Current Diagnostic and Therapeutic Approaches to Patients with Acquired von Willebrand Syndrome: A 2013 Update

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Abstract

Acquired von Willebrand syndrome (AVWS) is an acquired bleeding disorder, first reported in 1968, with clinical and laboratory features similar to inherited von Willebrand disease. This rare bleeding disorder occurs mainly in patients with underlying lymphoproliferative, cardiovascular, myeloproliferative, and immunologic disorders. In contrast to acquired hemophilia A, AVWS is rarely associated with measurable anti-von Willebrand factor inhibitors. In most instances, AVWS is identified because of bleeding complications: in fact, more than 80% of the patients with this syndrome are active bleeders. Recurrent bleeding episodes occur in approximately 20 to 33% of patients with AVWS, especially following major trauma and surgery. Because of the heterogeneous mechanisms of AVWS, more than one therapeutic approach is often required to prevent or treat acute bleedings. Remission from some forms of AVWS can be obtained when the underlying disorders are treated.

Keywords

- acquired von Willebrand syndrome
- inhibitors
- lymphoproliferative diseases
- cardiovascular diseases
- thrombocythemia
- autoimmune conditions

General Definition, History, and Epidemiology of Acquired von Willebrand Syndrome

In 1968, the first report of an apparently acquired form of von Willebrand disease (VWD) was published that described a few patients with systemic lupus erythematosus (SLE) and a severe bleeding tendency.[1] Although this report preceded the development of quantitative von Willebrand factor (VWF) assays, the description of prolonged bleeding times in the presence of normal platelet counts and the reduced factor VIII (FVIII) activity of the reported subjects described features that are common to patients with inherited VWD. To differentiate between the congenital and acquired VWF deficiencies, the term *acquired von Willebrand syndrome* (AVWS) is now generally accepted as the name for the acquired disorder.

After the first cases were described, the next four patients reported with AVWS also had immunological disease.[2] Subsequently, additional clinical conditions were associated with AVWS (116 publications for 266 cases between 1968 and 1998), predominantly in the form of single case reports. It has been challenging to collect data on AVWS as even large centers do not have sufficient patients with AVWS to comprehensively evaluate this rare bleeding disorder and there

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have been no large prospective studies of AVWS. Consequently, the actual prevalence of AVWS in the general population is somewhat uncertain. A single center prospective study that evaluated 260 patients with hematological disorders estimated AVWS to be present in approximately 10% of these patients.[3] In the years leading up to 2000, numerous reviews were published about the etiology, pathophysiology, laboratory features, clinical manifestations, and outcome of treatment modalities of AVWS,[4–9] although none estimated the actual prevalence of AVWS because they relied on case report information. Between 1998 and 1999, a retrospective survey was conducted and published as an official communication of the Scientific and Standardization Committee (SSC) of the International Society on Thrombosis and Hemostasis (ISTH), which described information on cases in the ISTH-SSC registry.[10] Since then, several major reports on AVWS cases have been published by single institutions.[11–15] The prevalence of AVWS is probably underestimated because few physicians search for VWF abnormalities among patients with hematological, cardiovascular, and immunologic disorders.[16] Recently, a panel of experts proposed recommendations for hematologists on the treatment of AVWS.[17]

Pathophysiological Mechanisms of Acquired von Willebrand Syndrome

In contrast to inherited VWD, in AVWS, VWF is synthesized in normal or even increased quantity in most patients. In patients with AVWS, low plasma levels of VWF can result from accelerated VWF removal from the plasma by the following three main pathogenic mechanisms: (1) specific or nonspecific autoantibodies that form circulating immune complexes with, and inactivate, VWF (these complexes are cleared by cells bearing Fc-receptors that bind immunoglobulin G [IgG]); (2) adsorption of VWF by malignant cell clones; and (3) loss of high-molecular-weight (HMW) VWF multimers under conditions of high shear stress.[14] The detailed mechanisms responsible for the quantitative and qualitative changes of VWF, in diseases associated with AVWS, are listed in ►**Table 1**. Compared with acquired hemophilia (which is always caused by autoantibodies against FVIII), AVWS has more heterogeneous pathogenic mechanisms. None of the proposed mechanisms appear to be disease specific, and the same mechanism can be responsible for AVWS in different underlying disorders associated with the syndrome. Additionally, in some patients, the pathophysiological mechanism is unknown.[10,17]

