 IU/dL, just below the usual normal range (50–200 IU/dL), pose problems for diagnosis and treatment. Among the total U.S. population of approximately 300 million, VWF levels <50 IU/dL are expected in about 7.5 million persons, who therefore would be at risk for a diagnosis of type 1 VWD. Because of the strong influence of ABO blood group on VWF level,[43] about 80 percent of U.S. residents who have low VWF also have blood type O. Furthermore, moderately low VWF levels and bleeding symptoms generally are not coinherited within families and are not strongly associated with intragenic VWF mutations.[100–102] In a recent Canadian study of 155 families who had type 1 VWD, the proportion showing linkage to the VWF locus was just 41 percent.[98] In a similar European study, linkage to the VWF locus depended on the severity of the phenotype. If plasma levels of VWF were <30 IU/dL, linkage was consistently observed, but if levels of VWF were >30 IU/dL, the proportion of linkage was only 51 percent.[97] Furthermore, bleeding symptoms were not significantly linked to the VWF gene in these families.[97]

Family studies suggest that 25–32 percent of the variance in plasma VWF is heritable.[103,104] Twin studies have reported greater heritability of 66–75 percent,[105,106] although these values may be overestimates because of shared environmental factors.[104,107] Therefore, it appears that, at least in the healthy population, a substantial fraction of the variation in VWF level is not heritable.

Few genes have been identified that contribute to the limited heritability of VWF level. The major genetic influence on VWF level is ABO blood group, which is thought to account for 20–30 percent of its heritable variance.[13,106,108] The mean VWF level for blood type O is 75 U/dL, which is 25–35 U/dL lower than other ABO types, and 95 percent of VWF levels for type O blood donors are between 36 and 157 U/dL.[43] The Secretor locus has a smaller effect. Secretor-null persons have VWF levels slightly lower than Secretors.[109]

Table 6. Bleeding and VWF Level in Type 3 VWD Heterozygotes

Reference (First author, year)	Setting	Population	Results
Castaman et al. 2002[a111]	1 family with type 3 proband	11 heterozygous	None with bleeding; 6 who had VWF <50 IU/dL
Eikenboom et al. 1998[21]	8 families with type 3 probands	22 heterozygous	2 who had mild bleeding among 9 who had VWF <50 IU/dL
Zhang et al. 1995[112]	13 families with type 3 probands	55 heterozygous	22 who had mild bleeding among 38 who had VWF <50 IU/dL; 9 who had mild bleeding among 17 who had VWF >50 IU/dL
Schneppenheim et al. 1994[113]	22 families with type 3 probands	44 heterozygous	5 who had epistaxis, bruising, or menorrhagia among 24 who had VWF <50 IU/dL; 1 who had postoperative bleeding among 20 who had VWF >50 IU/dL
Eikenboom 1993[114]	1 family with type 3 probands	4 heterozygous	2 who had mild bleeding among 4 who had VWF <50 IU/dL
Inbal et al. 1992[115]	4 families with type 3 probands	20 heterozygous	None who had bleeding; 15 who had VWF <50 IU/dL
Nichols et al. 1991[116]	1 family with type 3 proband	6 heterozygous	None who had bleeding; 2 who had VWF <50 IU/dL
Mannucci et al. 1989[44]	15 families with type 3 probands	28 heterozygous	None who had bleeding; 19 who had VWF <50 IU/dL

An effect of the VWF locus has been difficult to discern by linkage analysis. One study suggested that 20 percent of the variance in VWF levels is attributable to the VWF gene,[108] whereas another study could not demonstrate such a relationship.[110]

In sum, known genetic factors account for a minority of the heritable variation in VWF level, and moderately low VWF levels (30–50 IU/dL) do not show consistent linkage to the VWF locus.[97,98,100,101] The diagnosis and management of VWD would be facilitated by better knowledge of how inherited and environmental factors influence the plasma concentration of VWF.

The attribution of bleeding to a low VWF level can be difficult because mild bleeding symptoms are very common, as discussed in the section on "Diagnosis and Evaluation," and the risk of bleeding is only modestly increased for persons who have moderately decreased VWF levels.[45] For example, in the course of investigating patients who have type 3 VWD, approximately 190 obligate heterozygous relatives have had bleeding histories obtained and VWF levels measured (see Table 6). The geometric mean VWF level was 47 IU/dL,45 with a range (±2 SD) of 16–140 IU/dL. Among 117 persons who had VWF <50 IU/dL, 31 (26 percent) had bleeding symptoms. Among 74 persons who had VWF >50 IU/dL, 10 (14 percent) had bleeding symptoms. Therefore, the relative risk of bleeding was 1.9 ($P = 0.046$, Fisher's exact test) for persons who had low VWF. There was a trend for an increased frequency of bleeding symptoms at the lowest VWF levels: among 31 persons who had VWF levels <30 IU/dL, 12 (39 percent) had symptoms. Bleeding was mild and consisted of epistaxis, bruising, menorrhagia, and bleeding after tooth extraction. The one person who experienced postoperative bleeding had a VWF level >50 IU/dL.[113]

The management of bleeding associated with VWF deficiency would be facilitated by better understanding of the heritability of low VWF levels (in the range of 20–50 IU/dL), their association with intragenic VWF mutations, and their interactions with other modifiers of bleeding risk. Such data could provide a foundation for treating VWF level as a biomarker for a moderate risk of bleeding, much as high blood pressure and high cholesterol are treated as biomarkers for cardiovascular disease (CVD) risk.

Acquired von Willebrand Syndrome

Acquired von Willebrand syndrome (AVWS) refers to defects in VWF concentration, structure, or function that are not inherited directly but are consequences of other medical disorders. Laboratory findings in AVWS are similar to those in VWD and may include decreased values for VWF:Ag, VWF:RCo, or FVIII. The VWF multimer distribution may be normal, but the distribution often shows a decrease in large multimers similar to that seen in type 2A VWD.[117,118] AVWS usually is caused by one of three mechanisms: autoimmune clearance or inhibition of VWF, increased shear-induced proteolysis of VWF, or increased binding of VWF to platelets or other cell surfaces. Autoimmune mechanisms may cause AVWS in association with lymphoproliferative diseases, monoclonal gammopathies, systemic lupus erythematosis, other autoimmune disorders, and some cancers. Autoantibodies to VWF have been detected in less than 20 percent of patients in whom they have been sought, suggesting that the methods for antibody detection may not be sufficiently sensitive or that AVWS in these settings may not always have an autoimmune basis.

Pathologic increases in fluid shear stress can occur with cardiovascular lesions, such as ventricular septal defect and aortic stenosis, or with primary pulmonary hypertension. The increased shear stress can increase the proteolysis of VWF by ADAMTS13 enough to deplete large VWF multimers and thereby produce a bleeding diathesis that resembles type 2A VWD. The VWF multimer distribution improves if the underlying cardiovascular condition is treated successfully.[117–122]

Increased binding to cell surfaces, particularly platelets, also can consume large VWF multimers. An inverse relationship exists between the platelet count and VWF multimer size, probably because increased encounters with platelets promote increased cleavage of VWF by ADAMTS13. This mechanism probably accounts for AVWS associated with myeloproliferative disorders; reduction of the platelet count can restore a normal VWF multimer distribution.[123–125] In rare instances, VWF has been reported to bind GPIb that was expressed ectopically on tumor cells.[118,126]

AVWS has been described in hypothyroidism caused by nonimmune mechanism.[127] Several drugs have been associated with AVWS; those most commonly

reported include valproic acid, ciprofloxacin, griseofulvin, and hydroxyethyl starch.[117,118]

AVWS occurs in a variety of conditions, but other clinical features may direct attention away from this potential cause of bleeding. More studies are needed to determine the incidence of AVWS and to define its contribution to bleeding in the many diseases and conditions with which it is associated.

Prothrombotic Clinical Issues and VWF in Persons Who Do Not Have VWD

Whether elevation of VWF is prothrombotic has been the subject of several investigations. Both arterial and venous thrombotic disorders have been studied.

Open-heart surgery. Hemostatic activation after open-heart surgery has been suggested as a mechanism of increased risk of postoperative thrombosis in this setting. A randomized trial comparing coronary artery surgery with or without cardiopulmonary bypass ("off-pump") found a consistent and equivalent rise in VWF:Ag levels at 1–4 postoperative days in the two groups,[128] suggesting that the surgery itself, rather than cardiopulmonary bypass, was responsible for the rise in VWF. There is no direct evidence that the postoperative rise in VWF contributes to the risk of thrombosis after cardiac surgery.

Coronary artery disease. Three large prospective studies of subjects without evidence of ischemic heart disease at entry have shown, by univariate analysis, a significant association of VWF:Ag level at entry with subsequent ischemic coronary events.[129–131] However, the association remained significant by multivariate analysis in only one subset of subjects in these studies,[129] a finding that could have occurred by chance. These findings suggest that the association of VWF with incidence of coronary ischemic events is relatively weak and may not be directly causal.

Thrombosis associated with atrial fibrillation. A prospective study of vascular events in subjects with atrial fibrillation found, by univariate analysis, a significant association of VWF:Ag level with subsequent stroke or vascular events. The association with vascular events remained significant with multivariate analysis.[132]

Thrombotic thrombocytopenic purpura (TTP). The hereditary deficiency or acquired inhibition of a VWF-cleaving protease, ADAMTS13, is associated with the survival in plasma of ultralarge VWF multimers, which are involved in the propensity to development of platelet-rich thrombi in the microvasculature of individuals who have TTP.[133,134]

Deep vein thrombosis (DVT). In a case-control study of 301 patients, evaluated at least 3 months after cessation of anticoagulation treatment for a first episode of DVT, plasma levels of VWF:Ag and FVIII activity were related to risk of DVT, according to univariate analysis. In multivariate analysis, the relation of VWF level with risk of DVT was not significant after adjustment for FVIII levels.[135]

Diagnosis and Evaluation

Introduction

The evaluation of a person for possible VWD or other bleeding disorders may be initiated because of a variety of clinical indications (see Figure 3). These indications and situations may include evaluation of: (1) an asymptomatic person who will undergo a surgical or interventional procedure; (2) persons who present with current symptoms of or a history of increased bleeding, abnormal laboratory studies, and/or a positive family history of a bleeding disorder; or (3) persons who present with a prior diagnosis of VWD but do not have supporting laboratory documentation. In all cases, the initial step in assessment should focus on key aspects of the person's clinical history to determine whether the person may benefit from further diagnostic evaluation. This section is divided into two parts. The first part uses a summary of the medical literature to provide suggested questions for an initial assessment of persons presenting for concerns about bleeding issues or for evaluation prior to procedures that may increase their risk of bleeding. Using the answers to the initial assessment, the second part focuses on a strategy for optimal laboratory assessment of those persons who potentially have bleeding disorders and suggests guidelines for interpretation of laboratory results.

Evaluation of the Patient

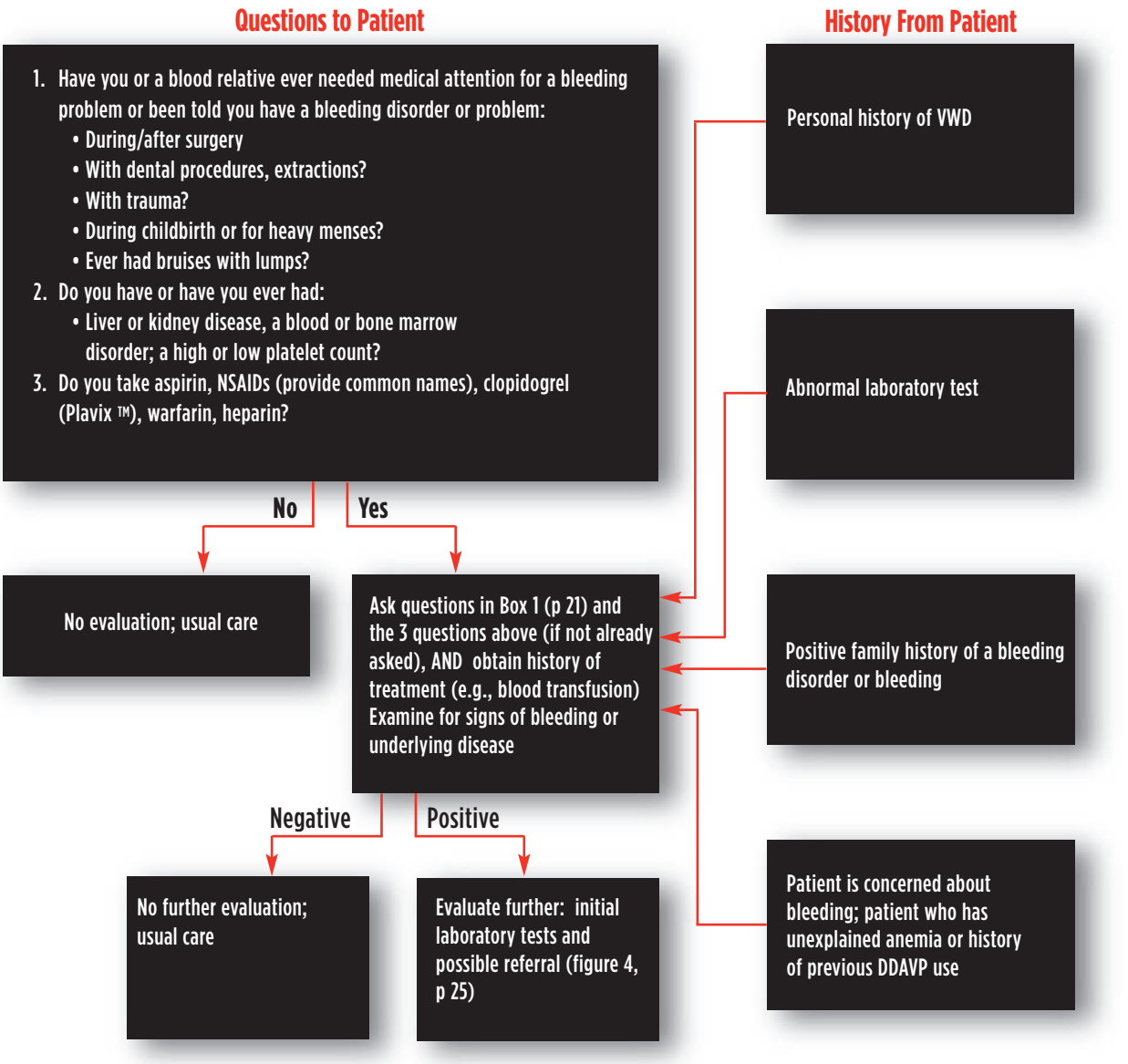
History, Signs, and Symptoms

The initial clinical assessment of a person who is being evaluated for VWD should focus on a personal history of excessive bleeding throughout the person's life and any family history of a bleeding disorder. The history of bleeding should identify the spontaneity and severity, sites of bleeding, duration of bleeding, type of insult or injury associated with bleeding, ease with which bleeding can be stopped, and concurrent medications—such as aspirin, other nonsteroidal anti-inflammatory drugs (NSAIDs), clopidogrel (Plavix™), warfarin, or heparin—at the onset of bleeding. Particularly when an invasive procedure is anticipated, the person should be asked whether he or she is currently taking any of these medications and also whether he or she has any history of liver or kidney disease, blood or bone marrow disease, or high or low platelet counts. If a history of any of these illnesses is present, further appropriate evaluation or referral should be undertaken.

Clinical manifestations. The most common presenting symptoms in persons subsequently diagnosed with VWD are summarized in Table 7. Symptoms usually involve mucous membranes and skin sites, and bleeding is of mild to moderate severity (bleeding that does not require blood transfusions and usually does not require visits to the physician) for most persons who have VWD, reflecting the predominance of type 1 VWD. However, life-threatening bleeding (CNS, gastrointestinal) can occur in persons who have type 3 VWD, in some persons who have type 2 VWD, and rarely in persons who have type 1 VWD. Uncommon bleeding manifestations, such as hemarthrosis, are more common in persons who have a more severe deficiency, especially those who have type 3 VWD.[85,136] Clinical symptoms may also be modified by coexisting illnesses or other medications. For example, use of aspirin or other NSAIDs can exacerbate the bleeding tendency, whereas use of oral contraceptives can decrease bleeding in women who have VWD.

The clinical evaluation of bleeding symptoms is a challenge, because mild bleeding symptoms are also very common in healthy populations (Table 7, shaded column). Responses to questionnaires used to survey healthy controls indicate that they identify themselves as having specific bleeding manifestations as frequently as persons who have VWD, particularly type 1 VWD (Table 7).[137,138,140,143] In addition, a family history of bleeding was reported by 44 percent of healthy children undergoing tonsillectomy[143] and by 35 percent[138] or 60 percent[144] of persons referred because of bleeding. Because bleeding symptoms are

Figure 3. Initial Evaluation For VWD or Other Bleeding Disorders



Initial evaluation strategy to determine which patients would most benefit from further diagnostic evaluation for von Willebrand disease (VWD) Left Upper Box: Individuals would be asked three questions about their personal or family bleeding history which, if any are positive, would lead to a second set of questions selected for their sensitivity and specificity for VWD (Box1, p.21). Those patients answering positively to one or more of the second set of questions would benefit from laboratory evaluation. Right Boxes: Patients presenting with specific information or a concern about bleeding would be asked the Box 1 questions and the initial 3 questions if not already asked, and would also undergo laboratory evaluation.

so prevalent, it may be impossible to establish a causal relationship between bleeding and low VWF.

Some of the most important clinical issues in VWD apply specifically to women, particularly menorrhagia. Studies of women who have VWD report a high prevalence of menorrhagia (Table 7), although the definition of menorrhagia is not clearly specified in most of these studies and the diagnostic criteria for VWD are not uniform. The sensitivity of menorrhagia as a predictor of VWD may be estimated as 32–100 percent. However, menorrhagia is a common symptom, occurring with a similar frequency in healthy controls and women who have VWD; therefore, it is not a specific marker for VWD (Table 7). In a survey of 102 women who had VWD and were registered at hemophilia treatment centers in the United States, 95 percent reported a history of menorrhagia, but 61 percent of controls also reported a history of menorrhagia.[145] Studies have reported a prevalence of VWD of between 5–20 percent among women who have menorrhagia.[146–152] Therefore, the

Box 1. Suggested Questions for Screening Persons for a Bleeding Disorder

1. Do you have a blood relative who has a bleeding disorder, such as von Willebrand disease or hemophilia?
2. Have you ever had prolonged bleeding from trivial wounds, lasting more than 15 minutes or recurring spontaneously during the 7 days after the wound?
3. Have you ever had heavy, prolonged, or recurrent bleeding after surgical procedures, such as tonsillectomy?
4. Have you ever had bruising, with minimal or no apparent trauma, especially if you could feel a lump under the bruise?
5. Have you ever had a spontaneous nosebleed that required more than 10 minutes to stop or needed medical attention?
6. Have you ever had heavy, prolonged, or recurrent bleeding after dental extractions that required medical attention?
7. Have you ever had blood in your stool, unexplained by a specific anatomic lesion (such as an ulcer in the stomach, or a polyp in the colon), that required medical attention?
8. Have you ever had anemia requiring treatment or received blood transfusion?
9. For women, have you ever had heavy menses, characterized by the presence of clots greater than an inch in diameter and/or changing a pad or tampon more than hourly, or resulting in anemia or low iron level?

Sources: Dean JA, Blanchette VS, Carcao MD, Stain AM, Sparling CR, Siekmann J, Turecek PL, Lillicrap D, Rand ML. von Willebrand disease in a pediatric-based population—comparison of type 1 diagnostic criteria and use of the PFA-100® and a von Willebrand factor/collagen-binding assay. *Thromb Haemost* 2000 Sep;(3):401–409; Drews CD, Dilley AB, Lally C, Beckman MG, Evatt B. Screening questions to identify women with von Willebrand disease. *J Am Med Womens Assoc* 2002;57(4):217–218; and Laffan M, Brown SA, Collins PW, Cumming AM, Hill FG, Keeling D, Peake IR, Pasi KJ. The diagnosis of von Willebrand disease: a guideline from the UK Haemophilia Centre Doctors' Organization. *Haemophilia 2004* May;10(3):199–217.

Table 7. Common Bleeding Symptoms of Healthy Individuals and Patients Who Have VWD

Symptoms	Normals (n = 500;[137] n= 341;[‡138] n = 88;[‡‡139] n= 60[‡‡140]) %	All types VWD (n = 264;[137] n = 1,885[141]) %	Type 1 VWD (n = 42;[†142] n = 671[136]) %	Type 2 VWD (n = 497[136]) %	Type 3 VWD (n = 66;[136] n = 385[85]) %
Epistaxis	4.6–22.7	38.1–62.5	53–61	63	66–77
Menorrhagia*	23–68.4	47–60	32	32	56–69
Bleeding after dental extraction	4.8–41.9	28.6–51.5	17–31	39	53–70
Ecchymoses	11.8–50	49.2–50.4	50	N.R.	N.R.
Bleeding from minor cuts or abrasions	0.2–33.3	36	36	40	50
Gingival bleeding	7.4–47.1	26.1–34.8	29–31	35	56
Postoperative bleeding	1.4–28.2	19.5–28	20–47	23	41
Hemarthrosis	0–14.9	6.3–8.3	2–3	4	37–45
Gastrointestinal bleeding	0.6–27.7	14	5	8	20

* Calculated for females above 13 to 15 years of age.
‡ 341 individuals were sent a questionnaire, but the precise number of patients responding was not provided.
‡‡ Study included women only.
† Study included males only.
N.R., Not reported.

specificity of menorrhagia as a predictor of VWD can be estimated as 5–20 percent. Three findings that predict abnormal menstrual blood loss of >80 mL include:

- Clots greater than approximately 1 inch in diameter
- Low serum ferritin
- Changing a pad or tampon more than hourly[153]

Identification of people who may require further evaluation for inherited bleeding disorders. Since other "bleeding symptoms" besides menorrhagia are reported frequently by persons who have apparently normal hemostasis, it is important to use questions that can best identify persons who have a true bleeding disorder. Sramek and colleagues[138] used a written questionnaire with patients who had a proven bleeding disorder. When the responses were compared to those of a group of healthy volunteers, the most informative questions were related to: (1) prolonged bleeding after surgery, including after dental extractions, and (2) identification of family members who have an established bleeding disorder (Table 8, columns 2–5). A history of muscle or joint bleeding may also be helpful when associated with the above symptoms.

General questions that relate to isolated bleeding symptoms—such as frequent gingival bleeding, profuse menstrual blood loss, bleeding after delivery, and epistaxis in the absence of other bleeding symptoms—were not informative.[138] The study also found that an elaborate interview after referral to a hematologist was not particularly helpful when attempting to distinguish persons who have a true bleeding disorder from persons who have a "suspected" bleeding disorder, implying that the selection of those with bleeding disorders had already been made by the referring physician.[138]

Drews et al.[139] attempted to develop a questionnaire-based screening tool to identify women who might benefit from a diagnostic workup for VWD. They conducted a telephone survey of 102 women who had a diagnosis of type 1 VWD and were treated at a hemophilia treatment center compared with 88 friends who were controls. With the exception of postpartum transfusions, all study variables were reported more frequently by women who had VWD than by their friends (Table 8, columns 6 and 7). In addition, positive responses to multiple questions were more likely to be obtained from patients who have an inherited bleeding disorder.[139] An important limitation of this study is that these women were more symptomatic than most women diagnosed as having type 1 VWD, indicating a more severe phenotype of the disease; this fact might decrease the sensitivity of the questions in the setting of persons who have milder type 1 VWD and fewer symptoms.

More recently, Rodeghiero and colleagues[155] compared responses to a standardized questionnaire obtained from 42 obligatory carriers of VWD (from well-characterized families) to responses from 215 controls. The questionnaire covered 10 common bleeding symptoms (including all symptoms in Table 7, and postpartum hemorrhage), with assigned scores for each ranging from 0 (no symptoms) to 3 (severe symptoms, usually including hospitalization and/or transfusion support). With this instrument, the researchers found that having a cumulative total bleeding score of 3 in men, or 5 in women, was very specific (98.6 percent) but not as sensitive (69.1 percent) for type 1 VWD. Limitations of this study include that it was retrospective and that the person administering the questionnaire was aware of the respondent's diagnosis. This questionnaire is available online.[155]

A similar retrospective case–control study[154] used a standardized questionnaire like that of Rodegherio et al.[155] to assess bleeding symptoms of 144 index cases who had type 1 VWD, compared to 273 affected relatives, 295 unaffected relatives, and 195 healthy controls. The interviewers were not blinded to subject's status. At least one bleeding symptom was reported by approximately 98 percent of index cases, 89 percent of affected relatives, 32 percent of unaffected relatives, and 12 percent of healthy controls. The major symptoms of affected persons (excluding index cases) included bleeding after tooth extraction, nosebleeds, menorrhagia, bleeding into the skin, postoperative bleeding, and bleeding from minor wounds. Using a bleeding score calculated from the data for comparison, the severity of bleeding diminished with increasing plasma VWF, not only for subjects who had low VWF levels but throughout the normal range as well. Although the mean bleeding score was significantly different between several groups, the distribution was sufficiently broad that the bleeding score could not predict the affected or unaffected status of individuals.

Table 8. Prevalences of Characteristics in Patients Who Have Diagnosed Bleeding Disorders Versus Healthy Controls

Symptom	Univariate analysis*		Multivariate analysis*		Women who have VWD†		Type 1 VWD families‡	
	Odds ratio	95% CI	Odds ratio	95% CI	Sensitivity	95% CI	Odds ratio	95% CI
Family members have an established bleeding disorder	97.5	38.3–248	50.5	12.5–202.9	–	–	–	–
Profuse bleeding from small wounds	67.2	28.4–159	30.0	8.1–111.1	–	–	16.7	2.0–137.7
Profuse bleeding at site of tonsillectomy/ adenoidectomy	27.7	8.0–96.1	11.5	1.2–111.9	–	–	–	–
Easy bruising	12.7	8.0–20.2	9.9	3.0–32.3	9.8	4.8–17.3	8.1	2.1–30.5
Profuse bleeding after surgery	23.0	10.6–50.1	5.8	1.3–26.4	52.9	42.8–62.9	8.9	3.6–21.8
Muscle bleeding (ever)	13.3	6.4–27.7	4.8	0.7–31.4	9.8	4.8–17.3	–	–
Frequent nosebleeds	3.5	2.0–6.2	3.8	0.9–15.7	61.8	51.6–71.2	4.9	2.4–10.0
Profuse bleeding at site of dental extraction	39.4	20.6–75.5	3.2	0.9–11.3	54.9	44.7–64.8	4.6	2.5–8.4
Blood in stool (ever)	2.8	1.7–4.6	2.8	0.7–11.7	13.7	7.7–22.0	1.6	0.6–4.3
Family members with bleeding symptoms	28.6	15.0–54.6	2.5	0.7–9.4	–	–	–	–
Joint bleeding (ever)	8.6	4.8–15.2	2.5	0.6–10.2	20.6	13.2–29.7	–	–
Menorrhagia	5.4	3.0–9.8	2.5	0.6–9.9	–	–	5.1	2.6–10.1
Hemorrhage at time of delivery	5.3	2.3–12.0	2.1	0.3–13.5	50.0	39.9–60.1	0.9	0.3–3.2
Frequent gingival bleeding	2.8	1.9–4.2	0.7	0.3–2.0	76.5	67.0–84.3	1.3	0.3–6.7
Hematuria (ever)	3.2	1.8–5.6	0.5	0.1–2.3	–	–	–	–

Sources: Sramek A, Eikenboom JC, Briet E, Vandenbroucke JP, Rosendaal FR. Usefulness of patient interview in bleeding disorders. *Arch Intern Med* 1995 Jul;155(13):1409–1415; Drews CD, Dilley AB, Lally C, Beckman MG, Evatt B. Screening questions to identify women with von Willebrand disease. *J Am Med Womens Assoc* 2002;57(4):217–218; and Tosetto A, Rodeghiero F, Castaman G, Goodeve A, Federici AB, Batlle J, Meyer D, Fressinaud E, Mazurier C, Goudemand J, et al. A quantitative analysis of bleeding symptoms in type 1 von Willebrand disease: results from a multicenter European study (MCMDM-1 VWD). *J Thrombos Haemostas* 2006;4:766–773.