Clinical and Laboratory Markers of Acquired von Willebrand Syndrome

There are two main clinical situations in which the diagnosis of AVWS should be considered: (1) bleeding patients whose laboratory finding suggests abnormalities of VWF and (2) patients known to have a disorder associated with AVWS who are seen before undergoing procedures that are associated with a high risk of bleeding.[10,14,17] Distinguishing AVWS from inherited VWD is important because the approaches to treatment of these conditions can be quite different.[10,17] In most cases, the differentiation of an acquired from an inherited cause is straight forward, even though there is no single feature that on its own can distinguish these conditions. An onset of bleeding later in life and a negative family history should prompt the suspicion of AVWS, but additional workup can be required because mild VWD can be asymptomatic for decades and it may not be associated with a remarkable family history because of its low penetrance. On the contrary, the presence of an AVWS-associated disorder does not prove that AVWS is present because these disorders may occur together coincidentally. When it is difficult to ascertain if the cause is inherited or acquired, it can be helpful to gather additional evidence, for example, by testing of family members, performing genetic analysis for VWD mutations, and testing for VWF-specific antibodies and inhibitors. A typical example of the usefulness of these diagnostic approaches was recently reported in one patient with AVWS associated with essential thrombocythemia who had family members with inherited type 1 VWD and a specific mutation of the *VWF* gene.[18]

Laboratory Tests for Acquired von Willebrand Syndrome

The initial tests used to assess AVWS are the same as those used to assess inherited VWD. Bleeding time and activated partial thromboplastin time are not very useful, although they may be abnormal. FVIII activity (FVIII:C), VWF antigen (VWF:Ag), VWF ristocetin cofactor activity (VWF:RCo), and VWF collagen-binding activity (VWF:CB) are sometimes decreased, particularly in AVWS associated with lymphoproliferative disorders.[10,17] A reduced activity/antigen ratio (VWF:RCo/VWF:Ag or VWF:CB/VWF:Ag) can indicate structural or functional abnormalities of VWF in AVWS, even if the absolute activity is within normal limits. A loss or decrease of HMW VWF multimers can be quantified using densitometry. However, these methods are not available in many laboratories and have not yet been standardized. Moreover, preanalytical variables can contribute to artifactual losses of HMW multimers.

When used properly, VWF multimer analysis can be a very sensitive tool for detecting structural abnormalities of VWF, and the pattern of abnormalities can help to distinguish AVWS from inherited VWD.[10,17] Assessment of VWF propeptide (known previously as VWF antigen II or Ag II) levels has been suggested to improve the diagnosis of AVWS because it is a marker of VWF biosynthesis. An increased ratio of VWF propeptide/VWF:Ag is suggestive of accelerated VWF clearance from the plasma.[19] However, an increased ratio also occurs in patients with the forms of type 1 VWD that are associated with accelerated VWF clearance.[20] Therefore, the ratio for plasma VWF propeptide/VWF:Ag does not always discriminate between AVWS and VWD and cannot be recommended for routine use at the present time. Although platelet VWF can also be measured, the findings are not specific for AVWS because platelet VWF can be normal or abnormal in AVWS.[10]

Autoantibodies play a role in the pathogenesis of some forms of AVWS, in particular those associated with lymphoproliferative disorders, and their presence appears to be associated with a more severe bleeding tendency. In a

Table 1 List of the pathogenic mechanisms of acquired von Willebrand syndrome that have been characterized for the disorders associated with this syndrome

Main mechanisms
1. Specific autoantibodies or nonspecific autoantibodies that form circulating immune complexes and enhance the clearance of von Willebrand factor
a. Lymphoproliferative disorders
b. Neoplastic diseases
c. Immunologic disorders
2. Adsorption of von Willebrand factor onto malignant cell clones or other cell surfaces
a. Lymphoproliferative disorders
b. Neoplastic diseases
c. Myeloproliferative disorders
d. Enhanced shear stress
3. Enhanced shear stress
a. Congenital cardiac defects
b. Aortic stenosis
c. Endocarditis
d. Malformation of vessels (M. Osler, Kasabach–Merritt syndrome)
e. Severe atherosclerosis
f. β-thalassemia
Additional mechanisms
4. Decreased synthesis
a. Hypothyroidism
5. Increased proteolytic degradation of von Willebrand factor by specific proteases
a. Myeloproliferative disorders
b. Enhanced shear stress
c. Uremia
d. Ciprofloxacin
6. Increased proteolytic degradation of von Willebrand factor by nonspecific proteases (plasmin)
a. Primary hyperfibrinolysis
b. Secondary hyperfibrinolysis
c. Fibrinolytic therapy
7. Unknown mechanism
a. Valproic acid
b. Cefotaxime
c. Viral disease
d. Liver transplantation
e. Mixed cryoglobulinimia
f. Amyloid light-chain amyloidosis
g. Glycogen storage disease type 1
h. Turner syndrome

Table 2 Investigations for the diagnosis of acquired von Willebrand factor syndrome

1. First assessment procedures
a. Personal and family histories
b. Platelet function analyzer-100
c. Activated partial thromboplastin time
d. Platelet count
2. Confirmatory tests
a. VWF:Ag
b. VWF:RCo
c. FVIII:C
d. VWF:CB
3. Tests performed by specialized laboratories
a. Ristocetin-induced platelet agglutination
b. VWF multimeric structure (low resolution gel)
c. Platelet von Willebrand factor
d. von Willebrand factor propeptide antigen
e. Search for antibodies against the factor VIII/ von Willebrand factor complex[21,25]

Abbreviations: FVIII, factor VIII; VWF:Ag, von Willebrand factor antigen; VWF:CB, von Willebrand factor collagen binding; VWF:RCo, von Willebrand factor ristocetin cofactor activity.

minority of patients, inhibitory (neutralizing) antibodies can be detected in mixing studies evaluated by VWF:RCo or VWF:CB as endpoints. In contrast to acquired hemophilia, where FVIII inhibitors are virtually always detectable with standard laboratory assays, the frequency of inhibitor detection is low in AVWS. This does not necessarily mean that autoantibodies are absent in AVWS, as some patients have non-neutralizing autoantibodies that accelerate VWF clearance from the circulation without inhibiting the measurable functions of VWF.[10,17] Moreover, inhibitors in AVWS are sometimes difficult to detect, and their detection in complexes with VWF may not be apparent unless the complex is dissociated by heating or other methods.[21–24] Non-neutralizing, VWF-binding antibodies can be detected by enzyme-linked immunosorbent assays (ELISAs), and such antibodies have been observed in patients with lymphoproliferative and other underlying disorders.[21,25] However, the detection of AVWS antibodies remains challenging as standardized assays are not yet available. Plasma-derived VWF contains ABO blood group antigen and should not be used as an antigen for ELISA, because the presence of blood group isoagglutinins may cause false-positive results.[25] Recombinant human VWF expressed in cultured animal cells is currently under investigation as a reagent that may potentially resolve this issue. ►**Tables 2** and **3** summarize information on the laboratory tests that are useful for AVWS diagnosis, including the methods for anti-VWF assays.

Table 3 Methods used to search for antibodies in AVWS

Direct methods
1. Test similar to the Bethesda method for FVIII inhibitors using VWF:RCo, VWF:CB, and VWF:Ag assays (Acquired hemophilia A has to be ruled out in all cases of acquired von Willebrand syndrome by the absence of FVIII autoantibodies in the Bethesda assay).
2. Direct binding to immobilized VWF (high background for test with antihuman IgM and to lesser extent IgG, because blood group antigens are part of the VWF molecule even in patients with blood group O).
3. Adsorption of the immune complex on a solid phase (e.g., protein A sepharose). Because protein A binds VWF directly, spurious positive results are possible, whenever the reaction is not verified with rigorous experimental controls.
Indirect measures
4. Improvement in von Willebrand factor levels in response to desmopressin, factor VIII/VWF concentrate infusion, and/or high dose intravenous gammaglobulin.
5. Consider the potential underlying mechanism causing the acquired von Willebrand syndrome and, if appropriate, correction by appropriate treatment of the underlying disorder.