* Univariate and multivariate analyses from reference comparing 222 patients who had a known bleeding disorder (43 percent mild VWD) to 341 healthy volunteers [138].

† Compiled from responses to a questionnaire sent to 102 women, who had type 1 VWD, in a hemophilia treatment center.[139]

‡ Compiled from interviews comparing affected vs. unaffected family members of patients who have type 1 VWD. The index cases (patients who have VWD) were not included in the analysis (Tosetto et al. 2006, and personal communication from Dr. Francesco Rodeghiero on behalf of coauthors).[154]

CI, confidence interval

In a related study, bleeding symptoms were assessed with the same questionnaire in 70 persons who were obligatory carriers of type 3 VWD, 42 persons who were obligate carriers of type 1 VWD (meaning affected family members of index cases who had type 1 VWD), and 215 persons who were healthy controls.[156] Carriers of type 3 VWD were compared with carriers of type 1 VWD to address the question of whether the distinct types of VWF mutations associated with these conditions predisposed to the same or different severity of bleeding. Approximately 40 percent of carriers of type 3 VWD, 82 percent of carriers of type 1 VWD, and 23 percent of healthy controls had at least one bleeding symptom. The major bleeding symptoms in carriers of type 3 VWD were bleeding into skin and postsurgical bleeding. The results suggest that carriers of type 3 VWD are somewhat distinct, as they have bleeding symptoms more frequently than healthy controls but less frequently than persons who have or are carriers of type 1 VWD. Usually, carriers of type 1 VWD have lower VWF levels than carriers of type 3 VWD.

Family history. Although a family history that is positive for an established bleeding disorder is useful in identifying persons who are likely to have VWD, such a history is frequently not present. This is most commonly the case for persons who have milder forms of VWD and whose family members may have minimal, if any, symptoms. As shown in Table 8, the presence of a documented bleeding disorder in a family member is extremely helpful in deciding which persons to evaluate further, whereas a family history of bleeding symptoms is less helpful.

Box 1 (page 21) summarizes suggested questions that can be used to identify persons who should be considered for further evaluation for VWD with laboratory studies.

Physical examination. The physical examination should be directed to confirm evidence for a bleeding disorder, including size, location, and distribution of ecchymoses (e.g., truncal), hematomas, petechiae, and other evidence of recent bleeding. The examination should also focus on findings that may suggest other causes of increased bleeding, such as evidence of liver disease (e.g., jaundice), splenomegaly, arthropathy, joint and skin laxity (e.g., Ehlers-Danlos Syndrome), telangiectasia (e.g., hereditary hemorraghic telangiectasia), signs of anemia, or anatomic lesions on gynecologic examination.

Acquired von Willebrand Syndrome (AVWS). Persons who have AVWS present with bleeding symptoms similar to those described, except that the past personal and family history are negative for bleeding symptoms. AVWS may occur spontaneously or in association with other diseases, such as monoclonal gammopathies, other plasma cell dyscrasias, lymphoproliferative diseases, myeloproliferative disorders (e.g., essential thrombocythemia), autoimmune disorders, valvular and congenital heart disease, certain tumors, and hypothyroidism.[117,157] The evaluation should be tailored to finding conditions associated with AVWS.

Laboratory Diagnosis and Monitoring

An algorithm for using clinical laboratory studies to make the diagnosis of VWD is summarized in Figure 4.

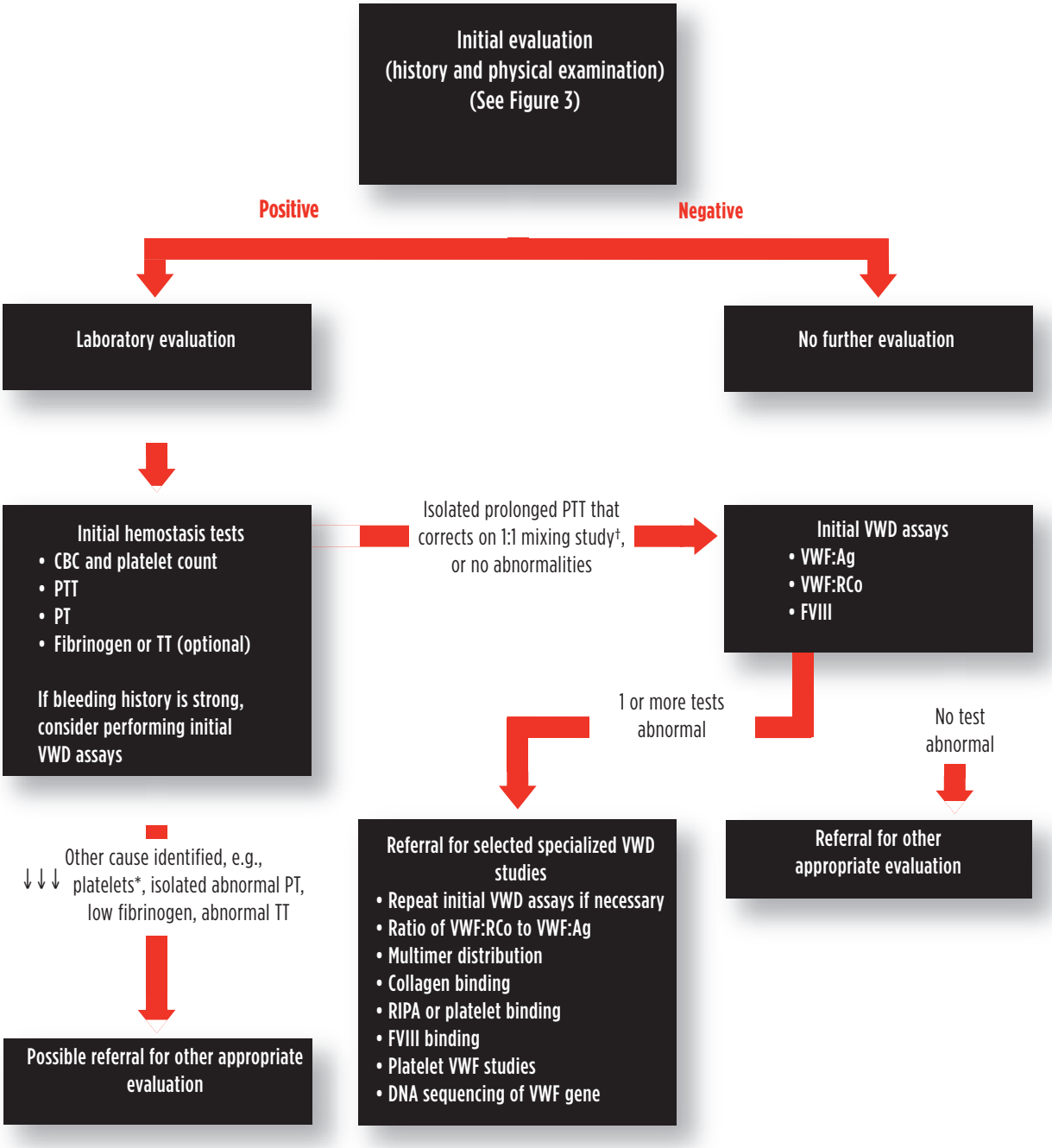
Ideally, a simple, single laboratory test could screen for the presence of VWD. Such a screening test would need to be sensitive to the presence of most types of VWD and would have a low false-positive rate. Unfortunately, no such test is available. In the past, the activated partial thromboplastin time (PTT) and bleeding time (BT) were recommended as diagnostic tests. These tests were probably satisfactory for detecting severe type 3 VWD, but as variant VWD and milder forms of VWD were characterized, it became apparent that many of the persons who have these conditions had normal PTT and normal BT results.

An initial hemostasis laboratory evaluation (see Box 2) usually includes a platelet count and complete blood count (CBC), PTT, prothrombin time (PT), and optionally either a fibrinogen level or a thrombin time (TT). This testing neither "rules in" nor "rules out" VWD, but it can suggest whether coagulation factor deficiency or thrombocytopenia might be the potential cause of clinical bleeding. If the mucocutaneous bleeding history is strong, consider performing

Box 2. Initial Laboratory Evaluation of Hemostasis

- CBC and platelet count
- PTT
- PT
- Fibrinogen or TT (optional)

Figure 4. Laboratory Assessment For VWD or Other Bleeding Disorders



* Isolated decreased platelets may occur in VWD type 2B.
† Correction in the PTT mixing study immediately and after 2-hour incubation removes a factor VIII (FVIII) inhibitor from consideration. Investigation of other intrinsic factors and lupus anticoagulant also may be indicated.
CBC, complete blood count; PT prothrombin time; PTT partial thromboplastin time; RIPA, ristocetin-induced platelet aggregation; TT, thrombin time; VWF:Ag, VWF antigen; VWF:RCo, VWF ristocetin cofactor activity.

If the initial clinical evaluation suggests a bleeding disorder, the "initial hemostasis tests" should be ordered, followed by or along with the next tests ("initial VWD assays") indicated in the algorithm. Referral to a hemostasis specialist is appropriate for help in interpretation, repeat testing, and specialized tests.

initial VWD assays (VWF:Ag, VWF:RCo, and FVIII) at the first visit.

Some centers add a BT or a platelet function analyzer (PFA-100®) assay to their initial laboratory tests. The BT test is a nonspecific test and is fraught with operational variation. It has been argued that it was a population-based test that was never developed to test individuals.[158] Variables that may affect results include a crying or wiggling child, differences in the application of the blood pressure cuff, and the location, direction, and depth of the cut made by the device.

This test also has a potential for causing keloid formation and scarring, particularly in non-Caucasian individuals. The PFA-100® result has been demonstrated to be abnormal in the majority of persons who have VWD, other than those who have type 2N, but its use for population screening for VWD has not been established.[159–162] Persons who have severe type 1 VWD or who have type 3 VWD usually have abnormal PFA-100® values, whereas persons who have mild or moderate type 1 VWD and some who have type 2 VWD may not have abnormal results.[163–165] When persons are studied by using both the BT and PFA-100®, the results are not always concordant.[162,164,166]

When using the PTT in the diagnosis of VWD, results of this test are abnormal only if the FVIII is sufficiently reduced. Because the FVIII gene is normal in VWD, the FVIII deficiency is secondary to the deficiency of VWF, its carrier protein. In normal individuals, the levels of FVIII and VWF:RCo are approximately equal, with both averaging 100 IU/dL. In type 3 VWD, the plasma FVIII level is usually less than 10 IU/dL and represents the steady state of FVIII in the absence of its carrier protein. In persons who have type 1 VWD, the FVIII level is often slightly higher than the VWF level and may fall within the normal range. In persons who have type 2 VWD (except for type 2N VWD in which it is decreased), the FVIII is often 2–3 times higher than the VWF activity (VWF:RCo).[167,168] Therefore, the PTT is often within the normal range. If VWF clearance is the cause of low VWF, the FVIII reduction parallels that of VWF, probably because both proteins are cleared together as a complex.

Initial Tests for VWD

Box 3 lists the initial tests commonly used to detect VWD or low VWF. These three tests, readily available in most larger hospitals, measure the amount of VWF protein present in plasma (VWF:Ag), the function of the VWF protein that is present as ristocetin cofactor activity (VWF:RCo), and the ability of the VWF to serve as the carrier protein to maintain normal FVIII survival, respectively. If any of the above tests is abnormally low, the next steps should be discussed with a coagulation specialist, who may recommend referral to a specialized center, and/or repeating the laboratory tests plus performing additional tests.

VWF:Ag is an immunoassay that measures the concentration of VWF protein in plasma. Commonly used methods are based on enzyme-linked immunosorbent assay (ELISA) or automated latex immunoassay (LIA). As discussed below, the standard reference plasma is critical and should be referenced to the World Health Organization (WHO) standard. The person's test results should be reported in international units (IU), either as international units per deciliter (IU/dL) or as international units per milliliter (IU/mL). Most laboratories choose IU/dL, because it is similar to the conventional manner of reporting clotting factor assays as a percentage of normal.

VWF:RCo is a functional assay of VWF that measures its ability to interact with normal platelets. The antibiotic, ristocetin, causes VWF to bind to platelets, resulting in platelet clumps and their removal from the circulation. Ristocetin was removed from clinical trials because it caused thrombocytopenia. This interaction was developed into a laboratory test that is still the most widely accepted functional test for VWF. (In vivo, however, it is the high shear in the microcirculation, and not a ristocetin-like molecule, that causes the structural changes in VWF that lead to VWF binding to platelets.)

Box 3. Initial Tests for VWD

- VWF:Ag
- VWF:RCo
- FVIII

Several methods are used to assess the platelet agglutination and aggregation that result from the binding of VWF to platelet GPIb induced by ristocetin (ristocetin cofactor activity, or VWF:RCo). The methods include: (1) time to visible platelet clumping using ristocetin, washed normal platelets (fresh or formalinized), and dilutions of patient plasma; (2) slope of aggregation during platelet aggregometry using ristocetin, washed normal platelets, and dilutions of the person's plasma; (3) automated turbidometric tests that detect platelet clumping, using the same reagents noted above; (4) ELISA assays that assess direct binding of the person's plasma VWF to platelet GPIb (the GPIb may be derived from plasma glycocalicin) in the presence of ristocetin;[169–171] and (5) the binding of a monoclonal antibody to a conformation epitope of the VWF A1 loop.[172] Method 5 can be performed in an ELISA format or in an automated latex immunoassay. It is not based on ristocetin binding. The first three assays (above) may use platelet membrane fragments containing GPIb rather than whole platelets. The sensitivity varies for each laboratory and each assay; in general, however, Methods 1 and 2, which measure platelet clumping by using several dilutions of the person's plasma, are quantitative to approximately 6–12 IU/dL levels. Method 3 is quantitative to about 10–20 IU/dL. Method 4 can measure VWF:RCo to <1 IU/dL, and a variation of it can detect the increased VWF binding to GPIb seen in type 2B VWD.[173] Some automated methods are less sensitive and require modification of the assay to detect <10 IU/dL. Each laboratory should define the linearity and limits of its assay. Several monoclonal ELISAs (Method 5) that use antibodies directed to the VWF epitope containing the GPIb binding site have been debated because the increased function of the largest VWF multimers is not directly assessed.[174]

The ristocetin cofactor activity (VWF:RCo) assay has high intra- and interlaboratory variation, and it does not actually measure physiologic function. The coefficient of variation (CV) has been measured in laboratory surveys at 30 percent or greater, and the CV is still higher when the VWF:RCo is lower than 12–15 IU/dL.[175–179] This becomes important not only for the initial diagnosis of VWD, but also for determining whether the patient has type 1 versus type 2 VWD (see discussion on VWF:RCo to VWF:Ag ratio, page 30). Despite these limitations, it is still the most widely accepted laboratory measure of VWF function. Results for VWF:RCo should be expressed in international units per deciliter (IU/dL) based on the WHO plasma standard.

FVIII coagulant assay is a measure of the cofactor function of the clotting factor, FVIII, in plasma. In the context of VWD, FVIII activity measures the ability of VWF to bind and maintain the level of FVIII in the circulation. In the United States, the assay is usually performed as a one-stage clotting assay based on the PTT, although some laboratories use a chromogenic assay. The clotting assay, commonly done using an automated or semiautomated instrument, measures the ability of plasma FVIII to shorten the clotting time of FVIII-deficient plasma. Because this test is important in the diagnosis of hemophilia, the efforts to standardize this assay have been greater than for other hemostasis assays. FVIII activity is labile, with the potential for spuriously low assay results if blood specimen collection, transport, or processing is suboptimal. Like those tests discussed above, it should be expressed in international units per deciliter (IU/dL) based on the WHO plasma standard.

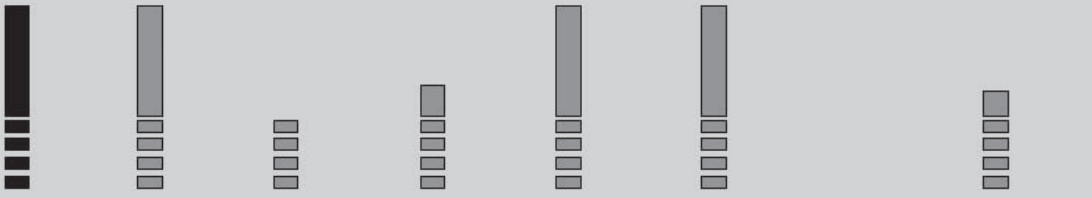
Expected patterns of laboratory results in different subtypes of VWD, depicted in Figure 5, include results of the three initial VWD tests (VWF:Ag, VWF:RCo, FVIII) and results of other assays for defining and classifying VWD subtypes. The three initial tests (or at least the VWF:RCo and FVIII assays) are also used for monitoring therapy.

Other Assays To Measure VWF, Define/Diagnose VWD, and Classify Subtypes

The VWF multimer test, an assay that is available in some larger centers and in commercial laboratories, is usually performed after the initial VWD testing indicates an abnormality, preferably using a previously unthawed portion of the same sample or in association with a repeated VWD test panel (VWF:Ag, VWF:RCo, FVIII) using a fresh plasma sample. VWF multimer analysis is a qualitative assay that depicts the variable concentrations of the different-sized VWF multimers by using sodium dodecyl sulfate (SDS)-protein electrophoresis followed by detection of the VWF multimers in the gel, using a radiolabeled polyclonal antibody or a combination of monoclonal antibodies. Alternatively, the protein is transferred to a

Figure 5. Expected Laboratory Values in VWD

	Normal	Type 1	Type 2A	Type 2B	Type 2M	Type 2N	Type 3	PLT-VWD*
VWF:Ag	N	L, ↓ or ↓↓	↓ or L	↓ or L	↓ or L	N or L	absent	↓ or L
VWF:RCo	N	L, ↓ or ↓↓	↓↓ or ↓↓↓	↓↓	↓↓	N or L	absent	↓↓
FVIII	N	N or ↓	N or ↓	N or ↓	N or ↓	↓↓	1-9 IU/dL	N or L
RIPA	N	often N	↓	often N	↓	N	absent	often N
LD-RIPA	absent	absent	absent	↑↑↑	absent	absent	absent	↑↑↑
PFA-100® CT	N	N or ↑	↑	↑	↑	N	↑↑↑	↑
BT	N	N or ↑	↑	↑	↑	N	↑↑↑	↑
Platelet count	N	N	N	↓ or N	N	N	N	↓
VWF multimer pattern	N	N	abnormal	abnormal	N	N	absent	abnormal



The symbols and values represent prototypical cases. In practice, laboratory studies in certain patients may deviate slightly from these expectations.

L, 30-50 IU/dL; ↓, ↓↓, ↓↓↓, relative decrease; ↑, ↑↑, ↑↑↑, relative increase; BT, bleeding time; FVIII, factor VIII activity; LD-RIPA, low-dose ristocetin-induced platelet aggregation (concentration of ristocetin ≤ 0.6 mg/mL); N, normal; PFA-100® CT, platelet function analyzer closure time; RIPA, ristocetin-induced platelet aggregation; VWF, von Willebrand factor; VWF:Ag, VWF antigen; VWF:RCo, VWF ristocetin cofactor activity.

*Note: persons who have platelet-type VWD (PLT-VWD) have a defect in their platelet GPIb. Laboratory test results resemble type 2B VWD, and both have a defect in their LD-RIPA. In the VWF:platelet binding assay (see text), persons who have type 2B VWD have abnormally increased platelet binding. Normal persons and those who have PLT-VWD have no binding of their VWF to normal platelets at low ristocetin concentrations.

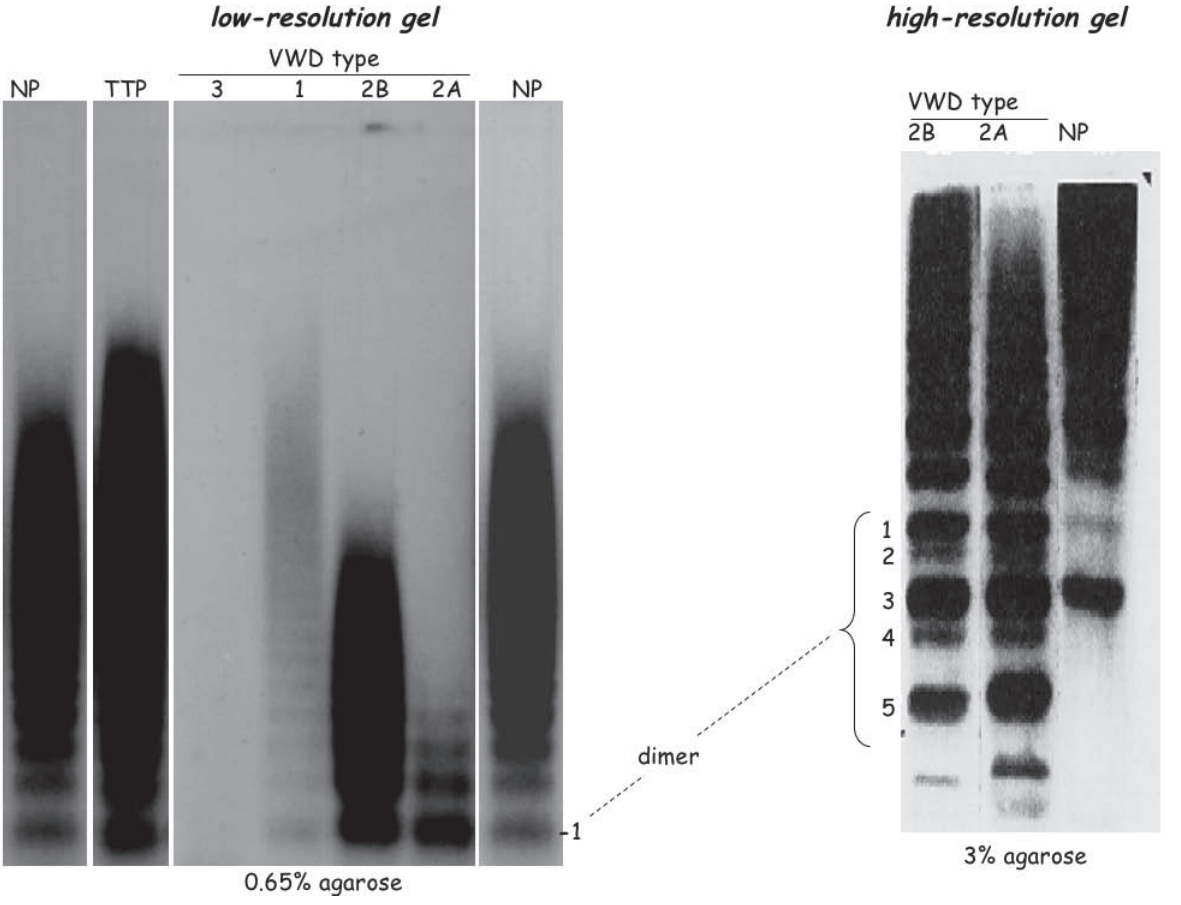
Note: this figure is adapted from and used by permission of R.R. Montgomery.

membrane (Western blot), and the multimers are identified by immunofluorescence or other staining techniques.[99,180,181]

Multimer assays are designated as "low resolution" (which differentiate the largest multimers from the intermediate and small multimers) or "high resolution" (which differentiate each multimer band of the smaller multimers into three to eight satellite bands). For diagnostic purposes, the low-resolution gel systems are used primarily; these systems help to differentiate the type 2 VWD variants from types 1 or 3 VWD. Figure 6 illustrates the differences between these two techniques with regard to the resolution of high- and low-molecular-weight multimers. It should be noted that multimer appearance alone does not define the variant subtype and that only types 2A, 2B, and platelet-type VWD (PLT-VWD) have abnormal multimer distributions with relative deficiency of the largest multimers. An exception is Vicenza variant VWD with ultralarge VWF multimers and low VWF. For more information about VWF multimer findings in type 2 VWD variants, see pages 13–15 and associated references.

Low-Dose RIPA. RIPA and VWF platelet-binding assay (VWF:PB assay) are two tests that are performed to aid in diagnosing type 2B VWD. RIPA

Figure 6. Analysis of VWF Multimers



The distribution of VWF multimers can be analyzed using sodium dodecyl sulfate (SDS)-agarose electrophoresis followed by immunostaining. Low-resolution gels (0.65% agarose, left side) can demonstrate the change in multimer distribution of the larger multimers (top of the gel), while high-resolution gels (2–3% agarose, right side) can separate each multimer into several bands that may be distinctive. For example, the lowest band in the 0.65% gel (1) can be resolved into 5 bands in the 3% agarose gel, but the 3% gel fails to demonstrate the loss of high molecular weight multimers seen at the top in the 0.65% gel. The dotted lines (1) indicate the resolution of the smallest band into several bands in the 3% agarose gel. In each gel, normal plasma (NP) is run as a control. Type 1 VWD plasma has all sizes of multimers, but they are reduced in concentration. Type 2A VWD plasma is missing the largest and intermediate multimers, while type 2B VWD plasma is usually missing just the largest VWF multimers. No multimers are identified in type 3 VWD plasma. Patients who have thrombotic thrombocytopenic purpura (TTP) may have larger than normal multimers when studied with low-resolution gels.
Note: Used by permission of R.R. Montgomery.

may be done as part of routine platelet aggregation testing. RIPA is carried out in platelet-rich plasma, using a low concentration of ristocetin (usually <0.6 mg/mL, although ristocetin lots vary, resulting in the use of slightly different ristocetin concentrations). This low concentration of ristocetin does not cause VWF binding and aggregation of platelets in samples from normal persons, but it does cause VWF binding and aggregation of platelets in samples from patients who have either type 2B VWD or mutations in the platelet VWF receptor. The latter defects have been termed platelet-type (PLT-VWD) or pseudo VWD, and they can be differentiated from type 2B VWD by VWF:PB assay. At higher concentrations of ristocetin (1.1–1.3 mg/mL), RIPA will be reduced in persons who have type 3 VWD. However, the test is not sufficiently sensitive to reliably diagnose other types of VWD.

VWF: platelet-binding (VWF:PB) assay measures the binding of VWF to normal paraformaldehyde-fixed platelets using low concentrations of ristocetin (usually 0.3–0.6 mg/mL).[182] The amount of VWF bound to the fixed platelets is determined by using

a labeled antibody. Normal individuals, or those who have types 1, 2A, 2M, 2N, and 3 VWD, exhibit minimal or no binding to platelets at the concentration of ristocetin used, but patients who have type 2B VWD exhibit significant binding that causes their variant phenotype (a loss of high-molecular-weight multimers, decreased ristocetin cofactor activity, and thrombocytopenia). Both type 2B VWD and platelet-type VWD have agglutination of platelet-rich plasma (PRP) to low-dose ristocetin, but the VWF:PB assay can differentiate type 2B VWD from platelet-type VWD. Only VWF from persons who have type 2B VWD has increased VWF:PB, while VWF from persons who have platelet-type VWD has normal VWF:PB with low doses of ristocetin.

VWF collagen-binding (VWF:CB) assay measures binding of VWF to collagen. The primary site of fibrillar collagen binding is in the A3 domain of VWF. Like the ristocetin cofactor assay, the collagen binding assay is dependent on VWF multimeric size, with the largest multimers binding more avidly than the smaller forms. The VWF:CB assay performance and sensitivity to VWD detection or discrimination among VWD subtypes is highly dependent on the source of collagen, as well as on whether type 1 collagen or a mixture of type 1/3 collagen is used.[183,184] Only a few patients have been identified who have specific collagen-binding defects that are independent of multimer size, and the defects have been associated with a mutation of VWF in the A3 domain.[73] The prevalence of such defects is unknown. The place of VWF:CB in the evaluation of VWD has not been established. In principle, however, patients who have defects in collagen binding may have a normal VWF:RCo and thus escape clinical diagnosis unless a VWF:CB assay is performed. Limited studies suggest that supplementary VWF:CB testing, complementing assays of VWF:RCo and VWF:Ag, can improve the differentiation of type 1 VWD from types 2A, 2B, or 2M VWD.[175,185,186]

VWF:FVIII binding (VWF:FVIIIB) assay measures the ability of a person's VWF to bind added exogenous FVIII and is used to diagnose type 2N VWD.[75,77,78,187,188] The assay is performed by capturing the person's VWF on an ELISA plate, removing the bound endogenous FVIII, and then adding back a defined concentration of exogenous recombinant FVIII. The amount of FVIII bound is determined by a chromogenic FVIII assay. The level of this bound FVIII is then related to the amount of the person's VWF initially bound in the same well. In clinical experience, Type 2N VWD is usually recessive; the person is either homozygous or compound heterozygous (one allele is type 2N, and the other is a type 1 or "null" allele). In either case, the VWF in the circulation does not bind FVIII normally, and the concentration of FVIII is thus decreased.

The *VWF:RCo to VWF:Ag ratio* can aid in the diagnosis of types 2A, 2B, and 2M VWD and help differentiate them from type 1 VWD. For example, VWF:RCo/VWF:Ag <0.6[189] or <0.7 has been used as a criterion for dysfunctional VWF.[8,190] A similar approach has been proposed for the use of the VWF:CB/VWF:Ag ratio.[8,190] In type 2A VWD, the ratio is usually low; and in type 2B VWD, the VWF:RCo/VWF:Ag ratio is usually low but may be normal. In type 2M VWD, the VWF:Ag concentration may be reduced or normal, but the VWF:RCo/VWF:Ag ratio will be <0.7. One study[70] determined the VWF:RCo/VWF:Ag ratio in nearly 600 individuals with VWF levels <55 IU/dL who had normal VWF multimers. The study used this ratio to identify families who had type 2 VWD, but most centers do not have the ability to establish normal ranges for patients who have low VWF. Additionally, the VWF:RCo assay has a coefficient of variation (CV) as high as 30 percent or more, depending on methodology, whereas the CV for the VWF:Ag assay is somewhat lower. The high intrinsic variability of the VWF:RCo assay, especially at low levels of VWF, can make the VWF:RCo/VWF:Ag ratio an unreliable criterion for the diagnosis of type 2 VWD.[175,177–179] (See Recommendations II.C.1.a., page 35, and III.B.1, page 36). It is important that the same plasma standard be used in both the VWF:RCo and VWF:Ag assays and that the normal range for the VWF:RCo/VWF:Ag ratio and its sensitivity to types 2A and 2M VWD be determined in each laboratory. Because no large multicenter studies have evaluated the precise ratio that should be considered abnormal, a ratio in the range of less than 0.5–0.7 should raise the suspicion of types 2A, 2B, or 2M VWD. Further confirmation should be sought by additional testing (e.g., repeat VWD test panel and VWF multimer study or sequencing of the A1 region of the VWF gene).[191]

ABO blood types have a significant effect on plasma VWF (and FVIII) concentrations.[43,192] Individuals who have blood type O have concentrations

Table 9. Influence of ABO Blood Groups on VWF:Ag

ABO type	N	VWF:Ag mean	Range
O	456	74.8*	35.6–157.0* (41–179)†
A	340	105.9*	48.0–233.9* (55–267)†
B	196	116.9*	56.8–241.0* (65–275)†
AB	109	123.3*	63.8–238.2* (73–271)†

*U/dL; †IU/dL
Source: Gill JC, Endres-Brooks J, Bauer PJ, Marks WJ, Jr., Montgomery RR. The effect of ABO blood group on the diagnosis of von Willebrand disease. *Blood* 1987 Jun;69(6):1691–1695. Copyright American Society of Hematology, used with permission. In this publication, VWF:Ag was expressed as U/dL, but the range in IU/dL (WHO) is higher for all blood groups, as noted in the values in parentheses (personal communication from R.R. Montgomery, J.L. Endres, and K.D. Friedman).

approximately 25 percent lower compared to persons who have other ABO blood types. The diagnosis of type 1 VWD occurs more frequently in individuals who have blood group type O.[43] Table 9 illustrates the significant effect of blood type on VWF:Ag level.

Although it has been recommended to stratify reference ranges for VWF:Ag and VWF:RCo with respect to blood group O and nongroup O,[193,194] evolving limited information supports the concept that, despite the ABO blood grouping and associated VWF reference ranges, the major determinant of bleeding symptoms or risk is low VWF.[189,195,196] Therefore, referencing VWF testing results to the population reference range, rather than to ABO-stratified reference ranges, may be more useful clinically.

Platelet VWF studies are performed by some laboratories, including VWF:RCo, VWF:Ag, and VWF multimers, using VWF extracted from washed platelets. The methods and interpretations of these studies, however, are not well standardized.

DNA sequencing of patient DNA has been used to make a molecular diagnosis of variants of type 2 VWD,[197–199] but DNA sequencing is not widely available. Most of the mutations found in types 2B, 2M, and 2N VWD cluster in the cDNA that directs the synthesis of specific regions of VWF (see Figure 2).[200] In the common forms of type 2A VWD, in which the VWF is spontaneously cleaved by ADAMTS13, mutations cluster in the A2 domain (which contains the cleavage site). In the less common type 2A variants of VWD, in which multimer formation is inhibited, the mutations may be scattered throughout the gene. In most persons who have type 1 VWD, the genetic mutations have not been established, although several studies are being conducted at present to characterize these mutations.

Assays for Detecting VWF Antibody

Assays for detecting anti-VWF antibodies are not as well established as the assays for detecting antibodies to FVIII in patients who have hemophilia A. Some patients who have AVWS do appear to have anti-VWF antibodies that decrease the half-life of infused VWF. Although a few antibodies do inhibit VWF function and can be demonstrated in 1:1 mixing studies with normal plasma using the VWF:RCo assay, most anti-VWF antibodies are not "inhibitors" of VWF function. The presence of these antibodies, however, promotes rapid clearance of VWF. The plasma level of VWF propeptide (VWFpp) is normally proportionate to the level of VWF:Ag, and the VWFpp level can be measured to aid in the detection of the rapid clearance of VWF. Accelerated plasma clearance of VWF:Ag—as occurs in some patients who have AVWS, in those who have certain type 1 VWD variants, or in those who have type 3 VWD and have alloantibodies to VWF—is associated with an increase in the ratio of VWFpp to VWF:Ag.[201,202] Persons who have type 3 VWD, with large deletions of the VWF gene, are prone to develop alloantibodies to transfused VWF.[203] Patients who have AVWS, VWF antibodies, or mutations that affect VWF clearance can be studied using VWF-survival testing after administration of DDAVP or VWF concentrate.

Making the Diagnosis of VWD

Scoring systems and criteria for assessing the bleeding history and the probability of having VWD, especially type 1 VWD, are in evolution but have not yet been subjected to prospective studies outside of defined populations.[155,194] Establishing the diagnosis of VWD in persons who have type 2 VWD variants and type 3 VWD is usually straightforward, based on the initial VWD tests (described in Box 3, Initial Tests for VWD). Treatment depends on the specific subtype

(e.g., type 2A, 2B, 2M, or 2N), which is determined by additional tests including VWF multimer analysis. In contrast, the diagnosis of type 1 VWD is often more difficult,[21,44,93,114,204] partly because not all persons who have decreased levels of VWF have a molecular defect in the VWF gene. Whether individuals who do not have an abnormality in the VWF gene should be diagnosed as having VWD or should be given another designation is currently under consideration (see section on "Type 1 VWD Versus Low VWF"). The reasons for reduced VWF levels in many of these persons who have a normal VWF gene sequence are not understood. A "low" VWF level is believed to confer some bleeding risk, despite having a normal VWF gene, and those persons who have clinical bleeding and low VWF may benefit from treatment to raise the VWF level. Most clinicians would agree that persons having VWF levels below 30 IU/dL probably have VWD. It is likely that most of these persons have a mutation in the VWF gene. Currently, several large European Union, Canadian, and U.S. studies are trying to define that frequency. Persons whose plasma VWF levels are below the lower limit of the laboratory reference range, but >30 IU/dL, may have VWD but are sometimes referred to as having "possible type 1 VWD" or "low VWF." There is no generally accepted designation for these persons. Although type 3 VWD is usually the result of inheriting two "null" alleles, the heterozygous "carriers" in these families do not universally have a significant bleeding history; therefore, type 3 VWD has been called a recessive disorder.[21,44,101]

Special Considerations for Laboratory Diagnosis of VWD

Repeated testing for VWD is sometimes needed to identify low levels of VWF. Stress—including surgery, exercise, anxiety, crying in a frightened child, as well as systemic inflammation, pregnancy, or administration of estrogen/oral contraceptives—can cause an increase in plasma levels of VWF and mask lower baseline values. VWF levels vary with the menstrual cycle, and lowest values are detected on days 1–4 of the menstrual cycle. However, the importance of timing of the testing with respect to the menstrual cycle is not clear. Family studies may be helpful to diagnose hereditary decreases in VWF levels.

Problems may occur in preparing samples for testing. As noted, anxiety may falsely elevate the VWF and FVIII levels, and the setting for phlebotomy should be as calm as possible. It is important that the sample be obtained by atraumatic collection of blood, drawn into the appropriate amount of citrate anticoagulant. The College of American Pathologists (CAP), as well as the Clinical Laboratory Standards Institute (CLSI, formerly NCCLS), recommend collecting blood into 3.2 percent citrate, although some laboratories still use 3.8 percent citrate. Fasting or nonlipemic samples should be used for testing, and icteric or hemolyzed samples may also compromise the quality of testing results.[193,205] If a person has polycythemia or profound anemia, the amount of anticoagulant should be adjusted on the basis of nomograms for this purpose. Blood should be centrifuged promptly to obtain plasma, and the plasma should remain at room temperature if assays are to be completed within 2 hours. Whole blood should not be transported on wet ice (or frozen).[206,207] If plasma samples are frozen, they should be thawed at 37°C to avoid formation of a cryoprecipitate. Plasma assays should be performed on "platelet-poor" or "platelet-free" plasma.[193] Although a small number of platelets may not significantly affect studies done on fresh plasma, freezing these samples may result in the release of proteases or platelet membrane particles that affect plasma assays for VWF. Thus, plasmas should be centrifuged carefully. Some laboratories perform double centrifugation to ensure platelet removal. The integrity of samples may suffer during transport to an outside laboratory, and steps should be taken that can best ensure prompt delivery of frozen samples. (See Table 10.)

The VWF reference standard is critical to the laboratory diagnosis of VWD. When possible, all laboratory assays of VWF should use the same standard to avoid artifactual discrepancies. Results of VWF assays can be reported in international units (IUs) only if they have been referenced to the WHO standard for that analyte. If a reference plasma pool is used, it is usually reported as a percentage of normal, as it cannot be called an IU. To assist the comparison, IUs are usually expressed as IU/dL so that the reported values have the same range as "percentage of normal plasma" values.

Table 10. Collection and Handling of Plasma Samples for Laboratory Testing

Phlebotomy conditions—An atraumatic blood draw limits the exposure of tissue factor from the site and the activation of clotting factors, minimizing falsely high or low values.

Patient stress level—Undue stress, such as struggling or crying in children or anxiety in adults, may falsely elevate VWF and FVIII levels. Very recent exercise can also elevate VWF levels.

Additional conditions in the person—The presence of an acute or chronic inflammatory illness may elevate VWF and FVIII levels, as may pregnancy or administration of estrogen/oral contraceptives.

Sample processing—To prevent cryoprecipitation of VWF and other proteins, blood samples for VWF assays should be transported to the laboratory at room temperature. Plasma should be separated from blood cells promptly at room temperature, and the plasma should be centrifuged thoroughly to remove platelets. If plasma samples will be assayed within 2 hours, they should be kept at room temperature. Frozen plasma samples should be carefully thawed at 37°C and kept at room temperature for <2 hours before assay.

Sample storage—Plasma samples that will be stored or transported to a reference laboratory must be frozen promptly at or below –40°C and remain frozen until assayed. A control sample that is drawn, processed, stored, and transported under the same conditions as the tested person's sample may be helpful in indicating problems in the handling of important test samples.

Laboratory variables also occur. The variability (CV) of the VWF:RCo assay is high (20–30 percent or greater) and the CV of the VWF:Ag assay is also relatively high (10–20 percent or greater), as is the CV for the FVIII assay.[175,177–179,183,208–210] The quality of laboratory testing also varies considerably among laboratories (high interlaboratory CV). Coupled with variability of VWF and FVIII contributed by conditions of the patient and the blood sample, the high variability of these three diagnostic tests can contribute to difficulty in diagnosing VWD or classifying the VWD subtype (e.g., type 1 vs. type 2 variant, using the VWF:RCo to VWF:Ag ratio). Some of the more specialized tests, such as VWF multimer analysis likely also have high variability of test performance and interpretation,[180,181] and they are often not available at local testing laboratories.

Summary of the Laboratory Diagnosis of VWD

The diagnosis of VWD can be complex, and no single diagnostic approach is suitable for all patients. Improvements in laboratory testing and quality, along with further research into the frequency of mutations of the VWF gene, alterations of other proteins that result in reduced VWF levels, and the correlation of clinical symptoms with laboratory test levels will be necessary to place the diagnosis of VWD on a more secure foundation. (See Table 10.)

The following recommendations include specific clinical history, physical findings, laboratory assays, and diagnostic criteria that this Panel suggests will allow the most definitive diagnosis of VWD.

- **Tests such as the bleeding time, PFA-100®, or other automated functional platelet assays have been used but there are conflicting data with regard to sensitivity and specificity for VWD.[162,164,166] Therefore, the Panel believes current evidence does not support their routine use as screening tests for VWD.**
- **The Panel believes that platelet-based assays should be used for the ristocetin cofactor method.**
- **The Panel emphasizes the importance of the timing of the phlebotomy for assays, with the patient at his/her optimal baseline as far as possible. (For example, VWF levels may be elevated above baseline during the second and third trimesters of pregnancy or during estrogen replacement, during acute inflammation such as the perioperative period, during infections, and during acute stress.) The careful handling and processing of the sample is also critical, particularly if the sample will be sent out for testing at a distant location.**

Diagnostic Recommendations

The recommendations are graded according to criteria described on page 3 and in Table 1. Evidence tables are provided for recommendations given a grade of B and having two or more references (see pages 83–111).

I. Evaluation of Bleeding Symptoms and Bleeding Risk by History and Physical Examination

Summarized in Figure 3 (page 20), and Box 1 (page 21)

A. Ask the following broad questions:
   1. Have you or a blood relative ever needed medical attention for a bleeding problem, or have you been told you had a bleeding problem?
      Grade B, level IIb[138]

   If the answer is "Yes" to either of the broad questions above, ask the additional probes:

      a. Have you needed medical attention for bleeding? After surgery? After dental work? With trauma?
      b. Have you ever had bruises so large they had lumps?
         Grade B, level IIb[138]

   2. Do you have or have you ever had:

      a. Liver or kidney disease?
      b. A blood or bone marrow disorder?
      c. A high or low platelet count?

      If the answer is "Yes" to any of these questions, obtain relevant details.
      Grade C, level IV

   3. Are you currently taking, or have you recently taken anticoagulation or antiplatelet medications (warfarin, heparin, aspirin, NSAIDs, clopidogrel)? If the answer is "Yes", obtain relevant details. *Grade C, level IV*

B. If answers to questions I.A.1 are positive, ask if the patient or any blood relatives have had:

   1. A bleeding disorder, such as von Willebrand disease or hemophilia?
   2. Prolonged bleeding, heavy, or recurrent from:

      a. Trivial wounds, lasting more than 15 minutes or recurring spontaneously during the 7 days after the wound?
      b. Surgical procedures, such as tonsillectomy?

   3. Bruising with minimal or no apparent trauma, especially if you could feel a lump?
   4. Spontaneous nosebleeds that required more than 10 minutes to stop or needed medical attention?
   5. Dental extractions leading to heavy, prolonged, or recurrent bleeding?
   6. Blood in your stool, unexplained by a specific anatomic lesion (such as an ulcer in the stomach, or a polyp in the colon), that required medical attention?
   7. Anemia requiring treatment or received a blood transfusion?
   8. For women, heavy menses, characterized by the presence of clots greater than an inch in size and/or changing a pad or tampon more than hourly, or resulting in anemia or low iron level?

   If answers to above questions I.B.1–8 are positive, obtain relevant specific information.
   Grade B, level IIb[138,139] *See Evidence Table 1.*

C. Perform a physical examination to include evaluation for:

   1. Evidence for a bleeding disorder, including size, location, and distribution of ecchymoses (e.g., truncal), hematomas, petechiae, and other evidence of recent bleeding and/or anemia. *Grade C, level IV*
   2. Evidence that suggests other causes or risks of increased bleeding, such as jaundice or spider angiomata (liver disease), splenomegaly, arthropathy, joint and skin laxity (e.g., Ehlers-Danlos Syndrome), telangiectasia (e.g., hereditary hemorraghic telangiectasia), or evidence of anatomic lesions on gynecologic examination. *Grade C, level IV*

Laboratory testing should be guided by the history and physical findings (section I.) and the initial laboratory evaluation (see II.A., below). For example, findings of liver disease may lead to a different or additional laboratory evaluation rather than an evaluation for VWD (see II.B., below).

II. Evaluation by Laboratory Testing

A. Initial laboratory evaluation for the etiology of a bleeding disorder should include:

1. A complete blood count (CBC including platelet count), prothrombin time (PT), activated partial thromboplastin time (PTT), and optionally either thrombin time or fibrinogen level.

2. If laboratory abnormalities besides the PTT are present (the platelet count may also be decreased in type 2B VWD), in conjunction with the history and physical examination findings, consider bleeding disorders other than VWD or additional underlying diseases.

3. If the mucocutaneous bleeding history is strong, consider performing initial VWD assays at the first visit (see II.B., below).

4. If there are no abnormalities on initial blood testing, or if there is an isolated prolonged PTT that corrects on the 1:1 mixing study, the following three tests for VWD should be performed (II.B., below), unless another cause for bleeding has been identified and VWD is not likely (see Figure 4, page 25). For further laboratory evaluation, physicians may consider referral to a hemostasis center because of the special sample handling and testing requirements (see Table 10).
Grade C, level IV

B. Initial tests for diagnosing or excluding VWD include the following three tests:

1. VWF:RCo

2. VWF:Ag

3. Factor VIII activity
Grade B, level III[3,43,175,176] *See Evidence Table 2.*

C. If any one of the above test results is abnormally low, a discussion with or a referral to a hemostasis expert is appropriate. In addition to repeating the initial three tests (in most cases), the specialist may recommend appropriate studies from the following:

1. The first set of additional tests may include:

a. Evaluation of the ratio of VWF activity (VWF:RCo and/or VWF:CB) to VWF antigen (only in laboratories that have defined reference ranges for the ratio[s])
Grade B, level III[70,71,91,163,175,190]
See Evidence Table 3.

b. VWF multimer study
Grade B, level III[181]

c. Ristocetin-induced platelet aggregation
Grade B, level III[46]

d. VWF collagen binding activity (VWF:CB)
Grade B, level IIb[175,185,186] *See Evidence Table 4.*

2. Studies in selected patients, especially those who have discordantly low FVIII activity compared to VWF levels and who are suspected of having type 2N VWD, should include a FVIII binding assay (VWF:FVIIIB)
Grade B, level IIb[77,78,188] *See Evidence Table 5.*

3. Additional studies in selected persons may include:

a. Gene sequencing
Grade C, level IV

b. Assays for antibodies to VWF
Grade C, level IV

c. Platelet-binding studies
Grade B, level III[182]

III. Making the Diagnosis

A. *Clinical criteria.* These criteria include personal and/or family history and/or physical evidence of mucocutaneous bleeding. Until further validation of scoring systems and criteria for assessing bleeding history and the probability of VWD, especially type 1 VWD, the Expert Panel suggests that an increasing number of positive responses to the questions about bleeding (Figure 3, page 20, and Box 1, page 21) and abnormal findings on physical

examination increase the likelihood that an individual has a bleeding disorder, including possible VWD.

AND

B. *Laboratory criteria.* The values in the following table represent prototypical cases without additional VWF (or other disease) abnormalities in the patient. In practice, exceptions occur, and repeat testing and clinical experience are important and may be necessary for interpretation of laboratory results.

1. Although published evidence is limited, for defining the ratio of VWF:RCo/VWF:Ag to use for distinguishing type 1 VWD versus type 2 VWD variants (A, B, or M), the Expert Panel recommends a ratio of <0.5–0.7 until more laboratories clearly define a reference range using large numbers of normal subjects and persons who have type 1 VWD and type 2 VWD variants.
Grade C, level IV[70,71,91,163,189,190]

2. The panel currently recommends that 30 IU/dL be used as the "cut-off" level for supporting the definite diagnosis of VWD for the following reasons:
   - There is a high frequency of blood type O in the United States, and it is associated with "low" VWF levels;[43]
   - Bleeding symptoms are reported by a significant proportion of normal individuals;[137–140] and
   - No abnormality in the VWF gene has been identified in many individuals who have mildly to moderately low VWF:RCo levels
   Grade C, level IV[100–102]

This recommendation does not preclude the diagnosis of VWD in individuals with VWF:RCo of 30–50 IU/dL if there is supporting clinical and/or family evidence for VWD. This recommendation also does not preclude the use of agents to increase VWF levels in those who have VWF:RCo of 30–50 IU/dL and may be at risk for bleeding.

Condition	VWF:RCo (IU/dL)	VWF:Ag (IU/dL)	FVIII	Ratio of VWF:RCo/ VWF:Ag
Type 1	<30*	<30*	↓or Normal	>0.5–0.7
Type 2A	<30*	<30–200*†	↓or Normal	<0.5–0.7
Type 2B	<30*	<30–200*†	↓or Normal	Usually <0.5–0.7
Type 2M	<30*	<30–200*†	↓or Normal	<0.5–0.7
Type 2N	30–200	30–200	↓↓	>0.5–0.7
Type 3	<3	<3	↓↓↓ (<10 IU/dL)	Not applicable
"Low VWF"	30–50	30–50	Normal	>0.5–0.7
Normal	50–200	50–200	Normal	>0.5–0.7

↓ refers to a decrease in the test result compared to the laboratory reference range.
* <30 IU/dL is designated as the level for a definitive diagnosis of VWD; there are some patients with type 1 or type 2 VWD who have levels of VWF:RCo and/or VWF:Ag of 30–50 IU/dL.
† The VWF:Ag in the majority of individuals with type 2A, 2B, or 2M VWD is <50 IU/dL.

Management of VWD

Introduction

Therapies to prevent or control bleeding in persons who have VWD follow three general strategies. The first strategy is to increase plasma concentration of VWF by releasing endogenous VWF stores through stimulation of endothelial cells with DDAVP. The second approach is to replace VWF by using human plasma-derived, viral-inactivated concentrates. The third strategy employs agents that promote hemostasis and wound healing but do not substantially alter the plasma concentration of VWF. The three treatment options are not mutually exclusive, and patients may receive any one or all three classes of agents at the same time. The appropriateness of therapeutic choice is dependent on the type and severity of VWD, the severity of the hemostatic challenge, and the nature of the actual or potential bleeding. Because some persons who have VWF:RCo >30 IU/dL manifest clinical bleeding, persons not having a definite diagnosis of VWD but who have low VWF and a bleeding phenotype may merit treatment or prophylaxis of bleeding in certain clinical situations.[196] Infusions of VWF to prevent bleeding episodes—known as prophylaxis—are less frequently required in patients who have severe VWD in contrast to patients who have severe hemophilia. The CDC Universal Data Collection Project Web site (http://www2a.cdc.gov/ncbddd/htcweb/) reports that 45 percent of patients who have severe hemophilia A use some type of prophylaxis, either continuous or intermittent, compared with 10 percent of patients who have severe VWD. Risks and benefits of prophylaxis should be carefully weighed when considering long-term therapy for VWD.[211,212] Treatment of VWD in the United States varies widely and frequently is based on local experience and physician preference. Few standard recommendations exist to guide therapy for VWD.[6,7,9] This guidelines document presents recommendations regarding the management and prevention of bleeding in persons who have VWD and reviews the strength of evidence supporting those recommendations.

Therapies To Elevate VWF: Nonreplacement Therapy

DDAVP (Desmopressin: 1-desamino-8-D-arginine vasopressin)

Mechanism of action of DDAVP. DDAVP is a synthetic derivative of the antidiuretic hormone, vasopressin. DDAVP has been used to treat VWD for 25 years, and its pharmacology, mechanism of action, and indications have been reviewed extensively.[213–215] DDAVP stimulates the release of VWF from endothelial cells through its agonist effect on vasopressin V2 receptors.[213,214,216] The mechanism by which DDAVP increases plasma concentration of VWF is probably through cyclic AMP-mediated release of VWF from endothelial cell Weibel-Palade bodies.[216,217] FVIII levels also increase acutely after administration of DDAVP, although the FVIII storage compartment and the mechanism of release by DDAVP have not been fully elucidated to date.[11,218] DDAVP induces the release of tissue plasminogen activator (tPA).[219,220] However, the secreted tPA is rapidly inactivated by plasminogen activator inhibitor (PAI-1) and does not appear to promote fibrinolysis or bleeding after DDAVP treatment.