Abbreviations: FVIII, factor VIII; VWF:Ag, von Willebrand factor antigen; VWF:CB, von Willebrand factor collagen binding; VWF:RCo, von Willebrand factor ristocetin cofactor activity.

General Management of Acquired von Willebrand Syndrome

The treatment goals in AVWS are to control acute bleeds, to prevent bleeding in high-risk situations, and to obtain long-term remission. The strategies used to obtain these goals depend on the underlying disease mechanisms. Whenever possible, treatment should address the underlying disorder, which can treat the AVWS as well.[10,17] However, it is not always possible to treat the underlying disorder. Furthermore, achieving a partial remission of the underlying disorder does not always result in an improvement of the bleeding symptoms of AVWS. The available evidence for efficacy and safety of the commonly used hemostatic treatments is summarized in the following text by single therapeutic approach.

Desmopressin

Desmopressin, a synthetic analog of vasopressin, can be used to prevent and control bleeding in some patients with AVWS. Desmopressin is usually administered in doses of 0.3 µg/kg of body weight, given intravenously over 30 minutes, once or twice daily. In the ISTH registry, desmopressin was reported to have an overall success rate of 32% for treatment of AVWS.[10] However, the success rates have varied, according to the underlying disorder, with lower success for patients with cardiovascular (10%) and myeloproliferative (21%) disorders compared with patients with AVWS associated with autoimmune (33%), lymphoproliferative (44%), and other neoplastic disorders (75%). In the only prospective clinical trial of desmopressin therapy, performed in 10 patients with monoclonal gammopathy of uncertain significance (MGUS), all subjects had improved VWF levels 30 minutes after treatment, whereas VWF levels were close to baseline by 4 hours after desmopressin treatment.[7] We therefore closely monitor VWF:Ag and VWF:RCo, along with FVIIIC, when desmopressin is used for prophylaxis and treatment of bleeds. Caution must be exercised with this therapy in patients who have cardiovascular disorders and/or are elderly, and measures need to be taken to prevent fluid overload and hyponatremia, which are the most common adverse effects of desmopressin.[17]

Von Willebrand Factor Containing Concentrates

Several plasma-derived concentrates containing VWF can be used for replacement therapy. In our own clinical practices, we start with doses between 30 and 100 VWF:RCo units/kg, depending on the patient's residual VWF activity, severity of bleeding, and presence of inhibitors. Similar to desmopressin, the half-life of infused VWF can be very short in AVWS, in particular in patients with AVWS associated with MGUS or inhibitors.[7] Close monitoring of the clinical response, with measurements of VWF activities, is needed for tailoring doses and dose intervals.[10,17]

Intravenous Immunoglobulin

The effectiveness of intravenous gammaglobulin (IVIG) for AVWS was demonstrated in an open-label crossover study in patients with AVWS associated with MGUS of the IgG class (IgG-MGUS): doses of 1 g/kg body weight per day were used for 2 days.[7] An increase of VWF and FVIII and shortening of the bleeding time were observed the day after the second infusion, with levels reaching their maximum after 4 days and slowly returning to baseline within 21 days. IVIG was not effective in AVWS patients with MGUS of the immunoglobulin M (IgM) class (IgM-MGUS).[7,17]

Recombinant Factor VIIa

There have been reports of using activated recombinant FVII (rFVIIa) as a hemostatic agent, in patients with AVWS, particularly for those who have significant bleeding manifestations and alloantibodies against VWF.[26] rFVIIa is usually administered at a dose of 90 µg/kg body weight (range, 40 to 150 µg/kg), for a median of three doses. Treatment is usually effective, with responses reported in 96% of patients.[17] Adverse events appear to be uncommon, although