DDAVP dosing and administration. Table 11 displays published reports of DDAVP effects on laboratory assays of VWF and FVIII in normal persons and persons who have various subtypes of VWD.[64,92,99,221–232] When administered intravenously to normal persons as well as to patients who have VWD or mild hemophilia, DDAVP consistently increases plasma VWF and FVIII from twofold to greater than fivefold over baseline levels.[92,218,223,225–227,230,231] Children under the age of 2 have a significantly lower response rate than older children.[230] Two controlled prospective studies in healthy volunteers form the basis for DDAVP dosing recommendations.[225,227] Maximal FVIII response was determined at 0.3 micrograms/kilogram in both studies, while maximal VWF release data were determined at 0.2 and 0.3 micrograms/kilogram in the two studies, respectively. Based on

these data, standard dosing of DDAVP is 0.3 microgram/kilogram given intravenously in 30–50 mL of normal saline over 30 minutes, with peak increments of FVIII and VWF 30 to 90 minutes postinfusion.[218,223,225,233] Nasal administration of high-dose desmopressin acetate (Stimate®) is often effective for minor bleeding, but intravenous administration is the preferred route for surgical bleeding prophylaxis and for treatment of major hemorrhage.

A retrospective review of DDAVP administration to 56 children who had nonsevere type 1 VWD found a 91 percent response rate, defined as FVIII and VWF activity increase of twofold, to at least 30 IU/dL.[230] In a small case series of VWD patients, the consistency of FVIII increases and the response of the bleeding time after a second test dose of DDAVP was within 10–20 percent of the initial value.[231] Evidence shows that response to DDAVP diminishes with repeated doses, probably due to depletion of the VWF storage compartment.[218,227] However, when DDAVP was given in four daily doses to 15 patients who had type I VWD, an increase in FVIII activity of at least twofold was found in 100 percent of the patients after the first administration, in 80 percent after the second, in 87 percent after the third, and in 74 percent after the fourth administration.[226]

Consistency of response to DDAVP has been studied using 24-hourly dosing for three to four daily doses.[226,227] A series of 15 type 1 VWD patients showed a mean rise of VWF:RCo to fivefold above baseline following the first dose of DDAVP, significantly decreased response to fourfold following the second daily dose, and no significant change in response among the second to fourth doses.[226] The proportion of VWD patients attaining at least a twofold rise in FVIII activity following the second to fourth daily doses—80 percent following the second daily dose of DDAVP to 74 percent following the fourth dose—was substantially higher than that for hemophilia A patients (55 to 37 percent). There is no published evidence regarding response to DDAVP given every 12 hours to compare with daily dosing of DDAVP. In addition to tachyphylaxis, hyponatremia may complicate repeated DDAVP dosing, and fluid restriction as well as serum sodium monitoring are recommended.

DDAVP can also be administered subcutaneously or intranasally.[225,227,233] The effective subcutaneous dose is identical to intravenous dose, but the subcutaneous preparation is not available in the United States. The preparation of DDAVP for nasal instillation (Stimate®) contains 150 micrograms per metered nasal puff (0.1 mL of a 1.5 mg/mL solution). The dose is one puff for persons who weigh <50 kg and two puffs (one to each nostril) for persons weighing 50 kg or more. Although the intra- and intersubject coefficient of variation for reproducibility of nasal spray effect is good, nasal absorption is variable, and all patients who have VWD and are responsive to intravenous DDAVP should undergo a trial of Stimate® to measure FVIII and VWF response before using it.[225] When used for epistaxis, Stimate® ideally is delivered into the nonbleeding nostril. Persons who have inadequate plasma responses to intravenous DDAVP will not respond to Stimate®.

There is also a nasal formulation of DDAVP (for enuresis) that contains 10 micrograms per puff (about 7 percent of the Stimate® concentration); however, this preparation is not suitable for treatment of VWD. Patients and parents must be carefully instructed regarding the two concentrations of nasal DDAVP—the one used for bleeding (1.5 mg/mL), and the one used for antidiuretic hormone replacement (diabetes insipidus) and bedwetting (0.1 mg/mL)—to avoid accidental underdosing for VWD.

Monitoring of VWD patients receiving DDAVP. Treatment of patients who have VWD with DDAVP should be based on results of a therapeutic trial, ideally one performed in a nonbleeding state and before clinical use.

Although the pattern of DDAVP responsiveness is fairly consistent within VWF subtypes, population results should not be used to plan treatment of individual patients (see Table 11). VWF:RCo and FVIII activities should be measured in all VWD patients at baseline and within 1 hour after administering DDAVP. Additional assay of VWF:RCo and FVIII, 2–4 hours after DDAVP, will evaluate for shortened survival and should be considered for patients who have a history of poor response to treatment.[41]

According to conservative definitions of laboratory response, the majority of patients who have type 1 VWD respond adequately to DDAVP (Table 11). Single infusions of DDAVP for common bleeding episodes—such as epistaxis, simple dental extraction, or menorrhagia—do not usually require laboratory monitoring. Patients should be monitored for VWF:RCo activity as well as FVIII activity around

Table 11. Intravenous DDAVP Effect on Plasma Concentrations of FVIII and VWF in Normal Persons and Persons Who Have VWD

Group/reference	N	Mean increase (fold)*			Type of evidence
		VWF:RCo	VWF:Ag	FVIII	
Normals					
Mannucci et al. 1981[227]	10	N/A	3.3	4.5	Case series
Lethagen et al. 1987[225]	10	N/A	2.7	3.7	Case series
VWD					
Type 1					
Mannucci et al. 1981[227]	15	N/A	3.6	5.5	Case series
de la Fuente et al. 1985[223]	13	5.0	4.5	5.7	Case series
Mannucci et al. 1988[92]	7	9.5	9.0	10.3	Case series
Rodeghiero et al. 1989[231]	14	N/A	N/A	7.8	Case series
Mannucci et al. 1992[226]	15	5.1	4.8	4.3	Case series
Revel-Vilk et al. 2003[230] 91% response rate†	56				Retrospective review
Federici et al. 2004[224] 27% response rate†	26	3.1	N/A	3.3	Case series
Type 1 Vicenza (ultra-large multimers)					
Mannucci et al.1988[92]	6	9.1	8.3	10.2	Case series
Rodeghiero et al. 1989[231]	5	N/A	N/A	10	Case series
Type 1, Severe (VWF:RCo <10 IU/dL OR Bleeding Time >15 min OR FVIII <20 IU/dL)					
Revel-Vilk et al. 2003[230] 36% response rate†	14	N/A	N/A	N/A	Retrospective review
Federici et al. 2004[224] 27% response rate†	26	3.1	N/A	1.4	Case series
Type 1, Severe with normal platelet VWF					
Rodeghiero et al. 1988[232]	14	N/A	N/A	7.8	Case series
Mannucci et al. 1985[99] 6/6 with increase in FVIII, VWF:RCo and VWF:Ag	6	N/A	N/A	N/A	Case series
Type 1, "Platelet low"					
Mannucci et al. 1985[99] 7/7 with increase in FVIII; 0/7 with increase in VWF:RCo or VWF:Ag	7	N/A	N/A	N/A	Case series
Rodeghiero et al. 1989[231] 2/2 with increase in FVIII; VWF response not reported	2	N/A	N/A	2.1	Case series

Table 11. Intravenous DDAVP Effect on Plasma Concentrations of FVIII and VWF in Normal Persons and Persons Who Have VWD (continued)

Group/reference	N	Mean increase (fold)*			Type of evidence
		VWF:RCo	VWF:Ag	FVIII	
Type 2A					
de la Fuente et al. 1985[223] 86% response rate†	7	6.4	4.9	4.9	Case series
Revel-Vilk et al. 2003[230] 40% response rate, results given for responders only	5	4.2	N/A	2.9	Retrospective review
Federici et al. 2004[224] 7% response rate†	15	2.6	N/A	3.4	Case series
Type 2B					
Casonato et al. 1990[64]	4	2.3	3.5	3.0	Case series
McKeown et al. 1996[229]	3	3.2	3.2	3.6	Case series
Castaman and Rodeghiero 1996[222]	33	Normalized in 18/33	Normalized in 33/33	Normalized in 33/33	
Type 2M					
Federici et al. 2004[224] 14% response rate†	21	3.3	N/A	3.0	Case series
Type 2N					
Mazurier et al. 1994[228]	8	1.4	2.2	9.7	Case series
Federici et al. 2004[224] 75% response rate†	4	3.8	N/A	6.6	Case series
Type 3					
Castaman et al. 1995[221] 0% response rate†	6	1.8	8.6	2.5	Case series

* Data are given as mean fold increase in plasma factor compared to baseline after a single administration of DDAVP. Mean fold increases were calculated from original data, where possible, if not included in the manuscript.
† Response defined as twofold increase AND to at least 30 IU/dL VWF:RCo and FVIII.
FVIII, factor VIII (8); N/A, not available; VWF:Ag, VWF antigen; VWF:RCo, von Willebrand factor (VWF) ristocetin cofactor.

major surgeries or major bleeding events. For major surgeries or bleeding events, patients who have VWD should be referred to hospitals with in-house or daily laboratory availability of FVIII and VWF:RCo activity assays. Care should be taken to monitor serum electrolytes, especially after surgery or multiple doses of DDAVP. Adult patients, especially those who are elderly, should be evaluated for CVD before using DDAVP because myocardial infarction rarely has been precipitated by DDAVP therapy in patients who have hemophilia or uremia.[234–236]

Pharmacokinetics of VWF and FVIII after DDAVP. After stimulation with DDAVP, released VWF and FVIII circulate with an apparent half-life characteristic of the patient's own proteins, or approximately 8–10 hours for both proteins in normal individuals.[218] Type 2 VWF proteins that are released by DDAVP will increase in concentration but retain their intrinsic molecular dysfunction.[237] For this reason, DDAVP has been efficacious in only a minority of patients who have types 2A or 2M VWD. Therefore, monitoring is necessary to document adequate correction of VWF:RCo. Type 2N VWF lacks FVIII stabilization;

consequently, patients who have 2N VWF will release FVIII and the abnormal VWF protein as expected, but the survival of released FVIII may be severely decreased, with an apparent plasma half-life as low as 2 hours, depending on the mutation.[168,228] Emerging information suggests that some individuals who have type 1 VWD have accelerated plasma clearance of VWF and may benefit from trial testing of VWF:RCo 2–4 hours after a dose of DDAVP.[40,238]

Following infusion of DDAVP into patients with type 2B VWD, VWF multimers of larger but still somewhat less than normal molecular weight can be detected in plasma after 15 to 30 minutes, with persistence throughout 4 hours of study.[63,168,237,239] Although formal pharmacokinetic studies have not been reported for type 2B VWD, VWF:RCo activity increases were less than that seen in type 1 VWD with an apparent half-life of approximately 4 hours.[63,229] Bleeding time response to DDAVP in type 2B VWD is inconsistent.[222,229]

Clinical response to DDAVP in VWD. The clinical effectiveness of DDAVP to prevent or control bleeding depends, in large part, on the plasma VWF:RCo or FVIII activity achieved after drug administration, which in turn depends primarily on the basal levels of plasma FVIII and VWF:RCo and to a lesser extent on the underlying qualitative VWF defect.[64,92,99,221–232] Table 12 and Evidence Tables 7–12 summarize published data on clinical response when using DDAVP in conjunction with common surgical procedures.[136,218,221–223,230,232,240–250] All data were derived from retrospective studies and small case series; there are no randomized clinical trials of the use of DDAVP in persons who have VWD.

Whether DDAVP will be adequate for prophylaxis around surgery or for treatment of bleeding events in persons who have type 1 VWD is dependent on the severity of the hemostatic challenge and the time required for healing. Major surgery requires hemostasis for 7–14 days,[247,251–256] whereas minor surgeries can be treated adequately in 1–5 days.[243,244,247,256] If treatment is necessary for more than 3 days, VWF concentrate is usually given to supplement therapy with DDAVP.[244,247] Currently, however, expert opinions are divided regarding the risk of delayed hemorrhage 5–10 days after a bleeding challenge in VWD patients, e.g., those who have had tonsillectomy or given birth. In small case series, persons who have type 1 VWD Vicenza manifest an exaggerated response to DDAVP.[41,92,231] Individuals who have type 2N VWD exhibit a brisk rise in plasma FVIII after receiving DDAVP, but they have a mean FVIII half-life of only 3 hours because of deficient FVIII stabilization by the defective VWF.[228] Persons who have low platelet VWF or type 2A VWD have a low likelihood of having a clinically relevant DDAVP response, but they may warrant a DDAVP trial.[224,231] Type 2B VWD previously was a contraindication to DDAVP therapy because platelet counts usually fell after DDAVP stimulation.[257] However, thrombocytopenia after DDAVP in type 2B VWD is usually transient and often is not associated with bleeding or thrombosis.[258] In patients who have type 2B VWD, decrease in platelet count after DDAVP administration has been considered "pseudothrombocytopenia" by some authors because it is related to platelet agglutination in vitro rather than in vivo agglutination and clearance.[63,239] Therefore, DDAVP may be cautiously considered for patients who have type 2B VWD. Patients who have type 3 VWD almost never experience a clinically relevant rise in VWF:RCo or FVIII activities, and DDAVP is not considered clinically useful in these patients.[224,230]

Complications and toxicities of DDAVP. Minor side effects of DDAVP are common and include facial flushing, transient hypertension or hypotension, headache, or gastrointestinal upset,[214,215,262] but these effects rarely limit clinical use. Water retention after a dose of DDAVP, with an increase in urinary osmolality, is universal; however, decreased serum sodium in otherwise healthy adults is variable and is related to multiple doses.[262,263] In the case of repeated dosing, all patients should be instructed to limit fluid intake to maintenance levels for 24 hours.[264–266] Prophylactic use of DDAVP complicates the management of fluids and electrolytes for surgery or during childbirth. Seizures have been associated with hyponatremia after DDAVP administration, primarily in young children.[263,266] Most pediatric hematologists do not use DDAVP in children under the age of 2 years.[230,261,266]

Myocardial infarction after treatment with DDAVP has been reported, although rarely, in patients who have mild hemophilia A.[234,236,267] DDAVP should be avoided in patients who are at very high risk for cardiovascular or cerebrovascular disease, especially the elderly, as underlying inhibition of plasminogen activation with DDAVP-related vasoconstriction contributes additional prothrombotic effects in these

Table 12. Clinical Results of DDAVP Treatment in Patients Who Have VWD*

Adult surgical prophylaxis	N	Frequency	Duration	Other treatment	Bleeding outcome
Dental procedures[63,64,221–223,232,242,246–248,250,259,260]	113	Once	Once or twice	Antifibrinolytics	Excellent/good 109/113
Gynecologic[218,223,246,247]	9	Daily	1–7 days	Antifibrinolytics 2/7	Delayed bleeding in 2/9 requiring extended DDAVP treatment for 3 and 6 days
Surgery[218,221,223,247,249,258,259]	26	Daily	1–5 days		Excellent/good in 25/26 Hemorrhage after 1 rhinoplasty

Experience in children	N	Frequency	Duration	Other treatment	Bleeding outcome
Primarily tonsillectomy and adenoidectomy[240,241,243–245,249,250]	146	Once or twice daily	1–7 days	Antifibrinolytics in most for 7 days	Excellent/good in 125/146
Primarily tonsillectomy/ adenoidectomy[261]	119	NA†	NA†	NA†	Excellent/good in 105/119
Otologic Surgery[249]	6	Daily	2 days		Excellent/good in 6/6

DDAVP, 1-desamino-8-D-arginine vasopressin (desmopressin, a synthetic analog of vasopressin)
* For additional detail and information, see Evidence Tables 7–11.
† NA, not available

patients.[268] Because of reported complications in other patient populations, DDAVP should be used with caution for brain, ocular, and coronary artery surgeries,[235,269,270] and VWF concentrate replacement generally is used in these settings. DDAVP does not appear to increase myometrial contractility significantly; consequently, pregnancy is not an absolute contraindication[271–274] but use of DDAVP is rarely indicated (see "Pregnancy").

Therapies To Elevate VWF: Replacement Therapy

As of January 2007, Humate-P® and Alphanate SD/HT® are the only plasma-derived concentrates licensed in the United Sates to replace VWF in persons who have VWD. One other plasma derivative—Koate DVI®—is licensed in the United States to treat hemophilia and has been used off-label for VWD. These products are not identical, have differing ratios of FVIII to VWF, and should not be considered as interchangeable.[275–277] All of these products are manufactured at U.S.-licensed facilities from pooled plasma collected from paid donors.

Products that contain FVIII and little or no VWF are generally not useful to treat VWD, but in rare circumstances these products may be used to treat patients who have antibody-mediated AVWS.[278] These products include the plasma-derived concentrates Monoclate P®, Monarc M®, and Hemofil M®; and recombinant products Helixate FS®, Kogenate FS®, Recombinate®, Advate®, and ReFacto®.

Humate-P®, a lyophilized concentrate of purified VWF and FVIII, contains other plasma proteins including fibrinogen and albumin. In Humate-P®, the quantity of the large, most hemostatically active multimers of VWF is decreased compared to fresh plasma.[279] When reconstituted at the recommended volume, each milliliter of the product contains 50–100 IU/mL VWF:RCo and 20–40 IU/mL FVIII activity (Humate-P® package insert). The median half-life of VWF:RCo activity was 10.3 hours (range: 6.4–13.3 hours) in one study (see package insert) and 11.3 hours in another study.[251] The product is

indicated for use in adult and pediatric patients for treatment of spontaneous and trauma-induced bleeding when use of DDAVP is thought or known to be inadequate or contraindicated. Humate-P® has received FDA approval for use in prophylactic management of surgery and invasive procedures in patients with VWD.

Alphanate SD/HT® is a lyophilized concentrate of VWF and FVIII, and other plasma proteins. It is prepared from pooled human plasma by cryoprecipitation of FVIII, fractional solubilization, and further purification employing heparin-coupled, cross-linked agarose. Upon reconstitution to the recommended volume, each milliliter of product contains 40-180 IU/mL FVIII activity, and not less than 16 IU/mL VWF:RCo activity (Alphanate SD/HT® package insert). The median half-life for VWF:RCo activity was 6.91 hours (mean: 7.46 +/- 3.20 hours; range: 3.68 to 16.22 hours. Package Insert). The product is indicated for surgical and/or invasive procedures in patients with VWD in whom either DDAVP is ineffective or contraindicated. It is not indicated for patients with severe VWD (Type 3) undergoing major surgery.

Adverse reactions are rare but include allergic and anaphylactic symptoms, urticaria, chest tightness, rash, pruritus, and edema.[253] If these reactions occur, the infusion should be stopped, and appropriate treatment should be given as required. The product should be used with caution in patients who have known risk factors for thrombosis, as there have been a few reports of venous thromboembolism associated with high levels of FVIII.[280,281] Risk factors include old age, previous thrombosis, obesity, surgery, immobility, hormone replacement therapy (HRT), and use of antifibrinolytic therapy. If patients receive VWF replacement therapy continuously for several days, it has been recommended that FVIII levels be monitored to avoid unacceptably high levels.[215,281]

The products that contain VWF:RCo activity differ significantly in their ratios of VWF:RCo to FVIII[252,282,283] and one should not assume that the dose or frequency of dosing is the same for all. The ratio of VWF:RCo to FVIII for Humate-P® in various reports is 2.7, 2, and 1.6; for Koate DVI®, the ratio is 1.2 and 0.8; and for Alphanate®, the ratio is 0.5.[251] These products also differ in their relative levels of high-molecular-weight multimers. Koate DVI®, in particular, has fewer large VWF multimers compared to Alphanate SD/HT®, which has fewer than Humate-P® or normal plasma.[277,284,285]

Cryoprecipitate, derived from plasma, historically has been used to treat hemophilia A and VWD. Although cryoprecipitate is not required to have a specified level of VWF, the final product must have on average at least 80 units of FVIII per standard donor unit.[286] Currently, cryoprecipitate is used under rare circumstances to treat VWD, such as when potential exposure to infectious agents can be limited by using directed donations to prepare the product.[287] However, the use of cryoprecipitate is strongly discouraged by the National Hemophilia Foundation, except in life-or limb-threatening situations when no VWF concentrate is available, because cryoprecipitate is not virally inactivated.[288] In developing countries, patients who have VWD may have no other options, because virally inactivated plasma concentrates are not available or are too expensive,[283] but use of cryoprecipitate poses a significant risk of transmitting disease.[289]

VWF concentrates are dosed primarily on the basis of labeled VWF:RCo units and secondarily on the basis of labeled FVIII units. A dosing trial with pharmacokinetic laboratory monitoring should be considered before major surgery for selected patients with type 3 VWD or AVWS who are at risk for poor VWF recovery because of inhibitors. Use of VWF concentrates to prevent or control bleeding has been clinically efficacious, as shown on Table 13. The ultimate goal of surgical prophylaxis is to achieve a therapeutic level of 100 IU/dL VWF:RCo and, at least for the first 3 days of treatment, a nadir of 50 IU/dL VWF:RCo, as well as similar targets for FVIII.[251,253–256,290] Successful surgical hemostasis was reported with the use of continuous infusion after initial bolus infusion at rates of 1–2 U/kg/hr VWF:RCo.[252]

Replacement therapy, using a VWF concentrate, is indicated for significant bleeding events or major surgery in patients who have types 2 and 3 VWD as well as in patients who have type 1 VWD and are unresponsive to DDAVP or require a protracted duration of therapy, or where DDAVP is contraindicated (see above). The dose and duration of therapy are dependent on the hemostatic challenge and expected duration required for hemostasis and wound healing. Major surgery requires hemostasis for 7–14 days,[247,251–256] whereas minor surgeries can be treated adequately in 1–5 days.[243,244,247,256] Certain

procedures can be managed adequately by using a single infusion of 20–40 U/kg VWF:RCo before the procedure. Table 14 lists examples of major and minor surgical procedures. Table 15 lists initial dosing recommendations for use of VWF replacement therapy to prevent or treat bleeding. These recommendations are based on published results (see Table 13) as well as consensus expert opinion. The adequacy of courses of VWF replacement usually should be confirmed by laboratory assessment of VWF:RCo and FVIII levels, although monitoring of single infusions for treatment of outpatients may not be necessary. Duration of VWF elevation after replacement therapy is highly variable in the surgical setting. Thromboembolic events have been reported in patients who have VWD and are in situations of high thrombotic risk and receiving VWF:RCo/FVIII complex replacement therapy, especially in the setting of known risk factors for thrombosis.[280–282] In all patients who have VWD and are receiving VWF concentrate, attention should be given to avoid exceeding maximal recommended levels of VWF:RCo and FVIII activities (see Recommendation VII.D, page 54), perform proper thrombotic-risk assessment, and institute appropriate preventive strategies. Recombinant VWF has been prepared and evaluated in animal models[292] but is not available for use in humans.

Human platelets contain 10–15 percent of total blood VWF and platelet transfusions have been used successfully to treat bleeding in VWD patients.[293,294] Platelet transfusion therapy should be considered as an adjunctive source of VWF, especially in patients with type 3 or platelet low VWD and platelet-type VWD, to control bleeding that is non- or poorly responsive to replacement therapy with VWF concentrate.

Table 13. Efficacy of VWF Replacement Concentrate for Surgery and Major Bleeding Events*

Reference	N	Uses	Loading dose† (U/kg)	Outcome
Michiels et al. 2004[255]	5	Surgeries	60–80	100% Excellent–Good
Thompson et al. 2004[256]	42	Surgeries	82.3	100% Excellent–Good
Gill et al. 2003[291]	53	Bleeding events	67	98% Excellent–Good
Lillicrap et al. 2002[253]	344/73	Bleeding events/ surgeries	55.3/69.1	99% Excellent–Good
Nitu-Whalley et al. 2001[247]	10	Surgeries	54	100% Excellent–Good
Lubetsky et al. 1999[254]	3/9	Bleeding events/ surgeries	39.5	92.5% Excellent–Good
Dobrkovska et al. 1998[251]	73	Surgeries	80 C.I.‡	99% Excellent–Good
Hanna et al. 1994[252]	5	Surgeries	25–100 C.I.‡§	100% Excellent–Good
Kreuz et al. 1994[244]	26/41	Bleeding events/ surgeries	10–50§	100% Excellent–Good
Scharrer et al. 1994[290]	66/70	Bleeding events/ surgeries	20–80§	100% Excellent–Good

* For additional detail and information, see Evidence Table 12.
† Loading dose (VWF:RCo IU/dL) reported as median except for Lubetsky (mean).
‡ Indicates that continuous infusion was used after the loading dose.
§ Loading dose (FVIII IU/dL).

Table 14. Suggested Durations of VWF Replacement for Different Types of Surgical Procedures

Major surgery 7–14 days*	Minor surgery 1–5 days*	Other procedures, if uncomplicated, single VWF treatment
Cardiothoracic	Biopsy: breast, cervical	Cardiac catheterization
Cesarean section	Complicated dental extractions	Cataract surgery
Craniotomy	Gingival surgery	Endoscopy (without biopsy)
Hysterectomy	Central line placement	Liver biopsy
Open cholecystectomy	Laparoscopic procedures	Lacerations
Prostatectomy		Simple dental extractions

*Individual cases may need longer or shorter duration depending on the severity of VWD and the type of procedure.

Table 15. Initial Dosing Recommendations for VWF Concentrate Replacement for Prevention or Management of Bleeding

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

*Loading dose is in VWF:RCo IU/dL.

Other Therapies for VWD

Antifibrinolytics. The antifibrinolytic drugs aminocaproic acid and tranexamic acid are agents that inhibit the conversion of plasminogen to plasmin, inhibiting fibrinolysis and thereby helping to stabilize clots that have formed. Studies in hemophilia and in prostatectomy provided the basis for initial trials of antifibrinolytic agents in VWD.[295] The drugs can be used orally or intravenously to treat mild mucocutaneous bleeding in patients who have VWD. In patients who have mild to moderate VWD, tranexamic acid given topically in the oral cavity ("swish and swallow or spit") every 6 hours has been used for prophylaxis in dental surgery, in combination with applied pressure, other topical agents, and suturing of surgical sites.[242] The evidence for the effectiveness of local application of these agents is based on clinical case series,[296] but this route of administration is not currently approved by the U.S. Food and Drug Administration (FDA). When DDAVP and/or VWF/FVIII concentrates are indicated, the use of antifibrinolytic agents as adjuncts to DDAVP or VWF concentrates has been helpful in controlling bleeding, such as in the oral cavity[136,221,223,232,242,246–-248] and in the gastrointestinal and genitourinary tracts.

The usual adult dose of aminocaproic acid is 4–5 g as a loading dose orally or intravenously (1 hour before invasive procedures), and then 1 g per hour, intravenously or orally, or 4–6 g every 4–6 hours orally, until bleeding is controlled, or for 5–7 days postoperatively.[215] Total daily dose of aminocaproic acid is limited to 24 g per 24 hours to minimize potential side effects. Weight-based dosing is required in children and can also be used in adults (50–60 mg/kg).[215,296] Lower doses (25 mg/kg) may be effective and can be used when gastrointestinal side effects interfere with therapy. Tranexamic acid is given intravenously at a dose of 10 mg/kg every 8 hours.[215] The oral form is not currently available in the United States, and use of the intravenous form as an oral rinse ("swish and swallow" approach) is not an FDA-approved indication. The package insert for each drug should be consulted for more detailed guidance and for a full list of risks and contraindications. Both drugs can cause nausea and vomiting; less frequent but serious side effects include thrombotic complications. Both drugs are excreted renally, and dose adjustment or avoidance is advisable when significant renal insufficiency is present. Disseminated intravascular coagulation (DIC) and/or bleeding from the renal parenchyma or upper urinary tract are relative contraindications to antifibrinolytic agents. Renovascular thrombi have followed use of fibrinolytic agents in patients with DIC and have caused renal failure. Patients have also experienced urinary tract obstruction with upper urinary tract bleeding related to large clots in the renal pelvis or lower urinary tract. Changes in color vision during therapy with tranexamic acid require cessation of the drug and ophthalmologic examination.