Table 4 Main diseases that are associated with acquired von Willebrand syndrome[a]

Underlying disorders	ISTH-SSC registry 2000 (*n* = 186)	Previous literature 1968–1998 (*n* = 266)	German registry 2006–2011 (*n* = 840)
Lymphoproliferative	89 (48)	79 (30)	153 (18)
Monoclonal gammopathy of undetermined significance	43 (23)	37(14)	113 (14)
Multiple myeloma	16 (9)	19 (7)	17 (2)
Waldenström macroglobulinemia	8 (4)	5 (2)	15 (2)
Non-Hodgkin lymphoma	8 (4)	10 (4)	5
Hairy cell leukemia	0	1	1
Acute lymphocytic leukemia	1	0	2
Myeloproliferative	29 (15)	48 (18)	287 (34)
Essential thrombocythemia	21 (11)	17 (6)	174 (21)
Polycythemia vera	1	9 (3)	78 (9)
Chronic myeloid leukemia	5 (3)	22 (8)	3
Myelofibrosis	2 (1)	0	32 (4)
Neoplasia	9 (5)	15 (6)	8 (1)
Wilms' tumor	0	11 (5)	6
Carcinomas and solid tumors	9 (5)	3 (1)	2
Peripheral neuroectodermal tumor	0	1	0
Immune	4 (2)	15 (6)	2
Systemic lupus erythematosus	0	6 (2)	1
Autoimmune disease	4 (2)	6 (2)	0
Mixed connective tissue disease	0	1	0
Graft-versus-host disease	0	1	1
Ehlers–Danlos syndrome	0	1	0
Cardiovascular	39 (21)	31 (12)	344 (41)
Congenital and acquired cardiac defects			
Multiple or not defined	24 (13)	0	30 (4)
Ventricular septal defect	0	10 (4)	3
Atrial septal defect	2 (1)	1	5
Aortic stenosis	7 (4)	5 (2)	189 (23)
Mitral valve prolapse	2 (1)	10 (4)	0
Endocarditis	0	0	2
Cardiac assist device	0	0	110 (13)
Angiodysplasia	4 (2)	5 (2)	5
Miscellaneous	16 (9)	78 (28)	41 (5)
Drugs			
Ciprofloxacin	0	2 (1)	0
Griseofulvin	0	1	0
Valproic acid	1	19 (7)	6 (2)
Hydroxyethyl starch	0	11 (4)	0
Infectious diseases			
Hydatid cyst	0	1	0
Epstein Barr virus infection	1	1	0
Hepatitis C	0	0	14 (2)

(*Continued*)

Table 4 (*Continued*)

Underlying disorders	ISTH-SSC registry 2000 (*n* = 186)	Previous literature 1968–1998 (*n* = 266)	German registry 2006–2011 (*n* = 840)
Other systemic diseases			
Hypothyroidism	3 (2)	21 (8)	0
Diabetes	0	7 (3)	0
Uremia	6 (3)	3 (1)	6
Hemoglobinopathies	2 (1)	10 (4)	0
Sarcoidosis	1	0	0
Teleangiectasia	1	0	0
Ulcerative colitis	1	0	0
Liver cirrhosis	0	0	15 (2)
Idiopathic	1	1	5

Abbreviation: ISTH-SSC, Scientific Subcommittee of the International Society on Thrombosis and Haemostasis.
[a]Values indicate numbers of cases (percentages).

myocardial infarction was reported in one patient with type 2A VWD.[26] Thromboembolic complications are rare among hemophilia patients receiving rFVIIa, but it is unclear if this is also true for patients receiving this therapy for AVWS. Caution should be exerted, particularly when treating elderly patients and others at increased risk for thromboembolism.[7,17]