Topical agents. Topical bovine thrombin (Thrombin-JMI) is marketed in the United States as an aid to hemostasis for topical therapy of accessible minor bleeding from capillaries and small venules. Fibrin sealant (Tisseel VH®, consisting of human thrombin, fibrinogen concentrate, and bovine aprotinin) is indicated as an adjunct to hemostasis in certain surgical situations, but it is not effective for the treatment of massive and brisk arterial bleeding. Fibrin sealants have been used with good results as adjunctive therapy for dental surgery in persons who have hemophilia or VWD.[242,297] Topical collagen sponges are also approved for control of bleeding wounds.[298] Other topical agents approved for limited indications include Coseal®, Bioglue®, and Quickclot®; however, no reports of their use in treating VWD could be found. Quickclot®, containing the mineral zeolite, was approved recently for use with compression dressings for control of external traumatic bleeding in the prehospital setting (e.g., battlefield). The added benefit of topical agents—when used with single or combination therapies including antifibrinolytic drugs, DDAVP, and VWF/FVIII concentrate—is unproven. The topical use of plasma-derived bovine or human proteins imparts a theoretical risk of disease transmission and of potential allergic and other immune reactions. The use of fibrin sealants in addition to drugs and/or concentrates may be viewed as optional adjunctive therapy for dental surgery and for cases in which surface wound bleeding continues despite combined therapy with drugs and concentrates. The safety of these topical agents in therapy for VWD remains to be demonstrated.

Other Issues in Medical Management

All persons who have significant bleeding symptoms related to VWD are likely to require human blood product administration and should receive

immunizations for hepatitis A and B as recommended for individuals with hemophilia.[299] Persons who have VWD should be counseled to avoid aspirin, other NSAIDs, and other platelet-inhibiting drugs.[300–302]

Treatment of AVWS

In an international registry of 189 cases of AVWS, DDAVP produced clinical and laboratory improvement in one-third of cases, although this effect was often short lived.[117] If FVIII activity and the PTT were abnormal, a good DDAVP response was less common than in hereditary VWD and was often brief. In the international registry series, most patients who had AVWS also received VWF/FVIII concentrates; the extent and duration of response was varied. Therefore, VWF:RCo and FVIII levels must be measured pre- and postinfusion of DDAVP or VWF/FVIII concentrates in patients who have AVWS to determine the extent and duration of response and to guide subsequent dosage and dosing intervals.[117,157]

In patients who had a previous inadequate response to DDAVP and VWF/FVIII concentrates, intravenous immunoglobulin G (IGIV; 1 g/kg daily for 2 days) given alone was effective in controlling bleeding and raising VWF:RCo activity for 3 weeks in all eight patients who had excessive bleeding and an IgG-monoclonal gammopathy of uncertain significance (MGUS).[303] In the international registry series, one-third of the 63 patients treated with high-dose IGIV had a good response.[117] The underlying diagnoses of the responders were lymphoproliferative disorders (including MGUS), solid tumors, and autoimmune diseases. An anti-VWF antibody could be demonstrated in vitro in about two thirds of those responders. High dose IGIV therapy in the setting of AVWS is an off-label use but should be considered when DDAVP and VWF/FVIII concentrate therapy fail to control bleeding symptoms adequately.[304–306] Some patients who have immune-mediated AVWS have responded to plasmapheresis, corticosteroids, and immunosuppressive agents.[117] Because many patients in the international registry series received multiple therapeutic modalities, the independent contribution of each therapy to clinical improvement was unclear.

When all other therapeutic modalities fail to control bleeding adequately, the infusion of recombinant FVIIa may be considered, but this agent should be used with caution. Little experience has been reported for its use in treating VWD. A recent report described acute myocardial infarction immediately after the second dose of 90 microgram/kilogram in a 50 year old man who had hereditary type 2A VWD, gastrointestinal bleeding, and several risk factors for, but no history of, coronary artery disease.[307]

Cardiac Valvular Diseases. Congenital or acquired heart disease has been associated with AVWS.[117,119,308] Elevated shear stress around a stenotic valve or septal defect may promote the proteolysis and depletion of high-molecular-weight VWF multimers.[134] Patients who had associated aortic stenosis or other cardiac valvular disorders infrequently responded to any of the therapies described above.[117,122] After surgical correction of the cardiac defect, the multimer pattern has improved at least transiently in most patients studied.[119,122,308] Administration of VWF/FVIII concentrate immediately preoperatively should be considered for patients who demonstrate transient improvement in VWF activity with a test dose.

Angiodysplasia. Bleeding from gastrointestinal angiodysplasia has been reported in persons who have AVWS[309] as well as in persons who have various types of congenital VWD. For example, bleeding from angiodysplasia is a classic presentation of AVWS associated with aortic stenosis[122,310] and is often resistant to medical therapy, requiring surgical correction of the valve defect to ameliorate bleeding symptoms. In the absence of a correctable underlying etiology of angiodysplasia and bleeding associated with AVWS or congenital VWD, management of the condition can be challenging, as no single treatment modality is successful in all cases.[311]

Thrombocytosis. Thrombocytosis, especially in persons who have essential thrombocythemia, is associated with a relative reduction in the proportion of high-molecular-weight multimers.[125] Although the relation of this abnormality to bleeding is inconsistent, treatment is aimed at reduction of the platelet count.

Hypothyroidism. In contrast to the above syndromes, AVWS that occurs in hypothyroidism is caused by decreased synthesis, and the VWF multimer patterns are normal.[312,313] A minority of patients who have hypothyroidism have VWF levels below normal, and not all who have low VWF levels have bleeding symptoms. The decrease in VWF is corrected by thyroid hormone replacement.[127,313]

Management of Menorrhagia in Women Who Have VWD

Menorrhagia is often the primary bleeding symptom in women who have VWD.[85,314,315] Menorrhagia, however, may be a sign of a gynecological disorder rather than VWD.[316] Therefore, a full gynecological evaluation is required before therapy is initiated.[316]

Medical therapies that have been described to control menorrhagia in women who have VWD include combined oral contraceptives, tranexamic acid, DDAVP, and, most recently, the levonorgestrel-releasing intrauterine system (Table 16). Data regarding the effectiveness of these therapies are limited. The only published randomized clinical trial of DDAVP for menorrhagia was small and failed to demonstrate efficacy compared to placebo.[317] The available data show no evidence that DDAVP is more effective than other therapies used to treat menorrhagia.[318] Depending on the woman's age, underlying gynecologic condition, and reproductive plans, any of the therapies demonstrated to be effective for the treatment of menorrhagia in women without VWD may be suitable, with the exception of NSAIDs, which decrease platelet function and systemic hemostasis.[319] In one retrospective review of 36 adolescent girls with VWD and menorrhagia, treatment using oral contraceptive pills (OCPs) or intranasal DDAVP were equally efficacious.[320]

Table 16. Effectiveness of Medical Therapy for Menorrhagia in Women Who Have VWD

Reference	Population	Treatment	Controls	Results	Setting
Kouides et al. 2000[321]	41 women known to have type 1 VWD	Oral contraceptives	No	76% "ineffective"	Patient survey
Foster 1995[322]	25 women known to have VWD	Oral contraceptives	No	88% "effective"	Survey of hemophilia treatment centers
Greer et al. 1991[323]	7 women who had VWD	Oral contraceptives	No	3 "good effect" 3 "slight improvement" 1 "no effect"	Retrospective review, single hemophilia treatment center
Kingman et al. 2004[324]	13 women who had VWD	Levonorgestrel intrauterine system	No	Periods "much better" in 100% 50% developed amenorrhea Increased hemoglobin concentrations	Prospective, open label
Kadir et al. 2002[317]	39 women known to have VWD	DDAVP	Placebo	No significant difference	Prospective, double-blind, randomized trial
Leissinger et al. 2001[325]	90 women who had a variety of bleeding disorders	DDAVP	No	92% "excellent" or "good"	Prospective, open label
Rodeghiero et al. 1996[326]	43 women who had VWD	DDAVP	No	65% "very effective" 21% effective 14% not effective	Prospective, open label
Mohri 2002[327]	3 women who had VWD	Tranexamic acid	No	3 "well-controlled"	Case series
Greer et al. 1991[323]	2 women who had VWD	Tranexamic acid	No	2 "no effect"	Retrospective review, single hemophilia treatment center

In the adolescent or adult female who does not desire pregnancy, but may desire future childbearing, the first choice of therapy should be combined oral contraceptives. Combined oral contraceptives contain a synthetic estrogen (ethinyl estradiol) and a progestin.[328] The progestin prevents ovulation, and the synthetic estrogen prevents breakthrough bleeding.[329] A majority of studies have found that combined oral contraceptives increase fibrinogen, prothrombin, factor VII, FVIII, and/or VWF[330–332] and, consequently, promote hemostasis. It is not known whether the increase in coagulation factors associated with combined oral contraceptives contributes to the clinical response, but combined oral contraceptives do reduce menstrual blood loss[333] and increase hemoglobin concentrations in women who have anemia.[334–336] Combined oral contraceptives, used by tens of millions of women for prolonged periods of time, have been proven to be safe for long-term use[337] except in women with thrombophilia.[329] Although no formal studies of the effects of the contraceptive patch on hemostasis have been performed, the patch likely has effects similar to those of combined oral contraceptives.[338]

For a woman who has VWD and would otherwise be a suitable candidate for an intrauterine device, the second choice of therapy should be the levonorgestrel-releasing intrauterine system. The levonorgestrel-releasing intrauterine system is a progestin-impregnated intrauterine device that is believed to reduce menstrual blood loss by opposing estrogen induced growth of the endometrium or lining of the uterus.[339]

Women who do not respond to hormonal therapy and are being considered for treatment with DDAVP or VWF concentrate should be referred to a hemophilia treatment center or to a hematologist who has expertise in hemostasis. Treatments specific for VWD (such as DDAVP or VWF concentrate), or antifibrinolytic therapy, although they have not been proven to be effective for menorrhagia, may be tried.

In addition to medical therapies, surgical therapies have been used to treat menorrhagia in women who have VWD. Dilation and curettage (D & C), while occasionally necessary to diagnose intrauterine pathology, is not effective in controlling heavy menstrual bleeding.[323] In two cases reported by Greer et al.[323] and two cases reported by Kadir et al.,[340] D & C resulted in further blood loss. Endometrial ablation, on the other hand, reduced menstrual blood loss in seven out of seven women who had VWD.[341] Three, however, ultimately required hysterectomy, compared to 12–34 percent of women who did not have VWD who usually require hysterectomy.[342–346] Women who have VWD and undergo hysterectomy may be at greater risk of perioperative bleeding complications than other women, and bleeding may occur despite prophylactic therapy.[137,315] Hysterectomy carries the risk of bleeding complications, but women who require the operation should not be deprived of its benefits. Because menorrhagia is often the primary bleeding symptom experienced by a woman who has VWD, hysterectomy offers the possibility of the elimination of bleeding symptoms for menorrhagia and significant improvement in quality of life.[345,347,348]

Hemorrhagic Ovarian Cysts

There are multiple case reports of women who have VWD and have experienced hemorrhagic ovarian cysts.[322,323,349–353] Silwer, for example, reported that 9 of 136 (6.8 percent) women who had VWD experienced this problem.[137] Ovulation is not normally accompanied by any significant bleeding, but in a woman who has a congenital bleeding disorder such as VWD, the potential exists for bleeding into the peritoneal cavity or bleeding into the residual follicle, resulting in a hemorrhagic ovarian cyst[352] or retroperitoneal hematoma.[323] Acute treatment of hemorrhagic ovarian cysts with surgical therapy, tranexamic acid, and factor replacement has been reported.[323,351,352] Oral contraceptives have been used to prevent recurrences.[349,350,352]

Pregnancy

Few options are available for the management of menorrhagia or recurrent hemorrhagic ovarian cysts in women who have VWD and desire pregnancy. Although data are limited to case reports, DDAVP, antifibrinolytics, or VWF concentrate may be tried.[322]

Ideally, planning for pregnancy begins before conception. Women who have VWD and are contemplating a pregnancy should be aware that they may be at an increased risk of bleeding complications during pregnancy[354] and are definitely at increased risk of postpartum hemorrhage.[145] Before conception

or during pregnancy, women should be offered the opportunity to speak with a genetic counselor regarding the inheritance of VWD[355] and with a pediatric hematologist regarding the evaluation of the infant after delivery.

Women who have type 1, type 2, or type 3 VWD and have FVIII levels <50 IU/dL, VWF:RCo <50 IU/dL, or a history of severe bleeding should be referred for prenatal care and delivery to a center that, in addition to specialists in high-risk obstetrics, has a hemophilia treatment center and/or a hematologist with expertise in hemostasis. Laboratory, pharmacy, and blood bank support is essential. Before any invasive procedure, such as chorionic villus sampling, amniocentesis, or cervical cerclage, women who have VWD should have laboratory assays for FVIII and VWF:RCo in order to receive appropriate prophylaxis.[355,356] FVIII and VWF:RCo levels should be obtained in the third trimester of pregnancy to facilitate planning for the delivery.[356] Before delivery, all women who have VWD should meet with an anesthesiologist to plan for the possible need for the administration of hemostatic agents, and/or alternatives, if necessary, for regional anesthesia at the time of delivery.[355] A pregnant woman carrying a baby at risk for type 3 or severe types 1 or 2 VWD should be referred to a pediatric hematologist to discuss neonatal testing and potential bleeding in the infant.[85,354,375]

There are limited data on the use of DDAVP for VWD in pregnancy. Mannucci reported using DDAVP for prophylaxis prior to procedures in 31 pregnant women "without mishap,"[357] but specific data are not provided. DDAVP, in the lower doses used to treat diabetes insipidus, however, is generally thought to be safe for mother and fetus. In a review of 53 cases of women who were pregnant and used DDAVP, administered in doses of 7.5–100 micrograms a day for diabetes insipidus, no adverse maternal or neonatal effects were attributable to the medication.[274] In an in vitro placenta model, DDAVP did not cross the placenta in detectable amounts.[274]

Tranexamic acid crosses the placenta[358] but has been used to treat bleeding during pregnancy in a limited number of cases without adverse fetal effects.[359–364] Data regarding aminocaproic acid in pregnancy are limited, but aminocaproic acid was not found to be teratogenic in rabbits.[365] In cases of its use during pregnancy, no adverse fetal effects have been reported.[366]

Miscarriage and Bleeding During Pregnancy

In the general population, miscarriage is common, and 12–13.5 percent of diagnosed pregnancies result in spontaneous abortion.[367,368] Although detailed data were not provided, in a study of 182 females who had severe VWD, Lak et al.[85] reported that miscarriage was no more frequent than in the general population. Other studies, however, have found a higher incidence of miscarriage among women who have VWD compared to controls[145] or compared to the background rate.[322,354]

Bleeding complications during pregnancy other than miscarriage have been reported.[322,323,369–371] Kadir et al.[354] found that 33 percent of women who had VWD bled during their first trimester.

Childbirth

Table 17 summarizes nine case series reporting pregnancy outcomes in women who had VWD, including rates of miscarriage, peripartum prophylaxis, postpartum hemorrhage, and perineal hematoma. Prophylaxis included cryoprecipitate, fresh frozen plasma, DDAVP, and factor replacement.

No large prospective studies correlate VWF:RCo and FVIII levels with the risk of bleeding at the time of childbirth, but the opinion of experts is that VWF:RCo and FVIII levels of 50 IU/dL should be achieved before delivery[323] and maintained for at least 3–5 days afterward.[9,215,323,354–356] There is no consensus on levels of VWF:RCo and FVIII that are safe for regional anesthesia,[372] but if VWF:RCo and FVIII levels are ≥50 IU/dL and the coagulation screen is normal, regional anesthesia may be considered safe.[354]

DDAVP may be used to raise factor levels in responders, but care must be taken in its administration at the time of childbirth. Women commonly receive 1–2 liters or more of fluid at the time of a vaginal delivery and 2–3 liters or more at the time of cesarean delivery. Fluids containing oxytocin, which also causes fluid retention, combined with DDAVP may result in fluid retention and life-threatening hyponatremia. Chediak and colleagues reported complications of fluid retention in two women who received DDAVP at the time of childbirth. One woman who received three doses 18 hours apart developed severe hyponatremia (sodium level of 108 mEq/L) and experienced grand mal seizures.[371]

Table 17. Pregnancies in Women Who Have VWD

Study	Population	Miscarriage	Prophylaxis	Postpartum hemorrhage	Perineal hematoma
Burlingame et al. 2001[369]	5 pregnancies in 2 women	None	FVIII concentrates for 1/5	1/5	None
Lak et al. 2000[85]	100 women who had type 3 VWD and had delivered at least 1 child	Rate not "higher than …the general Iranian population"	FFP Cryo FVIII concentrates	15/100 (15%) of women	Not reported
Caliezi et al. 1998[370]	2 pregnancies in 1 woman who had type 3 VWD	None	FVIII concentrates for 2/2	1/2 on day 15 from episiotomy	None
Kadir et al. 1998[354]	84 pregnancies in 31 women	18 of 72 pregnancies not terminated	10/54 with "no bleeding complications"	10/54 (18%) primary* 6/54 (11%) required transfusion 11/54 (20%) secondary†	3/54
Foster 1995[322]	69 pregnancies in 31 women who had VWD unresponsive to DDAVP	15 of 68 pregnancies not terminated	25/55 (46%) of those for whom data were available FVIII concentrates (9) Cryo (8) FFP (1)	In women who had type 2A, 2B, or 3 VWD, 6/18 who were treated; 3/4 who were not treated	Not reported
Ramsahoye et al. 1995[376]	24 pregnancies in 13 women	None reported (1 fetal demise at 38 weeks)	5 cesarean deliveries: • Cryo for 2/5 • FVIII (Haemate- P®) for 2/5 • DDAVP for 1/5 19 vaginal deliveries: • Cryo for 3/19 • FVIII (Haemate-P®, NHS 8Y) for 2/19	3/24 (12.5%) primary* 6/24 (25%) secondary† 2/6 secondary† had been treated	None
Greer et al. 1991[323]	14 deliveries in 7 women who had VWD	Not reported	Cryo (9)	5/9 who were treated (1 primary*, 3 secondary†, 1 both); 2/5 who were not treated (2 primary*)	1/14
Chediak et al. 1986[371]	10 pregnancies in 6 women who had VWD	3 of 10 pregnancies	Cryo for 5/7 deliveries DDAVP for 2/7 deliveries	4/5 "massive"	1 had "lumbar hematomas"
Conti et al. 1986[377]	5 deliveries in 5 women who had VWD	None	None	2/5 "late"	None

Cryo, cryoprecipitate; DDAVP, 1-desamino-8-D-arginine vasopressin (desmopressin, a synthetic analog of vasopressin); FFP, fresh frozen plasma; FVIII, FVIII concentrate; Haemate P®, European equivalent of Humate-P®; NHS 8Y, National Health Services (United Kingdom) factor VIII concentrate (8Y); VWD, von Willebrand disease.

* Primary, postpartum hemorrhage within the first 24 hours after delivery

† Secondary, postpartum hemorrhage after 24 hours after delivery

Because NSAIDs, commonly prescribed for pain after childbirth, may decrease platelet function and systemic hemostasis,[319] alternative analgesics should be considered.

Postpartum Hemorrhage

Postpartum hemorrhage is an anticipated problem among women who have VWD. By the end of gestation, an estimated 10–20 percent of a woman's blood volume, or at least 750 mL/minute, flows through the uterus.[373] After delivery of the infant and placenta, the uterus must contract, and the uterine vasculature must constrict to prevent exsanguination.[374] Failure of the uterus to contract is the single most important cause of postpartum hemorrhage.[374] Nonetheless, women who have VWD are at an increased risk of postpartum hemorrhage compared to controls.[137,145,321] Multiple case series document an increased incidence of postpartum hemorrhage in women who have VWD (see Table 17).

Perineal hematoma, a rare complication of vaginal birth, occurs with some frequency in women who have VWD. Greer et al.[323] reported one hematoma in 13 vaginal deliveries, and Kadir and colleagues[354] reported three hematomas in 49 vaginal deliveries. This is a relatively high frequency compared to a rate of only 2.2/1,000 in a cohort of 26,187 spontaneous or operative vaginal deliveries.[378]

In women who have VWD, vaginal bleeding is frequently reported to occur more than 2–3 weeks postpartum. The duration of bleeding after delivery in a normal patient is a median of 21–27 days.[379–381] However, the VWF levels that are elevated during pregnancy return to baseline within 7–21 days,[382,383] predisposing women who have VWD to delayed postpartum hemorrhage. In the absence of a bleeding disorder, delayed or secondary postpartum hemorrhage is rare and occurs following less than 1 percent of deliveries.[384,385] In contrast, 20–25 percent of women who had VWD had delayed postpartum hemorrhage, making delayed postpartum hemorrhage 15–20 times more common among these women compared to normal subjects.[354,376]

Among the published series of cases of women who were pregnant and had VWD (Table 17), multiple cases of postpartum hemorrhage occurred despite prophylaxis. The average time of presentation of postpartum hemorrhage in women who have VWD was estimated to be 15.7 ± 5.2 days after delivery.[386] The implication is that women who have VWD may require frequent evaluation—and possibly prophylaxis—for 2 weeks or more postpartum. Weekly contact with these women is recommended during the postpartum period.[356]

Management Recommendations

The recommendations are graded according to criteria described on page 3 and in Table 1. Evidence tables are provided for recommendations given a grade of B and having two or more references (See pages 83-111).

IV. Testing Prior to Treatment

A. Before treatment, all persons suspected of having VWD should have a laboratory-confirmed diagnosis of type and severity of VWD. This recommendation does not preclude treatment that may be indicated for urgent or emergency situations, despite the absence of confirmatory laboratory data.
Grade C, level IV[85,136–142]

B. Persons who do not have a definite diagnosis of VWD but who have VWF:RCo levels of 30–50 IU/dL and have a bleeding phenotype may merit treatment or prophylaxis of bleeding in certain clinical situations.
Grade B, level III[196]

C. Persons with >10 IU/dL VWF:RCo and >20 IU/dL FVIII activity levels should undergo a trial of DDAVP while in a nonbleeding state. Persons with levels below these thresholds are less likely to demonstrate clinical or laboratory responses to DDAVP, but a DDAVP trial should still be considered in these individuals.
Grade B, level IIa[99,223,224,227,231] *See Evidence Table 6.*

V. General Management

A. Treatment of persons who have VWD is aimed at cessation of bleeding or prophylaxis for surgical procedures.
Grade C, level IV[1,7,9]

B. Continued bleeding, despite adequately replaced VWF:RCo and FVIII activity levels, requires evaluation of the person for other bleeding etiologies, including anatomic.
Grade C, level IV

C. Long-term prophylaxis is currently under investigation in an international cooperative study, and the long-term risks and benefits should be considered carefully.
Grade C, level IV[211,212]

D. Individuals who are more than 2 years of age, who have VWD and have not already been vaccinated, should be immunized against hepatitis A and B.
Grade C, level IV[299]

E. Persons who have VWD should have the opportunity to talk to a knowledgeable genetic counselor.
Grade C, level IV[355]

F. At diagnosis, persons who have VWD should be counseled to avoid aspirin, other NSAIDs, and other platelet-inhibiting drugs.
Grade C, level IV[300–302]

G. Restriction of fluids to maintenance levels should be considered in persons receiving DDAVP (especially for young children and in surgical settings) to avoid the occurrence of hyponatremia and seizures.
Grade C, level IV[264–266]

VI. Treatment of Minor Bleeding and Prophylaxis for Minor Surgery

A. Epistaxis and oropharyngeal, soft tissue, or minor bleeding should be treated with intravenous or nasal DDAVP, if appropriate, based on trial testing.
Grade B, level IIa[221–223,230,246] *See Evidence Table 7.*

B. If elevation of VWF is necessary and response to DDAVP is inadequate, VWF concentrate should be used, with dosing primarily based on VWF:RCo units and secondarily on FVIII units.
Grade C, level IV[247,253]

C. For prophylaxis for minor surgery, initial treatment should be expected to achieve VWF:RCo and FVIII activity levels of at least 30 IU/dL and preferably >50 IU/dL.
Grade B, level III[223,230,242,247] *See Evidence Table 8.*

D. For minor surgery, VWF:RCo and FVIII activity levels of at least 30 IU/dL and preferably >50 IU/dL should be maintained for 1–5 days.
Grade B, level III[243,244,247,256] *See Evidence Table 9.*

E. For persons who have VWD, management of minor bleeding (e.g., epistaxis, simple dental extraction, or menorrhagia) with DDAVP and proper fluid restriction can be performed without laboratory monitoring unless Stimate® or DDAVP is used more than three times within 72 hours.
Grade C, level IV[263,320]

F. For persons who have mild to moderate VWD, antifibrinolytics combined with DDAVP are generally effective for oral surgery. VWF concentrate should be available for persons who cannot receive DDAVP or who bleed excessively despite this combined therapy.
Grade B, level IIb[221,223,232,242,246–248]
See Evidence Table 10.

G. Topical agents, such as fibrin sealant or bovine thrombin, may be useful adjuncts for oral surgery in persons who have VWD. Careful attention to hemostasis of an extraction socket and to suturing of sockets is also important in oral surgery in persons who have VWD.
Grade C, level IV[242,297]

VII. Treatment of Major Bleeding and Prophylaxis for Major Surgery

A. All treatment plans should be based on objective laboratory determination of response of VWF:RCo and FVIII activity levels to DDAVP or to VWF concentrate infusion.
Grade B, level IIb[136,231,240,241,244,245,247,249,251-256,290,291] *See Evidence Tables 11 and 12.*

B. Whenever possible, all major surgeries and bleeding events should be treated in hospitals with a 24-hour/day laboratory capability and with clinical monitoring by a team including a hematologist and a surgeon skilled in the management of bleeding disorders.
Grade C, level IV

C. For severe bleeding (e.g., intracranial, retroperitoneal) or for prophylaxis of major surgery, initial target VWF:RCo and FVIII activity levels should be at least 100 IU/dL. Subsequent dosing should maintain VWF:RCo and FVIII levels above a trough of 50 IU/dL for at least 7–10 days.
Grade B, level III[244,247,251–256,290,291]
See Evidence Table 12.

D. To decrease risk of perioperative thrombosis, VWF:RCo levels should not exceed 200 IU/dL, and FVIII activity should not exceed 250 IU/dL.
Grade C, level IV[280–282]

E. For major surgical procedures in selected patients with type 3 VWD or AVWS who are at risk for poor VWF recovery because of inhibitors, a pre-operative trial infusion of VWF concentrate with pharmacokinetic laboratory monitoring should be considered.
Grade C, level IV

VIII. Management of Menorrhagia and Hemorrhagic Ovarian Cysts in Women Who Have VWD

A. Women who have menorrhagia or abnormal vaginal bleeding should have a full gynecological evaluation before therapy.
Grade C, level IV[316]

B. In the adolescent or adult woman who does not desire pregnancy, but may desire future childbearing, the first choice of therapy for menorrhagia should be combined oral contraceptives.
Grade B, level III[322]

C. In the adolescent or adult woman who does not desire pregnancy, but may desire future childbearing, the first choice of therapy to prevent hemorrhagic ovarian cysts should be combined oral contraceptives.
Grade C, level IV[349,350,352]

D. If a woman would otherwise be a suitable candidate for an intrauterine device, the second choice of therapy for menorrhagia should be the levonorgestrel intrauterine system.
Grade B, level IIb[324]

E. For the woman who desires pregnancy, DDAVP, antifibrinolytics, or VWF concentrate may be tried to control menorrhagia.
Grade C, level IV[322]

F. Dilation and curettage is not usually effective to manage excessive uterine bleeding in women who have VWD.
Grade C level IV[323,340]

IX. Management of Pregnancy and Childbirth in Women Who Have VWD

A. Women planning for pregnancy should have, before conception, an evaluation with a hematologist and a high-risk obstetrician, both of whom are skilled in the management of VWD.
Grade C, level IV[355]

B. Women who have type 1, type 2, or type 3 VWD, with FVIII or VWF:RCo levels <50 IU/dL or a history of severe bleeding:

1. Should be referred to a center that has high-risk obstetrics capabilities and with expertise in hemostasis for prenatal care, delivery, termination of pregnancy, or management of miscarriage.
Grade C, level IV
2. Should receive prophylaxis with DDAVP or VWF concentrate before invasive procedures.
Grade C, level IV[355,356]
3. Should achieve VWF:RCo and FVIII levels of at least 50 IU/dL before delivery and maintain that level for at least 3–5 days afterward.
Grade C, level IV[9,215,323,354,356]

C. If VWF:RCo and FVIII levels can be monitored and maintained above 50 IU/dL during labor and delivery, and no other coagulation defects are present, then regional anesthesia may be considered.
Grade C, level IV[354]

D. Because coagulation factors return to prepregnancy levels within 14–21 days after delivery, health care providers should be in close contact with women during the postpartum period.
Grade C, level IV[356]

X. Acquired von Willebrand Syndrome

A. Individuals who have AVWS and who require surgery should be considered for a pharmacokinetic trial of therapy with DDAVP and/or VWF concentrate, with monitoring of VWF:RCo and FVIII levels, to evaluate for possible accelerated clearance of VWF.
Grade C, level IV[117,157]

B. For persons who have AVWS and who bleed excessively despite therapy with DDAVP and VWF concentrate, treatment with high-dose IGIV should be considered, especially in IgG isotype MGUS (see page 47 for discussion of this non-FDA-approved use).
Grade B, level IIa[117,303–306] *See Evidence Table 13.*

Opportunities and Needs in VWD Research, Training, and Practice

Many recommendations in this guideline are based on relatively limited evidence, thus underscoring the need for further research. Some of these opportunities are discussed below.

Pathophysiology and Classification of VWD

Determinants of VWF level and bleeding risk. The risk of bleeding in persons who have VWD depends on the level of functional VWF and on many other factors that are poorly understood. The plasma level of VWF can be influenced by mutations within or near the VWF gene. In addition, VWF levels depend on ABO blood type,[43] possibly on the *Secretor* locus,[109] and on hormonal status and stress, as discussed in "The VWF Protein and Its Functions In Vivo" section. Relatively few of the genetic and nongenetic determinants of VWF level have been characterized, and how they interact is not known. In addition, little quantitative information is available on the risk of specific bleeding symptoms as a function of the level of VWF in plasma. This information would be particularly useful for the management of patients who have VWF levels in the range of 30–50 IU/dL, for whom the risk of medically significant bleeding is not well defined.

VWF level in plasma alone does not account for the observed variation in bleeding symptoms, and recent studies are starting to uncover some of the underlying reasons. For example, persons who have both low VWF and defects in platelet aggregation have more severe bleeding.[387] Increased bleeding also has been associated with specific DNA markers for platelet membrane proteins.[388] It is likely that multiple hemostatic risk factors interact with VWF level in plasma to determine the likelihood of bleeding or thrombosis. Understanding these interactions and incorporating them into clinical practice will require additional basic, clinical, and epidemiological research.

Heterogeneity of type 1 VWD. Partial quantitative deficiency of VWF can be caused by several mechanisms, as discussed in the section on "Classification of VWD Subtypes." Some persons have dominant VWF mutations that either decrease the secretion of VWF multimers or accelerate their clearance from the circulation. The prevalence of increased clearance as a cause of type 1 VWD is not known. Whether these different disease mechanisms correlate with distinct clinical features, including response to specific treatments, also is not known. Because type 1 VWD is the most common form of VWD, answers to these questions may have important consequences for medical practice.

Heterogeneity of type 2 VWD. The concentration of hemostatically effective large VWF multimers can be selectively decreased by accelerated proteolysis or by a variety of defects in multimer assembly.[49] These variants now are grouped together as type 2A VWD, but further subdivision of this category would be justifiable if specific mechanisms of disease were associated with different clinical symptoms or responses to therapy.

Most persons who have type 2M VWD have been identified by finding a profound defect in ristocetin-induced binding to platelets associated with a normal VWF multimer pattern.[55,67,72] Defects in binding to collagen or other connective tissue elements could cause a similar bleeding phenotype, but the VWF:RCo assay is insensitive to such defects.[73] Collagen-binding abnormalities can be detected by the VWF:CB assays, but those assays are not used widely in the United States. The prevalence and medical significance of collagen-binding defects in type 2M VWD deserve further study.

Diagnosis and Evaluation

Assessment of bleeding signs and symptoms. The initial evaluation of patients for a medically significant bleeding disorder can be difficult because mild bleeding is very common in the healthy population. Specific symptoms have been assessed for clinical relevance in retrospective studies, and some appear to discriminate among healthy controls and persons who have diagnosed bleeding disorders (Box 1, page 21). However, the utility of these questions must be established prospectively for less highly selected persons.

Quality and availability of laboratory testing. Reliable testing for VWF:Ag and FVIII is widely available, but VWF:RCo, RIPA, and VWF multimer analysis are much more variable in their performance characteristics and can be difficult to obtain. Also, tests of VWF–FVIII binding (VWF:FVIIIB) are offered by very few laboratories. More robust methods for assessing VWF function and multimer structure must be developed for routine use in the diagnosis of VWD. In addition, the sensitivity and specificity of test ratios such as VWF:RCo/VWF:Ag should be established for identifying the qualitative defects that characterize type 2A and type 2M VWD. Criteria should be established for VWF multimer analysis to distinguish a significant decrease in large multimers (in types 2A and 2B VWD) from a substantially normal multimer distribution (in types 1, 2M, and 2N VWD).

VWF gene sequencing. Mutations that cause many types of VWD can be identified by sequencing the VWF gene in DNA samples from patients.[23] The locations of mutations appear to correlate well with some disease phenotypes, suggesting that DNA sequencing could be a useful diagnostic method in VWD. With appropriate study and experience, DNA sequencing may become economical and feasible for routine use. In addition, the widespread application of VWF gene sequencing would provide invaluable information about the prevalence of VWF mutations as a function of VWF level, the strength of the relationship between VWF genotype and VWD phenotype, the penetrance of specific mutations, and the biochemical mechanisms that cause VWD. This knowledge also would be an outstanding resource for the identification and characterization of other factors that modify bleeding symptoms in VWD.

Management of VWD

Many of the standard treatments for VWD have limited experimental support. For example, the intensity and duration of therapy necessary to control bleeding have not been established for many clinical situations and often have been extrapolated from anecdotal experience in hemophilia. The indications for prophylaxis of bleeding also are not well defined. These issues should be addressed by appropriate clinical studies.

DDAVP. Many persons who have VWD respond to DDAVP with a clinically useful rise in VWF and FVIII, but the likelihood of a good outcome depends on the type of VWD and the underlying biochemical mechanism of disease. In type 1 VWD, persons who have accelerated clearance of plasma VWF may have a transient response to DDAVP.[41,232] Whether DDAVP should be used at all in persons who have type 2B VWD is controversial.[229,237,257–259,389–391] In type 2N VWD, the baseline FVIII level may be a good predictor of the magnitude and duration of the FVIII response to DDAVP.[77,224,228,392] The drug is thought to be safe for use in pregnancy, but the published experience in this setting is limited.[273,274] Hyponatremia and thrombotic events have occurred after DDAVP, but risk factors for these events and their incidence have not been established. These important clinical issues should be addressed by studies of DDAVP in specific types of VWD. In addition, the availability of DDAVP for subcutaneous administration may improve management of VWD.

Factor Concentrates. The available plasma-derived products that contain VWF also contain FVIII as part of the FVIII–VWF complex, and only two such products (Humate-P® and Alphanate SD/HT®) are currently licensed in the United States for treatment of VWD. When administered to patients who have VWD, the infused FVIII may add to the endogenous FVIII production and cause markedly elevated FVIII levels that are much greater than the VWF levels achieved with treatment; these have been associated with thrombosis.[215] High FVIII levels can be avoided by adjusting the dose of product administered, but VWF levels then may be relatively low. Whether FVIII or VWF levels, or both, should be used to monitor treatment with FVIII–VWF concentrates is unknown. Use of a pure VWF product in place of FVIII–VWF concentrates would avoid the disproportionate increase in FVIII. A pure VWF concentrate

has been used in Europe[393] but is not currently available in the United States. Studies are needed to establish appropriate treatment and monitoring regimens for these products. In addition, prelicensure studies of recombinant VWF are needed to establish its safety, efficacy, and role in the treatment of VWD. The licensing of other products, containing both VWF and FVIII, also would enhance therapeutic options.

Platelets. Approximately 15 percent of the total VWF in blood is found within platelets, and platelet VWF appears to contribute to hemostasis. Although VWD patients who have abnormal or low platelet VWF have been described, there has been only limited exploration of the feasibility and utility of such testing, in part because of limitations of practical methodologies. Clinically, platelet transfusions have been reported to stop bleeding in some patients who have VWD and were not helped by transfusion of FVIII–VWF concentrates.[293,294] The efficacy and appropriate use of platelet transfusions in persons who have VWD or AVWS need to be established.

Antifibrinolytics. Tranexamic acid and aminocaproic acid have been used alone or as adjunctive therapy to treat bleeding in VWD. The safety, efficacy, and optimal dosing of these agents in VWD should be established by suitable clinical studies. In addition, the availability of orally administered tranexamic acid would broaden the therapeutic options for antifibrinolytic therapy.

Gene Therapy of VWD

Severe type 3 VWD potentially can be treated with gene therapy. The gene for VWF is larger than could easily be introduced into many vectors, but "gutless" adenoviral vectors could easily accommodate a gene the size of VWF (8.5 kilobases). The prevalence of type 3 VWD and its clinical symptoms, however, does not place it in a high priority category for gene therapy trials. Point mutation repair initially was an exciting approach for VWD,[394,395] but followup studies have not achieved the same rate of success in vitro.[396,397]

Issues Specific to Women

VWF is particularly important for hemostasis during menses and at childbirth. Consequently, women are affected disproportionately by having VWD, especially during their childbearing years.

Menorrhagia. The incidence of menorrhagia appears to vary inversely with VWF level, independent of whether women meet criteria for having VWD.[45] Because menorrhagia is so common, even a small reduction in its severity could have significant implications for women's health. As discussed in the section on menorrhagia (see page 48), several treatments have been used for menorrhagia associated with VWD, but their efficacy has not been demonstrated convincingly. Therefore, clinical studies would be useful to establish the effect of VWF level on menorrhagia and to evaluate specific treatments for women who have VWD or low plasma levels of VWF.

Labor and delivery. Several small case series indicate that women who have VWD and VWF levels <50 IU/dL at delivery have an increased incidence of immediate and delayed postpartum hemorrhage. These complications appear to be prevented by replacement therapy with FVIII–VWF concentrate before delivery and by either concentrate or DDAVP in the postpartum period.[85,354,377] How the risk of bleeding correlates with VWF level or FVIII level is not known, and the required intensity and duration of therapy have not been established.

Training of Specialists in Hemostasis

In the United States, despite scientific progress in basic and clinical research in bleeding and thrombotic disorders, including VWD, there is a shortage of skilled clinicians and laboratorians with expertise in hemostasis.[398] Training opportunities need to be developed and/or expanded for hemostasis specialists. Recent clinical training opportunities include a new NHLBI initiative for training in nonmalignant hematology (RFA HL06-006; information available at: http://grants.nih.gov/grants/guide/rfa-files/RFA-HL-06-006.html) and a recent initiative from the U.S. National Hemophilia Foundation (NHF Clinical Fellowship Program). Recognition of hemostasis as a bona fide clinical and laboratory subspecialty in the United States could enhance entry into the field.

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Evidence Tables

Evidence Table 1. Recommendation I.B.

If answers to probe questions I.B.1–8 are positive, obtain relevant specific information.
Grade B, level IIb

Citation	Population	Study Design	Intervention	Results	Comments
Drews CD, Dilley AB, Lally C, Beckman MG, Evatt B. Screening questions to identify women with von Willebrand disease. J Am Med Womens Assoc 2002;57(4):217–218.	Emory Hospital Clinic 102 women who had VWD, some had menorrhagia	Case/control retrospective telephone survey	Survey and known case status; presumed control status.	Presence of ≥6 symptoms in 80% of women who had VWD and 8% of women who did not have VWD.	CDC funded.
Sramek A, Eikenboom JC, Briet E, Vandenbroucke JP, Rosendaal FR. Usefulness of patient interview in bleeding disorders. Arch Intern Med 1995 Jul;155(13):1409–1415.	Hematology Clinic, The Netherlands Sample comprised 18- to 65-year-old persons: • 222 had a previously diagnosed bleeding disorder (95 mild VWD, 54 platelet dysfunction, 73 hemophilia A or B) • 134 referred for bleeding symptoms but with normal hemostasis tests • 341 healthy volunteers	Survey compared to gold standard evaluation of "elaborate" interview	Survey and indepth interview were compared to blood work.	Bleeders vs. referral control: • Tonsillectomy, 16.2 odds. • Muscle bleeding, 3.4 odds. • Joint bleeding, 2.5 odds. • Nose bleeds, 2.2 odds (observed but not useful). Multivariate positive: • Family history of bleeding with trauma. • Bleeding at delivery (not helpful). Bleeders vs. healthy volunteers: • Positive family history, 97.5 odds. • Minor trauma or muscle bleeding, 9.5 odds. • Joint bleeding, 5.8 odds. • Absence of menorrhagia, 1.8 odds.	Unknown sponsor.

CDC, Centers for Disease Control and Prevention

Evidence Table 2. Recommendation II.B

Initial tests for diagnosing or excluding VWD include the following three tests: VWF:RCo, VWF:Ag, and FVIII activity.
Grade B, level III

Citation	Population	Study Design	Intervention	Results	Comments
Favaloro EF, Bonar R, Kershaw G, Siufi J, Hertzberg M, Street A, Lloyd J, Marsden K. Laboratory diagnosis of von Willebrand's disorder: quality and diagnostic improvements driven by peer review in a multilaboratory test process. Haemophilia 2004,10:232–242.	45 laboratories in Australia, New Zealand, and Southeast Asia	Assessing testing proficiency in diagnostic tests for VWD using 8 VWD testing sample sets from normals or VWD subjects during 2003	Comparison of test results for patients who have and do not have VWD.	Initial diagnosis of VWD is usually correct (~90% accurate). Subtype diagnosis is aided by VWF:CB assay, clinical history, and possibly repeat testing.	All 45 labs measured FVIII, 42 measured VWF:Ag, 32 measured VWF:RCo, and 23 measured VWF:CB to diagnose or classify VWD. Only 3 performed VWF multimer analysis.
Favaloro EJ, Thom J, Baker R. Assessment of current diagnostic practice and efficacy in testing for von Willebrand's disorder: results from the second Australasian multi-laboratory survey. Blood Coagul Fibrinolysis 2000 Dec;11(8):729–737.	19 laboratories in Australia, New Zealand, and Southeast Asia	Assessment of testing proficiency in diagnostic tests for VWD using 7 VWD testing sample sets from normals (1) or from VWD subjects (n = 7)	Comparison of test results for patients who have or do not have VWD.	Continued problems with nonidentification of functional VWF discordance in type 2 VWD, misidentification of functional VWF in type 1 VWD, and difficulties in discriminating types 1 and 3 VWD. Increase in use of latex immunoassay and automated VWF:RCo testing noted.	All 19 labs measured FVIII and VWF:Ag, 18 measured VWF:RCo, and 7 measured VWF:CB to diagnose or classify VWD. Concluded that testing should comprise FVIII:C, VWF:Ag, and either/or both VWF:RCo and VWF:CB.
Gill JC, Endres-Brooks J, Bauer PJ, Marks WJ, Jr., Montgomery RR. The effect of ABO blood group on the diagnosis of von Willebrand disease. Blood 1987 Jun;69(6):1691–1695.	Adult blood donors in southeast Wisconsin	Cohort of blood donors (n = 1,117) to define levels of VWF:Ag relative to ABO groups	ABO blood group and VWF:Ag.	Level of VVF:Ag is affected by ABO blood type. Group O is lowest in VWF:Ag. .	Study of 142 persons with known VWD showed that 88% of patients who had type 1 VWD (n = 114) had blood group O (vs. 45% expected frequency). VWD diagnoses were based on measuring VWF:Ag, VWF:RCo, and FVIII, with supplemental VWF multimer assay.

Evidence Table 2. Recommendation II.B (continued)

Citation	Population	Study Design	Intervention	Results	Comments
Rodeghiero F, Castaman G, Dini E. Epidemiological investigation of the prevalence of von Willebrand's disease. Blood 1987Feb;69(2): 454–459.	Italian children who were 11–14 years old from 2 communities (n = 1,218 participants)	Population-based cohort using questionnaire about personal and family history of bleeding, and blood sample for testing	Blood group (ABO) and VWF:RCo as primary laboratory measures, with supplemental VWF:Ag, FVIII, and VWF multimer analysis for selected cases. Family history of bleeding over 3 generations.	Prevalence is 10/1,218 = 0.82 with allowance for different reference ranges for blood group O vs. non-O. Suggest using ristocetin cofactor for screening in those who have bleeding problems even if usual screening is normal.	Small sample for a rare condition. Of those who had findings consistent with VWD (all had type 1 VWD), nearly all had minimally or borderline decreased VWF:RCo.

VWF, von Willebrand factor; VWF:Ag, von Willebrand factor antigen; VWF:CB, von Willebrand factor collagen-binding activity; VWF:RCo, von Willebrand factor ristocetin cofactor activity

Evidence Table 3. Recommendation II.C.1.a

The first set of additional tests may include evaluation of ratio of VWF activity (VWF:RCo and/or VWF:CB) to VWF:Ag (only in laboratories that have defined reference ranges for the ratio(s))

Grade B, level III

Citation	Population	Study Design	Intervention	Results	Comments
Dean JA, Blanchette VS, Carcao MD, Stain AM, Sparling CR, Siekmann J, Turecek PL, Lillicrap D, Rand ML. von Willebrand disease in a pediatric-based population—comparison of type 1 diagnostic criteria and use of the PFA-100® and a von Willebrand factor/collagen-binding assay. Thromb Haemost 2000 Sep;84(3):401–409.	53 children (1.5–17 years old) registered at Bleeding Disorders Clinic of Hospital for Sick Children, Toronto, and 47 relatives Control group was 58 healthy children (2.5–17 years old)	Compared diagnostic criteria for VWD from Hospital for Sick Children with ISTH provisional consensus criteria	Bleeding history and laboratory testing, including an assessment of the sensitivity of PFA-100® and VWF:CB for diagnosis of VWD.	Used ratio of VWF:Ag/VWF:CB >3 as criterion for type 2 VWD. 13 patients had ratio >3, and 12 of these had type 2 VWD by criteria and the other had severe type 1 VWD. PFA-100® had higher sensitivity than bleeding time for VWD, and VWF:CB performed as well as VWF:RCo. The Hospital for Sick Children criteria were more sensitive than the provisional ISTH criteria for diagnosing VWD.	Study not designed to evaluate diagnostic validity of ratio in diagnosis, but reported results for ratio. Used ratio of VWF:Ag/VWF:CB and did not report the ratio of VWF:RCo/VWF:Ag.
Favaloro EJ, Bonar R, Kershaw G, Sioufi J, Hertzberg M, Street A, Lloyd J, Marsden K. Laboratory diagnosis of von Willebrand's disorder: quality and diagnostic improvements driven by peer review in a multilaboratory test process. Haemophilia 2004 May;10(3):232–242.	45 laboratories from Australia, New Zealand, Southeast Asia participating in multilaboratory surveys for VWD	2 sets of 4 masked samples, including both normal and VWD plasma, were sent to each laboratory for evaluation using each laboratory's tests for diagnosis of VWD	Laboratory testing including VWF:RCo, VWF:Ag, and FVIII activity in approximately 95% of laboratories.	Ratio of VWF:Ag/VWF:RCo >2 utilized for presumptive diagnosis in type 2A sample. Ratio >2 not obtained by 7 laboratories.	Study not designed to evaluate diagnostic validity of ratio in diagnosis, but reported results for ratio. Only 1 sample with type 2 VWD assessed; no type 2B or 2M plasma tested.

Evidence Table 3. Recommendation II.C.1.a (continued)

Citation	Population	Study Design	Intervention	Results	Comments
Federici AB, Canciani MT, Forza I, Cozzi G. Ristocetin cofactor and collagen binding activities normalized to antigen levels for a rapid diagnosis of type 2 von Willebrand disease. Single center comparison of four different assays. Thromb Haemost 2000 Dec;84(6):1127–1128.	Single laboratory study to evaluate VWF:RCo/VWF:Ag and VWF:CB/VWF:Ag to distinguish type 1 from type 2 VWD	72 previously diagnosed VWD patients who had type 1 or type 2A, 2B, or 2M VWD 27 normal blood donors served as controls	Laboratory testing including homemade and commercial ("ELISA VWF Activity" by Shield) VWF:RCo, and homemade and commercial ("Immunozyme VWF:CB" by Immuno-Baxter) VWF:CB kits.	Ratio of both VWF:RCo/VWF:Ag and VWF:CB/VWF:Ag using homemade assays was sensitive (92% and 88%, respectively) and specific (84% and 95%) for diagnosis of type 2 VWD. Cutoff for ratios for normal subjects was 0.7. Neither commercial kit was sensitive, although both were specific.	Study designed to evaluate the utility of VWF activity/antigen ratios for diagnosis of types 2A, 2B, or 2M VWD. Usefulness of ratio depends on the particular assay used in a given laboratory.
Hillery CA, Mancuso DJ, Sadler JE, Ponder JW, Jozwiak MA, Christopherson PA, Cox GJ, Paul SJ, Montgomery RR. Type 2M von Willebrand disease: F606I and I662F mutations in the glycoprotein Ib binding domain selectively impair ristocetin—but not botrocetin-mediated binding of von Willebrand factor to platelets. Blood 1998 Mar;91(5):1572–1581.	2 families with disproportionately low VWF:RCo/VWF:Ag	Identified 2 families, from large screening study, with decreased VWF:RCo/VWF:Ag	Laboratory testing including VWF:RCo using fresh platelets and ristocetin, VWF:Ag using Laurell electrophoresis, VWF multimer gel electrophoresis. Gene sequencing in 2 families.	Identified 2 families as having type 2M VWD using ratio of VWF:RCo/VWF:Ag more than 2 SD lower than 681 previously tested individuals and confirmed by gene sequencing.	Study not designed to evaluate diagnostic validity of ratio in diagnosis, but reported results for ratio. Only 2 families studied.

Evidence Table 3. Recommendation II.C.1.a (continued)

Citation	Population	Study Design	Intervention	Results	Comments
Mancuso DJ, Kroner PA, Christopherson PA, Vokac EA, Gill JC, Montgomery RR. Type 2M: Milwaukee-1 von Willebrand disease: an in-frame deletion in the Cys509-Cys695 loop of the von Willebrand factor A1 domain causes deficient binding of von Willebrand factor to platelets. Blood 1996;88:2559.	3 generations of a family with 5 affected members and 681 VWD control subjects who had VWF:Ag <50 and normal VWF multimers	Clinical and laboratory evaluation of patients who had type 1 VWD and family who had type 2M VWD	Laboratory testing including VWF:RCo using platelets and VWF:Ag using Laurell immunoelectrophoresis. Confirmed abnormality in family members affected by gene sequencing.	Ratio of VWF:RCo/VWF:Ag for 681 control subjects with type 1 VWD reported as ~0.78–1.27. Family members who had type 2M VWD had ratio of <0.4.	Study provides ratio of VWF:RCo/VWF:Ag for large numbers of patients who have type 1 VWD to establish reference range for ratio for this group. At present, however, very few laboratories use this method for VWF:Ag determination.
Nitu-Whalley IC, Riddell A, Lee CA, Pasi KJ, Owens D, Enayat MS, Perkins SJ, Jenkins PV. Identification of type 2 von Willebrand disease in previously diagnosed type 1 patients: a reappraisal using phenotypes, genotypes and molecular modelling. Thromb Haemost 2000 Dec;84(6):998–1004.	111 patients who had type 1 VWD at the Royal Free Haemophilia Centre; subgroup of 30 identified with VWF:RCo/VWF:Ag<0.7	Evaluation to determine whether some patients who had previously diagnosed type 1 VWD may have type 2 VWD	Laboratory testing including VWF:RCo using fresh platelets and ristocetin, and also using mouse anti-VWF binding site for GPIb receptor in ELISA format (VWF:Ac). ELISA used for VWF:Ag. Gene sequencing in selected patients.	Ratio of VWF:RCo/VWF:Ag was <0.7 in 7 (of 17) kindreds using assay with fresh platelets. VWF activity using ELISA for GPIb binding site (VWF:Ac) detected only 1 of these 7 kindreds. Used gene sequencing to confirm patients who had type 2 VWD.	Study not designed to evaluate diagnostic validity of ratio in diagnosis, but reported results for ratio. VWF:RCo/VWF:Ag ratio <0.7 more sensitive for diagnosis of type 2A, 2B, or 2M VWD than VWF:Ac/VWF:Ag (binding to GPIb) for detection of type 2 VWD. Small numbers of patients.

ELISA, enzyme-linked immunosorbent assay; GPIb, glycoprotein Ib; ISTH, International Society on Thrombosis and Haemostasis; PFA-100®, platelet function analyzer; VWF, von Willebrand factor; VWF:Ac, von Willebrand factor activity; VWF:Ag, von Willebrand factor antigen; VWF:CB, von Willebrand factor collagen-binding activity; VWF:RCo, von Willebrand factor ristocetin cofactor activity

Evidence Table 4. Recommendation II.C.1.d

The first set of additional tests may include VWF collagen binding activity (VWF:CB)
Grade B, level IIb

Citation	Population	Study Design	Intervention	Results	Comments
Favaloro EJ. Collagen binding assay for von Willebrand factor (VWF:CBA): detection of von Willebrand's disease (VWD), and discrimination of VWD subtypes, depends on collagen source. Thromb Haemost 2000 Jan;83(1):127–135.	Plasma samples from well-characterized VWD patients who had type 1 VWD (n = 8) and type 2 variant VWD (n = 9)	Comparison of multiple types of collagen for VWF:CB assay, and comparison to standard VWD tests, including VWF:RCo	Compared discriminant power of different collagens and power for differentiating type 1 from type 2 VWD.	Depending on the type of collagen, when optimized and used in conjunction with the VWF:Ag assay, the VWF:CB assay has better discriminant power for differentiating type 1 vs. type 2 VWD than does the VWF:RCo assay.	Very small sample size; not prospective.
Favaloro EJ, Bonar R, Kershaw G, Siufi J, Hertzberg M, Street A, Lloyd J, Marsden K. Laboratory diagnosis of von Willebrand's disorder: quality and diagnostic improvements driven by peer review in a multilaboratory test process. Haemophilia 2004;10:232–242.	45 laboratories in Australia, New Zealand, and Southeast Asia	Assessment of testing proficiency for diagnostic tests for VWD, using 8 VWD testing sample sets from normal subjects or persons who had VWD during 2003	Comparison of test results for patients who had and did not have VWD.	Initial diagnosis of VWD was usually correct (~90%). Subtype diagnosis was aided by VWF:CB assay in addition to other assays, clinical history, and possibly repeat testing.	All 45 labs measured FVIII, 42 measured VWF:Ag, 32 measured VWF:RCo, and 23 measured VWF:CB to diagnose or classify VWD. Only 3 performed VWF multimer analysis.
Favaloro EJ, Henniker A, Facey D, Hertzberg M. Discrimination of von Willebrands disease (VWD) subtypes: direct comparison of von Willebrand factor collagen binding assay (VWF:CBA) with monoclonal antibody (MAB) based VWF-capture systems. Thromb Haemost 2000;84:541–547.	Patients known to have type 1 (n = 9) VWD and type 2A and 2B (n = 11) VWD	Comparison of laboratory testing for diagnostic accuracy	Compared VWF:CB assay with platelet - based ristocetin cofactor assay and MAB-based ristocetin cofactor assay systems.	VWF:CB assay was better than either platelet-based ristocetin cofactor or commercial GPIb-binding MAB assay for identifying type 2 VWD defects.	Very small sample size; not prospective.

GPIb, glycoprotein Ib; MAB, monoclonal antibody; VWF:Ag, von Willebrand factor antigen; VWF:CB, von Willebrand factor collagen-binding activity; VWF:RCo, von Willebrand factor ristocetin cofactor activity

Evidence Table 5. Recommendation II.C.2

Studies in selected patients, especially those who have a discordantly low FVIII activity compared to VWF levels and who are suspected of having type 2N VWD, should include a FVIII binding assay (VWF:FVIIIB).

Grade B, level IIb

Citation	Population	Study Design	Intervention	Results	Comments
Mazurier C, Meyer D. Factor VIII binding assay of von Willebrand factor and the diagnosis of type 2N von Willebrand disease—results of an international survey. On behalf of the Subcommittee on von Willebrand Factor of the Scientific and Standardization Committee of the ISTH. Thromb Haemost 1996 Aug;76(2):270–274.	56 laboratories from across the world that specialize in VWD or hemophilia A	Survey	None.	Few sites do VWF:FVIIIB assays, but this is required to differentiate type 2N VWD from mild hemophilia A. Testing should be done in specialized centers.	Study does not address the epidemiology of type 2N VWD but focuses on the methodology of testing.
Rodgers SE, Lerda NV, Favaloro EJ, Duncan EM, Casey GJ, Quinn DM, Hertzberg M, Lloyd JV. Identification of von Willebrand disease type 2N (Normandy) in Australia: a cross-laboratory investigation using different methods. Am J Clin Pathol 2002 Aug;118(2):269–276.	101 selected patients who had suspected or known FVIII defects 5 specialized centers in Australia	After preliminary testing, samples from 31 patients were selected for detailed testing in 2 reference laboratories	Two-stage and one-stage FVIII assays, VWF:Ag, VWF:RCo, VWF:CB, and VWF:FVIIIB. Mutation detection by DNA sequencing to confirm diagnosis of type 2N VWD.	8 patients with type 2N VWD identified. VWF:FVIIIB or a 2-stage assay for FVIII activity could discriminate type 2N VWD. 1-stage assay did not perform as well as 2-stage assay.	Not many laboratories perform a 2-stage FVIII assay.
Schneppenheim R, Budde U, Krey S, Drewke E, Bergmann F, Lechler E, Oldenburg J, Schwaab R. Results of a screening for von Willebrand disease type 2N in patients with suspected haemophilia A or von Willebrand disease type 1. Thromb Haemost 1996 Oct;76(4):598–602.	Unrelated patients from Germany who were previously diagnosed as having either hemophilia or VWD	Assess screening program in 376 patients: • 177 diagnosed with hemophilia • 199 diagnosed with type 1 VWD Compare frequency of type 2N VWD for the 2 groups	FVIII:C, VWF:Ag, VWF:FVIIIB, and VWF multimers. DNA sequencing to detect type 2N VWD mutations.	5 patients thought to have hemophilia A and 13 patients thought to have type 1 VWD were reclassified as having type 2N VWD. VWF:FVIIIB should be performed to distinguish type 2N VWD from hemophilia A and other types of VWD.	Results for this population (patients at a hemostasis clinic) may not be representative of new patient referrals.

FVIII, [blood clotting] factor VIII; VWF:Ag, von Willebrand factor antigen; VWF:CB, von Willebrand factor collagen-binding activity; VWF:FVIIIB, von Willebrand factor: factor VIII binding assay; VWF:RCo, von Willebrand factor ristocetain cofactor activity

Evidence Table 6. Recommendation IV.C

Persons with >10 IU/dL VWF:RCo and >20 IU/dL FVIII activity levels should undergo a trial of DDAVP while in a nonbleeding state. Persons with levels below these thresholds are less likely to demonstrate clinical or laboratory responses to DDAVP, but a DDAVP trial should still be considered in these individuals. *Grade B, level IIa*

Citation	Population	Study Design	Intervention	Results	Comments
de la Fuente B, Kasper CK, Rickles FR, Hoyer LW. Response of patients with mild and moderate hemophilia A and von Willebrand's disease to treatment with desmopressin. Ann Intern Med 1985 Jul;103(1):6–14.	40 patients who had hemophilia A, 21 who had VWD, 5 hemophilia carriers, and 2 who had acquired FVIII inhibitors Bleeding history and laboratory criteria for subjects	Prospective, open-label, nonrandomized, controlled clinical trial Informed consent given Patient's baseline as his/her own control	One dose of DDAVP, 0.3 mcg/kg in 50 mL normal saline, was infused over 15 minutes. FVIII and VWF levels drawn at 0, 0.25, 0.5, 1, 3, 5, and 24 hours.	For patients who had VWD: • Rise in VWF:RCo activity from <0.2 to >10-fold baseline value. • Rise in VWF:Ag from 0.25 to >10-fold baseline value. • Rise in FVIII activity from 0.2 to 8-fold baseline value.	This study established the value of baseline testing because it showed that the magnitude of response could not be predicted by baseline VWF values. 10 of 21 patients who had VWD were in a nonbleeding state at the time of study.
Federici AB, Mazurier C, Berntorp E, Lee CA, Scharrer I, Goudemand J, Lethagen S, Nitu I, Ludwig G, Hilbert L, 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 Mar;103(6):2032–2038.	66 patients who had well-characterized VWD defined by laboratory criteria and life-long bleeding history: • 26 patients had type 1 VWD • 40 patients had type 2 VWD Each patient had received replacement therapy on at least 2 occasions	Prospective, open-label, nonrandomized, controlled clinical trial Patient's baseline as his/her own control Informed consent given	One dose of DDAVP 0.3 mcg/kg in 50–100mL normal saline, infused over 30 minutes. Blood drawn at 0, 0.5, 1, 2, and 4 hours. Bleeding time measured at 0 and 2 hours.	VWF:Ag, VWF:RCo, FVIII activity, and BT were measured. This study showed a wide degree of responses that could not be predicted a priori. Because of stringent patient response criteria, only 27% of persons who had type 1 VWD, 7% of persons who had type 2A VWD, 14% of persons who had type 2M VWD, and 75% of persons who had type 2N VWD responded for all criteria.	Response was defined as at least a 3-fold increase in FVIII and VWF:RCo activities AND reaching at least 30 IU/dL AND BT of 12 minutes or less.

Evidence Table 6. Recommendation IV.C (continued)

Citation	Population	Study Design	Intervention	Results	Comments
Mannucci PM, Canciani MT, Rota L, Donovan BS. Response of factor VIII/von Willebrand factor to DDAVP in healthy subjects and patients with haemophilia A and von Willebrand's disease. Br J Haematol 1981 Feb;47(2):283–293.	15 patients who had VWD 9 patients who had mild hemophilia 10 healthy normal controls Controlled preanalytic conditions	VWF:Ag and FVIII activities were measured 0, 1, 2, 4 and 6 hours after a standard dose of DDAVP Normal controls had been given a range of dose-response prior to patient studies to determine study dose	DDAVP, 0.4 mcg/kg, was given over 30 minutes according to published protocol.	VWD patients' percentage increase in plasma VWF over baseline was similar to that of healthy controls and patients who had hemophilia, on average. Tachyphylaxis occurred in some but not all patients.	Demonstrates that type 1 VWD often responds to DDAVP and that tachyphylaxis is variable.
Mannucci PM, Lombardi R, Bader R, Vianello L, Federici AB, Solinas S, Mazzucconi MG, Mariani G. Heterogeneity of type I von Willebrand disease: evidence for a subgroup with an abnormal von Willebrand factor. Blood 1985 Oct;66(4):796–802.	17 patients who had VWD from 13 kindreds Patients had positive bleeding history and met standard laboratory criteria; most severe patients were studied	VWF:Ag, VWF:RCo, and FVIII activity pre-/post-DDAVP Details not given of bleeding state at time of study	DDAVP, 0.4 mcg/kg, was given over 30 minutes according to published protocol.	Response for plasma VWF:RCo differed according to baseline platelet VWF concentration.	Supports the utility of a DDAVP test dose, and associates an inadequate response with qualitative VWF defects.
Rodeghiero F, Castaman G, Di Bona E, Ruggeri M. Consistency of responses to repeated DDAVP infusions in patients with von Willebrand's disease and hemophilia A. Blood 1989 Nov;74(6):1997–2000.	22 patients who had well-characterized VWD were studied on 2 occasions; median time interval was 14 months 13 affected family members were studied on 1 occasion each Bleeding history was not given	Retrospective analysis Comparison of DDAVP response data on 2 occasions in 22 patients Comparison of 2 or more family members on 1 occasion in 7 kindreds Informed consent given	One dose of DDAVP, 0.4 mcg/kg in 100 mL normal saline, was infused over 30 minutes. FVIII activity was measured at 0, 0.5, 1, 2, and 4 hours. BT was measured at 0, 0.5, and 2 hours.	Consistent response, with delta of less than 20%.	This study established the value of baseline testing because it showed consistent responses on repeated infusions within patients and between patients within a kindred.

BT, bleeding time; DDAVP, 1-desamino-8-D-arginine vasopressin (desmopressin, a synthetic analog of vasopressin); FVIII, [blood clotting] factor VIII; VWF, von Willebrand factor; VWF:Ag, von Willebrand factor antigen; VWF:RCo, von Willebrand factor ristocetin cofactor activity

Evidence Table 7. Recommendation VI.A

Epistaxis and oropharyngeal, soft tissue, or minor bleeding should be treated with intravenous or nasal DDAVP, if appropriate, based on trial testing.
Grade B, level IIa

Citation	Population	Study Design	Intervention	Results	Comments
Castaman G, Lattuada A, Mannucci PM, Rodeghiero F. Factor VIII:C increases after desmopressin in a subgroup of patients with autosomal recessive severe von Willebrand disease. Br J Haematol 1995 Jan;89(1):147–151.	6 selected patients who had "autosomal recessive" severe VWD	Prospective, nonrandomized, controlled trial	One dose of DDAVP 0.4 mcg/kg was infused over 30 minutes. BT and blood tests were measured at 0, 0.5, 1 hour. VWF assays were performed on some parents.	4/6 patients showed some rise in FVIII:C and VWF:Ag. 3/6 patients showed a small rise in VWF:RCo but no change in BT. 1 patient successfully underwent dental extraction.	Cases had variant type 3 VWD, as all had some measurable baseline VWF:Ag. One or both parents were unavailable for the study in 2/6 cases.
Castaman G, Rodeghiero F. Desmopressin and type IIB von Willebrand disease. Haemophilia 1996;2:73–77.	Cases of type 2B VWD treated with DDAVP	Literature review	Effects of DDAVP on FVIII, VWF:Ag, VWF:RCo, VWF multimers, BT, and platelet counts were tabulated.	31 cases were found in 10 reports: • In 18/23 cases, VWF:RCo was normal post-DDAVP. • BT was shortened, sometimes to normal. • 5 cases underwent 4 major operations and 3 dental extractions. • In 5/6 procedures, platelet counts were low postprocedure without excessive bleeding.	BT was normal after DDAVP in 5 of the 7 surgical procedures tabulated.

Evidence Table 7. Recommendation VI.A (continued)

Citation	Population	Study Design	Intervention	Results	Comments
de la Fuente B, Kasper CK, Rickles FR, Hoyer LW. Response of patients with mild and moderate hemophilia A and von Willebrand's disease to treatment with desmopressin. Ann Intern Med 1985 Jul;103(1):6–14.	21 subjects who had VWD: • 13 had type 1 VWD • 7 had type 2A VWD • 1 had type 2B VWD	Prospective, open-label, nonrandomized, controlled clinical trial, with patients' baselines as controls	One dose of DDAVP 0.3 mcg/kg infused over 15 minutes. FVIII and VWF levels drawn at 0, 0.25, 0.5, 1, 3, 5, and 24 hours. BT measured pre- and post-DDAVP.	3 subjects (1 had type 1 VWD, 2 had type 2A VWD) who were treated for minor bleeding episodes had excellent clinical responses and laboratory evidence of DDAVP responsiveness.	BT was normal in 2 subjects and shortened but not to normal in 1 subject who had type 2A VWD. See also comments in Evidence Table 6 for Recommendation IV.C.
Mariana G, Ciavarella N, Mazzucconi MG, Antoncecchi S, Solinas S, Ranieri P, Pettini P, Agrestini F, Mandelli F. Evaluation of the effectiveness of DDAVP in surgery and in bleeding episodes in haemophilia and von Willebrand's disease. A study on 43 patients. Clin Lab Haematol 1984;6(3):229–238.	20 patients who had type 1 or type 2 VWD 5 were treated for 8 episodes of mild to moderate bleeding	Open-label, non-randomized controlled study of DDAVP infusion, as well as tranexamic acid (oral or intravenous) in 7 of the 8 episodes	One or more doses of DDAVP 0.3 or 0.4 mcg/kg infused intravenously over 20–30 minutes. Baseline BT, FVIII:C, VWF:RCo. VWF:RCo and FVIII:C at 1 hour postinfusion.	5 patients showed good clinical responses in all 8 episodes.	Cases varied as to type of bleeding (epistaxis, muscle hematoma, menometrorrhagia, placental detachment), number and dose of DDAVP infusions, and use of tranexamic acid.
Revel-Vilk S, Schmugge M, Carcao MD, Blanchette P, Rand ML, Blanchette VS. Desmopressin (DDAVP) responsiveness in children with von Willebrand disease. J Pediatr Hematol Oncol 2003 Nov;25(11):874–879.	75 children who had VWD: • 70 had type 1 VWD, (43 males, 27 females) • 5 had type 2A VWD	Retrospective, single institution review of records (1989–2001)	One dose of DDAVP 0.3 mcg/kg infused over 20 minutes, with pre- and postinfusion blood sampling for FVIII:C and VWF:RCo.	DDAVP responsiveness was age-related. 26 of 28 DDAVP responders had good clinical outcomes with DDAVP treatment.	All cases, except hematuria, received tranexamic acid for bleeding episodes. Details on types of bleeding in the good outcomes category were not reported.

BT, bleeding time; DDAVP, 1-desamino-8-D-arginine vasopressin (desmopressin, a synthetic analog of vasopressin); FVIII, [blood clotting] factor VIII; FVIII:C, factor VIII coagulant activity; VWF, von Willebrand factor; VWF:Ag, von Willebrand factor antigen; VWF:RCo, von Willebrand factor ristocetin cofactor activity

Evidence Table 8. Recommendation VI.C

For prophylaxis for minor surgery, initial treatment should be expected to achieve VWF:RCo and FVIII activity levels of at least 30 IU/dL and preferably >50 IU/dL. *Grade B, level III*

Citation	Population	Study Design	Intervention	Results	Comments
de la Fuente B, Kasper CK, Rickles FR, Hoyer LW. Response of patients with mild and moderate hemophilia A and von Willebrand's disease to treatment with desmopressin. Ann Intern Med 1985 Jul;103(1):6–14.	13 patients who had type 1 VWD 7 patients who had type 2A VWD 1 patient who had type 2B VWD	Prospective, open-label, nonrandomized, controlled clinical trial	5 patients had dental surgery with DDAVP x 1 and epsilon aminocaproic acid for 3–5 days. 4 patients had minor surgery with DDAVP.	5/5 dental patients had good hemostasis with VWF:RCo 22–115 IU/dL (only 1 <50 IU/dL). 4/4 surgical patients had good hemostasis with VWF:RCo 57–132 IU/dL.	9/9 patients who had dental extractions/ minor surgeries had good hemostasis; 8/9 patients achieved 50 IU/dL VWF:RCo.
Federici AB, Sacco R, Stabile F, Carpenedo M, Zingaro E, Mannucci PM. Optimising local therapy during oral surgery in patients with von Willebrand disease: effective results from a retrospective analysis of 63 cases. Haemophilia 2000 Mar;6(2):71–77.	63 consecutive patients who had VWD: • 31 had type 1 • 22 had type 2 • 10 had type 3	Retrospective, single-center review of using a standard regimen for 4 years	All subjects underwent intravenous DDAVP trial with 0.3 mcg/kg. Response was defined as an increase to 3x baseline VWF:RCo and FVIII to a minimum of 30 IU/dL and a BT of 12 minutes or less. Topical and oral tranexamic acid x 7 days, plus DDAVP subcutaneous x 1 in responsive patients who had type 1 and 2A VWD, plus topical fibrin glue x 1 if >2 extractions or >4 periodontal flaps, +/- Haemate-P® x 1 for some patients who had type 2B and type 3 VWD.	Good hemostatic control in all but 2 cases (1 type 2B VWD, 1 type 3 VWD) who required additional therapy. Local therapy alone in 47.6%. Local plus single dose DDAVP in 42.8%. Local plus VWF concentrate in 9.5%.	Meticulous surgical technique by experienced oral surgeons and close collaboration with expert hematologists are likely to have contributed to the excellent outcomes.

Evidence Table 8. Recommendation VI.C (continued)

Citation	Population	Study Design	Intervention	Results	Comments
Nitu-Whalley IC, Griffioen A, Harrington C, Lee CA. Retrospective review of the management of elective surgery with desmopressin and clotting factor concentrates in patients with von Willebrand disease. Am J Hematol 2001 Apr;66(4):280–284.	65 patients who had VWD and underwent 103 operations	Retrospective, single-center summary of cases using similar regimens for 10 years	Most patients had a DDAVP test infusion preoperatively and were considered "responders" if FVIII/VWF >50 IU/dL. DDAVP x 1 or 2, or CFC. Tranexamic acid 4 x a day for 7–10 days, for 38% of surgeries.	DDAVP for 10 minor surgeries, median 2 doses, range 1–6. VWF concentrate for 26 minor surgeries, median load 48 IU/dL (range 14–70); follow-up dose 26 IU/kg (range 24–37); median days of treatment 4 (range 1–16). Bleeding requiring further VWF concentrate in 4/36 minor surgeries.	Most patients had a DDAVP test infusion preoperatively, and tranexamic acid plus DDAVP was effective for those patients. Dose and type of CFC were quite variable.
Revel-Vilk S, Schmugge M, Carcao MD, Blanchette P, Rand ML, Blanchette VS. Desmopressin (DDAVP) responsiveness in children with von Willebrand disease. J Pediatr Hematol Oncol 2003 Nov;25(11):874–879.	70 children who had type 1 VWD; 5 children who had type 2A VWD	Retrospective review; no control or comparison group	All subjects underwent intravenous DDAVP (0.3 mcg/kg) treatment trial with laboratory response defined as increase of 2x in VWF:RCo and to at least 30 IU/dL. Children were treated with DDAVP for minor surgeries and additionally received tranexamic acid, except for children with hematuria.	26/28 children who had laboratory responses had adequate clinical hemostasis when DDAVP was used to prevent or treat bleeding. 6/8 children who did not respond to DDAVP challenge also required VWF concentrate following unsuccessful use of DDAVP clinically.	In this study, children were defined as laboratory responders if they increased VWF:RCo and FVIII at least 2-fold over baseline and to at least 30 IU/dL. All cases, except in cases of hematuria, used tranexamic acid along with DDAVP.

BT, bleeding time; CFC, clotting factor concentrate; DDAVP, 1-desamino-8-D-arginine vasopressin; FVIII, [blood clotting] factor VIII; VWF:RCo, von Willebrand factor ristocetin cofactor activity

Evidence Table 9. Recommendation VI.D

For minor surgery, VWF:RCo and FVIII activity levels of at least 30 IU/dL and preferably >50 IU/dL should be maintained for 1–-5 days
Grade B, level III

Citation	Population	Study Design	Intervention	Results	Comments
Jimenez-Yuste V, Prim MP, De Diego JI, Villar A, Quintana M, Rabanal I, Sastre N, Hernandez-Navarro F. Otolaryngologic surgery in children with von Willebrand disease. Arch Otolaryngol Head Neck Surg 2002 Dec;128(12): 1365–1368.	41 children who had preoperative confirmed diagnosis of type 1 VWD	Prospective, single institution controlled study	37 children treated with DDAVP 0.3 mcg/kg, based on laboratory response to trial dosing. All treated preoperatively and at 24 hours, and some daily up to 4 days. 4 children treated with Haemate-P® secondary to history of seizures. All received tranexemic acid for 7 days.	2/37 (5%) treated with DDAVP had bleeding requiring intervention, not predicted by preoperative response to trial dose.	Mild hyponatremia was found in 24/24 given DDAVP for more than 1 day, and in 3/13 who were given DDAVP for 1 day. Seizures occurred in 1/2 patients with severe hyponatremia, both after 2 doses.
Kreuz W, Mentzer D, Becker S, Scharrer I, Kornhuber B. Haemate-P® in children with von Willebrand disease. Haemostasis 1994 Sep; 24(5):304-310.	Children who had VWD: • 183 had type 1 • 1 had type 2A • 14 had type 3	Retrospective review of data from a single center	DDAVP testing: 2–3-fold increase in VWF:RCo, VWF:Ag, and FVIII. CFC: therapy based on monitoring following 50 IU/kg. 64 surgeries, mostly tonsillectomy and adenoidectomy. 12 children who underwent tonsillectomy and adenoidectomy were given DDAVP twice daily for 3 days. 52 children underwent surgery with Humate-P® for at least 3 days: • Children who had type 1 VWD received 10–30 IU/kg twice daily. • Children who had type 2A VWD received 20–30 IU/dL once or twice daily. • Children who had type 3 VWD received 20–50 IU/dL once or twice daily.	2/12 had postoperative bleeding and required CFC. No bleeding.	All children treated with DDAVP had a 2–3-fold increase in VWF:RCo, VWF:Ag, and FVIII activity. Children treated with Humate-P® showed a half-time of 12 hours for FVIII, 10 hours for VWF:RCo. There was a 17% failure rate (postoperative bleeding) for tonsillectomy and adenoidectomy surgery with DDAVP, but no failures with Humate-P®.

Evidence Table 9. Recommendation VI.D (continued)

Citation	Population	Study Design	Intervention	Results	Comments
Nitu-Whalley IC, Griffioen A, Harrington C, Lee CA. Retrospective review of the management of elective surgery with desmopressin and clotting factor concentrates in patients with von Willebrand disease. Am J Hematol 2001 Apr;66(4):280–284.	65 patients who had VWD and underwent 103 operations	Retrospective, single-center summary of cases using similar regimens for 10 years	Most patients had a DDAVP test infusion preoperatively and were considered "responders" If FVIII/VWF >50 IU/dL. DDAVP x 1 or 2, or CFC. Tranexamic acid 4 x a day for 7–10 days, for 38% of surgeries.	DDAVP for 10 minor surgeries, median 1.5 days, range 1–6. VWF concentrate for 26 minor surgeries, median 4 days of treatment (range 1–16). Bleeding requiring further VWF concentrate in 4/36 minor surgeries.	Most patients had a DDAVP test infusion preoperatively, and tranexamic acid plus DDAVP was effective for patients who demonstrated increase in FVIII and VWF to >50 IU/dL on preoperative DDAVP trial. Patients were routinely monitored for FVIII activity following surgery (normal range achieved in all but 1 patient, who achieved 38 IU/dL after DDAVP). Dose and type of CFC were quite variable.
Thompson AR, Gill JC, Ewenstein BM, Mueller-Velten G, Schwartz BA. Successful treatment for patients with von Willebrand disease undergoing urgent surgery using factor VIII/VWF concentrate (Humate-P®). Haemophilia 2004 Jan;10(1):42–51.	Patients who had VWD: • 16 had type 1 VWD • 4 had type 2A VWD • 5 had type 2B VWD • 8 had type 3 VWD • 6 had type 2M, 2N, or unknown VWD	Prospective, multicenter, open-label, nonrandomized clinical trial	42 surgeries (17 minor). VWF concentrate, mean loading dose 82.3 IU/dL. Median duration for all 42 surgeries was 3 days.	39 evaluable surgical events rated Excellent/Good.	Patients who had type 3 VWD were treated for longer durations; no relationship between VWD type and loading or maintenance dose. 17 minor surgeries presumably accounted for most or all of the 16 cases treated 1–4 days.

CFC, clotting factor concentrate; DDAVP, 1-desamino-8-D-arginine vasopressin; FVIII, [blood clotting] factor VIII; VWF, von Willebrand factor; VWF:Ag, von Willebrand factor antigen; VWF:RCo, von Willebrand factor ristocetin cofactor avtivity

Evidence Table 10. Recommendation VI.F

For persons who have mild to moderate VWD, antifibrinolytics combined with DDAVP are generally effective for oral surgery. VWF concentrate should be available for persons who cannot receive DDAVP or who bleed excessively despite this combined therapy.
Grade B, level IIb

Citation	Population	Study Design	Intervention	Results	Comments
Castaman G, Lattuada A, Mannucci PM, Rodeghiero F. Factor VIII:C increases after desmopressin in a subgroup of patients with autosomal recessive severe von Willebrand disease. Br J Haematol 1995 Jan;89(1):147–151.	A single patient who had "autosomal recessive" severe VWD Within a study of 6 patients who had severe autosomal recessive VWD	Single case report within a prospective, nonrandomized, controlled trial	Four doses of DDAVP (0.4 mcg/kg) were infused over 30 minutes given every 6 hours, plus oral tranexamic acid (1 g, 3 times a day) for 5 days.	Patients showed rise of VWF:Ag 0.5 to 9, VWF:RCo <3 to 11, and FVIII 19 to 70 IU/dL following DDAVP. 1 patient successfully underwent dental extraction without bleeding.	Cases were variant type 3 VWD, as all had some measurable baseline VWF:Ag.
de la Fuente B, Kasper CK, Rickles FR, Hoyer LW. Response of patients with mild and moderate hemophilia A and von Willebrand's disease to treatment with desmopressin. Ann Intern Med 1985 Jul;103(1):6–14.	21 subjects who had VWD: • 13 had type 1 VWD • 7 had type 2A VWD • 1 had type 2B VWD	Prospective, open-label, nonrandomized, controlled clinical trial	One dose of DDAVP (0.3 mcg/kg) infused over 15 minutes. EACA given before and for 3–5 days following dental procedure.	Six dental procedures in 5 subjects (4 type 1 VWD, 1 type 2A VWD). Excellent hemostasis in all 5 subjects, including 4 subjects who had a rise in VWF:RCo to 66–115 IU/dL and 1 subject who had a small rise in VWF:RCo from 10–22 IU/dL.	Pharmacokinetic studies of VWF:RCo, VWF:Ag, FVIII activity, and FVIII:Ag following DDAVP in 13 patients who had VWD showed rapid return almost to baseline values within 5 hours in 5 patients and persistently elevated levels up to 5 hours in 8 patients.

Evidence Table 10. Recommendation VI.F (continued)

Citation	Population	Study Design	Intervention	Results	Comments
Federici AB, Sacco R, Stabile F, Carpenedo M, Zingaro E, Mannucci PM. Optimising local therapy during oral surgery in patients with von Willebrand disease: effective results from a retrospective analysis of 63 cases. Haemophilia 2000 Mar;6(2):71–77.	63 consecutive patients who had VWD: • 31 had type 1 • 22 had type 2 • 10 had type 3	Retrospective, single-center review of using a standard regimen for 4 years	Topical and oral tranexamic acid x 7 days, plus DDAVP subcutaneous x 1 in responsive patients who had type 1 and type 2A VWD, plus topical fibrin glue x 1 if >2 extractions or >4 periodontal flaps, +/- Haemate-P® x 1 for some patients who had type 2B and type 3 VWD.	Good hemostatic control in all but 2 cases (1 type 2B VWD, 1 type 3 VWD), who required additional therapy.	Meticulous surgical technique by experienced oral surgeons and close collaboration with expert hematologists are likely to have contributed to the excellent outcomes.
Mariana G, Ciavarella N, Mazzucconi MG, Antoncecchi S, Solinas S, Ranieri P, Pettini P, Agrestini F, Mandelli F. Evaluation of the effectiveness of DDAVP in surgery and in bleeding episodes in haemophilia and von Willebrand's disease. A study on 43 patients. Clin Lab Haematol 1984;6(3):229–238.	9 patients who had type 1 or type 2 VWD	Dental extractions performed on a standard protocol	12 dental extractions in 9 patients. 2 regimens: DDAVP 0.3 or 0.4 mcg/kg x1 infusion and tranexamic acid IV for 12 hours and then 3 times a day to complete 7 days OR DDAVP given preoperatively, at 24 hours, and when sutures were removed, and tranexamic acid IV for 2 days and then orally for 6 days. Tranexamic acid IV (80 mg/kg/day) for 2 days and then orally (100 mg/kg/day) for 6 days.	No bleeding.	FVIII activity was measured pre/post DDAVP in 5 patients who had VWD, and all had response to >100 U/dL.

Evidence Table 10. Recommendation VI.F (continued)

Citation	Population	Study Design	Intervention	Results	Comments
Nitu-Whalley IC, Griffioen A, Harrington C, Lee CA. Retrospective review of the management of elective surgery with desmopressin and clotting factor concentrates in patients with von Willebrand disease. Am J Hematol 2001 Apr;66(4):280–284.	65 patients who had VWD and underwent 103 operations, including 37 dental procedures	Retrospective, single-center summary of cases using similar regimens for dental surgery for 10 years	Tranexamic acid 4x/day for 7–10 days, plus DDAVP x 1 or 2, or CFC.	1 patient who had type 3 VWD re-bled postoperatively. All others had good outcomes to initial treatment plan.	Most patients had a DDAVP test infusion preoperatively, and tranexamic acid plus DDAVP was effective for those patients. Dose and type of CFC were quite variable.
Rodeghiero F, Castaman G, Di Bona E, Ruggeri M, Lombardi R, Mannucci PM. Hyper-responsiveness to DDAVP for patients with type 1 von Willebrand's disease and normal intra-platelet von Willebrand factor. Eur J Haematol 1988 Feb;40(2):163–167.	Patients who had severe type 1 VWD All subjects had VWF:RCo <3 IU/dL prior to DDAVP, and 36–110 IU/dL 30–60 minutes after infusion	Prospective, non-randomized, open-label clinical trial Control: All subjects had bleeding with previous dental extractions	DDAVP: 0.4 mcg/kg 30 minutes prior to and test dose 2 weeks prior to procedure. A second dose was given at 6–8 hours. All subjects received tranexamic acid 1 g 3 times a day orally.	2/9 patients had delayed bleeding, 3 and 7 days after tooth extraction, necessitating an additional dose of DDAVP.	All patients had baseline VWF:RCo <3 U/dL, VWF:Ag ≤10 U/dL, and FVIII activity ≤20 U/dL with normal platelet VWF. Post-DDAVP: plasma VWF:RCo ≥65, VWF:Ag ≥35, FVIII ≥65 U/dL, and normal BT were documented in all subjects.
Saulnier J, Marey A, Horellou MH, Goudemand J, Lepoutre F, Donazzan M, Gazengel C, Torchet M, Letang C, Schuhmann C, et al. Evaluation of desmopressin for dental extractions in patients with hemostatic disorders. Oral Surg Oral Med Oral Pathol 1994 Jan;77(1):6–12.	15 patients who had VWD: • 14 congenital (all responsive to DDAVP) and • 1 AVWS 16 patients who had hemophilia A 4 others	Retrospective, multicenter summary of cases using similar regimens for 5 years	DDAVP x 1 infused preoperatively and occasionally postoperatively plus antifibrinolytic, plus fibrin glue, in 1 of 3 centers.	Postextraction bleeding in 1 case (patient who had AVWS).	Patients selected by response to DDAVP: • >30 percent FVIII level postinfusion. • VWD subtypes not specified. • Contribution of fibrin glue not evaluable.

AVWS, acquired von Willebrand syndrome; CFC, clotting factor concentrate; DDAVP, 1-desamino-8-D-arginine vasopressin; EACA, epsilon aminocaproic acid; FVIII, [blood clotting] factor VIII; VWF, von Willebrand factor; VWF:Ag, von Willebrand factor antigen; VWF:RCo, von Willebrand factor ristocetin cofactor activity

Evidence Table 11. Recommendation VII.A

All treatment plans should be based on objective laboratory determination of response of VWF:RCo and FVIII activity levels to DDAVP or to VWF concentrate infusion.

Grade B, level IIb

Citation	Population	Study Design	Intervention	Results	Comments
Allen GC, Armfield DR, Bontempo FA, Kingsley LA, Goldstein NA, Post JC. Adenotonsillectomy in children with von Willebrand disease. Arch Otolaryngol Head Neck Surg 1999 May;125(5):547–551.	Adenotonsillar procedures in 67 children who had VWD 59/67 children had preoperative DDAVP trials	Retrospective cohort	DDAVP given once preoperatively.	7/67 had immediate bleeding but none required intervention; 2/7 went on to have delayed bleeding at 5–7 days. 9/67 had delayed bleeding on days 5–12 (mean 7.7); all were admitted to hospital; 4 required cauterization (all tonsillectomy). 3/67 had substantial hyponatremia. 1/67 had seizures.	Children who had VWD and delayed bleeding had significantly lower response of VWF:RCo to DDAVP than children without delayed bleeding (P <0.03).
Derkay CS, Werner E, Plotnick E. Management of children with von Willebrand disease undergoing adenotonsillectomy. Am J Otolaryngol 1996 May;17(3):172–177.	12 children who had VWD and underwent adenotonsillectomy	Retrospective review	DDAVP given preoperatively, at 12 hours and daily until eschar.	2/12 had excessive bleeding, 1 at 3 hours postoperation requiring electrocautery and a single dose of Humate-P® (DDAVP was continued), and 1 at day 10 requiring operative intervention. 3/12 developed hyponatremia (Na <132). 1/12 received cryoprecipitate for tachyphylaxis.	Surgical technique included Bovie electrocautery in 7 and scissor dissection in 5 patients. Surgical approach did not affect outcome.

Evidence Table 11. Recommendation VII.A (continued)

Citation	Population	Study Design	Intervention	Results	Comments
Dobrkovska A, Krzensk U, Chediak JR. Pharmacokinetics, efficacy and safety of Humate-P® in von Willebrand disease. Haemophilia 1998; (4 Suppl 3):33–39.	6 patients who had VWD	Prospective pharmacokinetic study	Humate-P® bolus, single infusion of VWF:RCo 80 IU/kg, FVIII 32 IU/kg.	Median half-time of VWF:RCo, 11.3 hours; range 6.4–13.3 hours. Recovery of VWF:RCo, median 2.1 IU/dL per kg; range 1.1–-2.74. Recovery of FVIII, median 2.69 IU/dL per kg; range 1.94–3.65.	Variable recovery and half-life indicate that laboratory monitoring is important to confirm adequate factor levels and adjust therapy if necessary.
	97 patients who had VWD and were treated with Humate-P®: • 32 had type 1 VWD • 5 had type 2A VWD • 18 had type 2B VWD • 28 had type 3 VWD • 14 others, including 4 who had AVWS 344 bleeding events; 73 surgeries; 93 invasive procedures, childbirth, or test infusions; 20 episodes of prophylaxis	Retrospective review of 97 Canadian patients	Humate-P®, specific dosing not given.	Excellent/good response in: • 100% of patients who had type 1 VWD. • 100% of patients who had type 2A VWD. • 99% of patients who had type 2B VWD. • 95% in patients who had type 3 VWD. • 95% in those who had conditions including AVWS and other.	Adverse events were rare and not serious.

Evidence Table 11. Recommendation VII.A (continued)

Citation	Population	Study Design	Intervention	Results	Comments
Federici AB. Clinical diagnosis of von Willebrand disease. Haemophilia 2004 Oct;10 (Suppl 4):169–176.	26 patients who had type 1 VWD 40 patients who had type 2 VWD	Prospective, controlled trial, not randomized	DDAVP 0.3 mcg/kg, with laboratory monitoring of response.	Very variable DDAVP response, between and within VWD subtypes.	Well-designed nonrandomized clinical trial. Study demonstrated lack of a priori prediction of response to DDAVP and lower response rate in type 1 VWD than previously suspected. Study supports need for baseline trial.
Kreuz W, Mentzer D, Becker S, Scharrer I, Kornhuber B. Haemate-P® in children with von Willebrand's disease. Haemostasis 1994 Sep;24(5):304–310.	12 children who had type 1 VWD and tonsillectomy and adenoidectomy	Case series	DDAVP, all based upon preoperation trial. DDAVP administered twice daily for 3 days.	2/12 required VWF concentrate replacement for bleeding.	Children in whom DDAVP treatment failed were successfully treated with Haemate-P®.
Manno CS, Bulter RB, Cohen AR. Successful management of patients with type 1 von Willebrand's disease with desmopressin acetate for tonsillectomy (abstract). Haemophilia 1998;4:288.	13 children who had type 1 VWD and tonsillectomies or adenoidectomies	Retrospective cohort	DDAVP 0.3 mcg/kg IV, preoperation, 12 hours (12/13), (24–36 hours in 3/12), and a third/fourth dose at 5–7 days (11/13). Epsilon aminocaproic acid in 50%.	13/13 had no bleeding or other treatment.	2 infusions of DDAVP on day of surgery and 1 followup at 5–7 days may be adequate for tonsillectomy and adenoidectomy in children who have VWD and are responsive to DDAVP.

Evidence Table 11. Recommendation VII.A (continued)

Citation	Population	Study Design	Intervention	Results	Comments
Rodeghiero F, Castaman G, Di Bona E, Ruggeri M. Consistency of responses to repeated DDAVP infusions in patients with von Willebrand's disease and hemophilia A. Blood 1989 Nov;74(6):1997–2000.	14 patients who had severe type 1 VWD and normal platelet VWF	Case series	DDAVP, 0.4 mcg/kg. All had preoperation trial.	14/14 increased VWF:RCo from <3 to 64–120 IU/dL. No bleeding complications.	Case series showed efficacy of DDAVP in patients who have severe type 1 VWD and positive trial responses.
Shah SB, Lalwani AK, Koerper MA. Perioperative management of von Willebrand's disease in otolaryngologic surgery. Laryngoscope 1998 Jan;108(1 Pt 1):32–36.	8 had type 1 VWD 3 had type 2A VWD 4 children had tonsillectomy and adenoidectomy; 1 child had adenoidectomy alone	Case series	DDAVP preoperation and at 24 hours. IV then oral antifibrinolytic therapy.	5/5 children who had tonsilloadenectomy procedures had no bleeding.	Importance of meticulous surgical technique was emphasized. Delayed therapy with DDAVP was not given, but sample size is very small.

AVWS, acquired von Willebrand syndrome; DDAVP, 1-desamino-8-D-arginine vasopressin (desmopressin, a synthetic analog of vasopressin); FVIII, [blood clotting] factor VIII; VWF, von Willebrand factor; VWF:RCo, von Willebrand Factor ristocetin cofactor activity

Evidence Table 12. Recommendation VII.C

For severe bleeding (e.g., intracranial, retroperitoneal) or for prophylaxis of major surgery, initial target VWF:RCo and FVIII activity levels should be at least 100 IU/dL. Subsequent dosing should maintain VWF:RCo and FVIII levels above a trough of 50 IU/dL for at least 7–10 days.
Grade B, level III

Citation	Population	Study Design	Intervention	Results	Comments
Dobrkovska A, Krzensk U, Chediak JR. Pharmacokinetics, efficacy and safety of Humate-P® in von Willebrand disease. Haemophilia 1998;(4 Suppl 3):33–39.	6 patients who had VWD (2 each had type 1, 2A, 3) for prospective pharmacokinetic study	Prospective pharmacokinetic study	Pharmacokinetic studies were performed for each patient given 80 IU/kg VWF:RCo and 32 IU/kg FVIII.	Median plasma values for VWF:RCo, VWF:Ag, and FVIII were maintained above 50 IU/dL for 48 hours.	
	73 patients who had VWD and were having surgery	Retrospective data collection	VWF concentrate (Humate-P®) 80 IU/kg bolus and continuous infusion.	72/73 Excellent/good hemostasis.	Duration of therapy for surgery not given.
Gill JC, Ewenstein BM, Thompson AR, Mueller-Velten G, Schwartz BA, for the Humate-P® study group. Successful treatment of urgent bleeding in von Willebrand disease with factor VIII/VWF concentrate (Humate-P®): use of the ristocetin cofactor assay (VWF:RCo) to measure potency and to guide therapy. Haemophilia 2003;9:688–695.	33 patients who had congenital VWD (9 type 1, 4 type 2A, 4 type 2B, 12 type 3, 4 unspecified VWD), treated for urgent bleeding episodes (n = 53 episodes)	Prospective open-label, nonrandomized study of patients from 19 participating centers	Initial Humate-P® bolus 60–80 IU VWF:RCo/kg, followed by intermittent bolus maintenance infusions (40–60 IU VWF:RCo/kg) at 8–12 hour intervals for 3 days, with supplemental daily dosing if needed up to 7 days total, with target nadir above 50 IU/dL VWF:RCo.	91% of patients (48 bleeding episodes) had complete followup. Efficacy 98% excellent/good for 53 bleeding episodes.	
Hanna WT, Bona RD, Zimmerman CE, Carta CA, Hebert GZ, Rickles FR. The use of intermediate and high purity factor VIII products in the treatment of von Willebrand disease. Thromb Haemost 1994 Feb;71(2):173–179.	5 patients who had VWD	Prospective, open-label, nonrandomized clinical trial	5 surgeries treated with Koate, 20–100 IU/kg load and continuous infusion.	5/5 had no surgical bleeding.	All patients treated with Koate and maintaining VWF:RCo >50 IU/dL had excessively high VWF:Ag (400–800 IU/dL) and 2/5 had FVIII activity >400 IU/dL.

Evidence Table 12. Recommendation VII.C (continued)

Citation	Population	Study Design	Intervention	Results	Comments
Kreuz W, Mentzer D, Becker S, Scharrer I, Kornhuber B. Haemate-P® in children with von Willebrand's disease. Haemostasis 1994 Sep;24(5):304–310.	Children who had congenital VWD (183 type 1, 1 type 2A, 14 type 3) as well as valproate-associated acquired von Willebrand syndrome (91 children)	Retrospective review, single center	41 surgeries in patients who had congenital VWD, treated with Haemate-P® (38 type 1, 3 type 3) generally for at least 3 days once or twice daily (10–20 IU FVIII/kg for type 1 VWD and 20–50 IU FVIII/kg for type 3 VWD).	Excellent/Good 41/41.	Most surgeries were oral procedures (tonsillectomy and adenoidectomy). 17% failure rate with DDAVP but none with Haemate-P®.
Lillicrap D, Poon MC, Walker I, Xie F, Schwartz BA. Efficacy and safety of the factor VIII/von Willebrand factor concentrate, Haemate-P/Humate-P: ristocetin cofactor unit dosing in patients with von Willebrand disease. Thromb Haemost 2002 Feb;87(2):224–230.	Patients who had type 1, 2, or 3 VWD	Retrospective data review	73 surgeries, types not specified. VWF concentrate (Humate-P®), loading dose mean 69.1 VWF:RCo IU/kg.	Excellent/Good 72/73.	Trough levels not given. 10% of surgeries were treated 7–10 days (the rest fewer). Presumably these were the major surgeries, but not specified. Only 55% of surgery patients were treated more than 1 day.
Lubetsky A, Schulman S, Varon D, Martinowitz U, Kenet G, Gitel S, Inbal A. Safety and efficacy of continuous infusion of a combined factor VIII-von Willebrand factor (vWF) concentrate (Haemate-P®) in patients with von Willebrand disease. Thromb Haemost 1999 Feb;81(2):229–233.	8 patients who had various types of VWD	Retrospective review	9 surgeries in 8 patients. Mean loading dose 39.5 VWF:RCo IU/dL (range 31–51) followed by continuous infusion 2 IU/kg/hr. Trough level maintained above 50 IU/dL VWF:RCo. Mean duration of therapy 9.1 days, range 5–12.	1/8 with excessive surgical bleeding (total hip replacement with 2,400 mL blood loss with inadequate levels of VWF:RCo).	Troughs and durations were reported for this study.

Evidence Table 12. Recommendation VII.C (continued)

Citation	Population	Study Design	Intervention	Results	Comments
Michiels JJ, Berneman ZN, van der Planken M, Schroyens W, Budde U, van Vliet HDM. Bleeding prophylaxis for major surgery in patients with type 2 von Willebrand disease with an intermediate purity factor VIII-VWF concentrate (Haemate-P®). Blood Coagul Fibrinolysis. 2004 Jun; 15(4): 323-330.	5 patients who had type 2 VWD	Prospective, nonrandomized, open-label clinical trial	Major surgery. VWF concentrate based on pharmacokinetic studies to maintain trough VWF:RCo and VWF:CB above 60 IU/dL: yielding recommendations for load 60–80 VWF:RCo IU/kg; 30–40 IU/kg VWF:RCo every 12 hours for 5–7 days.	Successful. No bleeding?	The meaning of the word successful in the manuscript was not defined, but it is presumed to mean no bleeding. Dosing was based on pharmacokinetic data.
Nitu-Whalley I, Griffioen A, Harrington C, Lee CA. Retrospective review of the management of elective surgery with desmopressin and clotting factor concentrates in patients with von Willebrand disease. Am J Hematol 2001Apr;66(4): 280-284.	27 persons who had type 1, 2, or 3 VWD	Retrospective review	Monitoring with FVIII levels. DDAVP response measured by increase to at least 50 IU/dL. Major surgery. 3 treated with DDAVP every 12–48 hours, with or without tranexamic acid. Median duration of treatment 5 days (range 2–5). 10 treated with VWF concentrate. Mean preoperation dose 54 IU/kg. Followup mean, 47 IU/kg/day for median of 10 days (range 4–14).	DDAVP: Poor response following rhinoplasty that was treated for only 24 hours; hematoma following hysterectomy. VWF concentrate: hemorrhage on day 2 after caesarean section.	All major surgeries treated for 5–10 days to levels >50 IU/dL had good outcomes. 3 patients treated for 1 or 2 days with bleeding complications.

Evidence Table 12. Recommendation VII.C (continued)

Citation	Population	Study Design	Intervention	Results	Comments
Scharrer I, Vigh T, Aygoren-Pursun E. Experience with Haemate-P® in von Willebrand's disease in adults. Haemostasis 1994 Sep–Oct;24(5):298–303.	Adult patients who had types 1, 2A, 2B, or 3 VWD (140 total; numbers of each type of VWD not specified) 66 treated for bleeding events, and 70 treated for a variety of minor and major surgical events	Retrospective review	Haemate-P® initial doses 20–80 IU FVIII/kg, with maintenance infusions at 12-hour intervals (recommended), with target nadir levels 50 IU FVIII and VWF:RCo (recommended).	100% Excellent/Good.	21 patients participated in pharmacokinetic studies with Haemate-P® bolus infusion (40 IU FVIII/kg) and demonstrated VWF:RCo increments with half-life 5–7 hours.
Thompson AR, Gill JC, Ewenstein BM, Mueller-Velten G, Schwartz BA. Successful treatment for patients with von Willebrand disease undergoing urgent surgery using factor VIII/VWF concentrate (Humate-P®). Haemophilia 2004 Jan;10(1):42–51.	Patients who had VWD: • 16 had type 1 VWD • 4 had type 2A VWD • 5 had type 2B VWD • 8 had type 3 VWD • 6 had type 2M, 2N, or unknown VWD	Prospective, multi-center, open-label, nonrandomized clinical trial	42 surgeries. VWF concentrate, mean loading dose 82.3 IU/dL.	39 evaluable surgical events rated Excellent/Good.	Patients who had type 3 VWD were treated for longer durations. No relationship was found between VWD type and loading or maintenance dose.

DDAVP, 1-desamino-8-D-arginine vasopressin; FVIII, [blood clotting] factor VIII; VWF, von Willebrand factor; VWF:Ag, von Willebrand factor antigen; VWF:CB, von Willebrand factor collagen-binding activity; VWF:RCo, von Willebrand factor ristocetin cofactor activity

Evidence Table 13. Recommendation X.B

For persons who have AVWS and who bleed excessively despite therapy with DDAVP and VWF concentrate, treatment with high-dose IGIV should be considered, especially in IgG isotype MGUS (see page 47 for discussion of this non-FDA-approved use).
Grade B, level IIa

Citation	Population	Study Design	Intervention	Results	Comments
Arkel YS, Lynch J, Kamiyama M. Treatment of acquired von Willebrand syndrome with intravenous immunoglobulin. Thromb Haemost 1994 Oct;72(4):643–644.	1 person who had AVWS, type 2A, with MGUS	Case report on person with prior brief response to DDAVP	IGIV 400 mcg/kg/day x 4 days prior to oral surgery. No other therapy.	Normalization of VWF:RCo, FVIII:C, VWF:Ag, by day 3 postinfusion. Maintained to day 17.	References include 3 previous case reports of effective therapy of AVWS with IGIV.
Federici AB, Stabile F, Castaman G, Canciani MT, Mannucci PM. Treatment of acquired von Willebrand syndrome in patients with monoclonal gammopathy of uncertain significance: comparison of three different therapeutic approaches. Blood 1998 Oct;92(8):2707–2711.	AVWS in 10 subjects who had MGUS	Open-label, controlled crossover trial of IGIV infusion	Sequential treatment with: • Intravenous DDAVP. • Intravenous FVIII/VWF concentrate at 40 IU/kg. • IGIV at 1 g/kg/day x 2 days.	Brief responses only to DDAVP and FVIII/VWF concentrate. Good to excellent sustained response to IGIV.	Laboratory monitoring pre- and postinfusion, up to 8–21 days for IGIV. Only IgG isotype, and not IgM isotype, MGUS patients who had AWVS responded to IGIV (8/8 vs. 0/2, respectively).
Federici AB, Rand JH, Bucciarelli P, Budde U, van Genderen PJ, Mohri H, Meyer D, Rodeghiero F, Sadler JE. Acquired von Willebrand syndrome: data from an international registry. Thromb Haemost 2000 Aug;84(2):345–349.		Literature search for published cases	Tabulation of previously published cases.	266 case reports found.	Definition of AVWS included acquired bleeding syndrome plus laboratory evidence, by prescribed assays, of decreased VWF activity.
	186 persons who had AVWS	International registry of previously unpublished cases	Tabulation of data from detailed questionnaires on cases submitted by ISTH members	In 186 new cases submitted by 54 members, high-dose IGIV was effective in 21 of 63 cases (13/21 had positive anti-VWF assay).	

Evidence Table 13. Recommendation X.B (continued)

Citation	Population	Study Design	Intervention	Results	Comments
Macik BG, Gabriel DA, White GC, High K, Roberts H. The use of high-dose intravenous gamma-globulin in acquired von Willebrand syndrome. Arch Pathol Lab Med 1988 Feb;112(2):143–146.	2 persons who had AVWS: • 1 had MGUS • 1 had splenic B-cell lymphoproliferative disorder	Case reports of patients who had prior poor response to DDAVP or FVIII/VWF concentrate	IGIV 1g/kg/day x 2 days before surgery, with no other therapy. Laboratory monitoring to 28 days or 177 days.	By day 2, normal levels of VWF:RCo, VWF:Ag, and FVIII:C were achieved, and sustained for 21–177 days, respectively.	Anti-VWF was measurable in case 1. Case 2 apparently was cured by splenectomy.
van Genderen PJ, Terpstra W, Michiels JJ, Kapteijn L, van Vliet HH. High-dose intravenous immunoglobulin delays clearance of von Willebrand factor in acquired von Willebrand disease. Thromb Haemost 1995 May;73(5):891–892.	1 person who had AVWS, type 2A, with MGUS	Case report with laboratory studies	Assays of VWF half-life pre- and post-IGIV therapy.	VWF:RCo half-life <1 hour pre-, and 14 hours post IGIV.	Increased binding of IgG fraction from patient plasma to immobilized VWF was shown.

AVWS, acquired von Willebrand syndrome; DDAVP, 1-desamino-8-D-arginine vasopressin (desmopressin, a synthetic analog of vasopressin); FVIII, [blood clotting] factor VIII; FVIII:C, factor VIII coagulant activity; IgG, immunoglobulin G; IGIV, immune globulin intravenous (also known as IVIG); IgM, immunoglobulin M; ISTH, International Society on Thrombosis and Haemostasis; MGUS, monoclonal gammopathy of uncertain significance; VWF, von Willebrand factor; VWF:Ag, von Willebrand factor antigen; VWF:RCo, von Willebrand factor ristocetin cofactor activity

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