Antifibrinolytic Drugs

The currently available antifibrinolytic drugs are the lysine analogs ε-aminocaproic acid (50 to 60 mg/kg body weight every 4 to 6 hours), tranexamic acid (20 to 25 mg/kg body weight every 8 to 12 hours), and 4-aminomethylbenzoic acid (50 to 100 mg every 6 to 8 hours). These drugs can be administered orally, intravenously, or topically. They are primarily used as adjunct therapies, together with desmopressin or VWF-containing concentrates, for surgery and bleeding in areas of high fibrinolytic activity, i.e., the nose, gastrointestinal, and urogenital tracts. For minor bleeds in these areas, treatment with antifibrinolytics alone may be sufficient. Caution must be exerted in patients with macroscopic or overt hematuria because of the risk of forming an obstruction by urinary tract clots.[17]

Plasmapheresis

Plasmapheresis can be used to reduce the levels of autoantibodies and paraproteins of any immunoglobulin class, although the treatment is more effective in reducing the levels of IgM antibodies. Plasmapheresis has been reported as therapy for patients with AVWS because of IgM-MGUS.[27] When this treatment is given, fresh frozen plasma replacement should be used, instead of albumin, to prevent depletion of fibrinogen and other coagulation factors that could worsen bleeding from AVWS. When the treatment is used for managing severe bleeding, the restoration of VWF levels can be accelerated by concurrent treatment with VWF-containing concentrate or desmopressin.

Treatment Considerations in Relationship to the Underlying Disorder Associated with Acquired von Willebrand Syndrome

Lymphoproliferative Disorders

This group of underlying disorders associated with AVWS accounts for a significant portion of patients (►**Table 4**), based on the ISTH-SSC registry, earlier literature (1968 to 1998), and data collected (2006 to 2011) in Hamburg (German registry) for German patients (Budde, personal data). Mohri et al reported on a prospective study that enrolled 260 patients, of whom 145 had lymphoproliferative disorders; among the patients with lymphoproliferative disorders, 11 (7.5%) had AVWS and 5 of the 11 (45% with AVWS and lymphoproliferative disorders) were active bleeders.[3] Nitu-Whalley et al reported on 17 AVWS patients associated with lymphoproliferative disorders, observed over a 10-year period.[8] In the German registry, 153/840 (18%) patients with AVWS had lymphoproliferative disorders. In the ISTH-SSC registry, 87% of the patients with AVWS were classified as bleeders.[10] Tiede et al reported that, before diagnosis, the 11 patients with AVWS in association with a lymphoproliferative disorder had experienced eight episodes of spontaneous bleedings (two severe): epistaxis; gum bleeding (one severe); and gastrointestinal bleeding (one severe) and provoked bleedings (seven in total, three severe) that occurred postoperatively (three severe) or after dental extractions.[15] During a 2 year follow-up period, all patients reported by Tiede et al remained alive, and their risk for new bleeding was estimated at 11% per year.[15] VWF was clearly decreased in these cases, and in the patient with AVWS and IgG-MGUS, the VWF abnormalities resembled inherited type 2 VWD. In contrast, the patients with IgM-MGUS had

AVWS that resembled inherited type 1 VWD, except for distinct multimer abnormalities associated with AVWS and IgM-MGUS: in these patients, the giant VWF-IgM complexes destroy the agarose gel matrix as they pass through the gel and sometimes these complexes even leave holes.

According to the data reported from the ISTH-SSC registry and other literature, patients with AVWS from lymphoproliferative disorders generally show the most severe bleeding symptoms compared with AVWS from other underlying conditions. For example, one patient with AVWS because of a lymphoproliferative disorder and gastrointestinal bleeding required more than 20 units of packed red blood cells per week (Tiede, personal data). Another such patient, misdiagnosed as having an inherited, severe form of type 1 VWD, experienced life-threatening bleeding complications during surgery that necessitated massive infusion of blood products, in addition to VWF/FVIII concentrates and rFVIIa (Federici, personal data). Data from the ISTH-SSC registry have indicated that AVWS in association with a lymphoproliferative disorder is often difficult to treat; the proportions that responded to different treatments were as follows: 26/59 (44%) for desmopressin; 28/50 (56%) for VWF/FVIII concentrates; 18/48 (38) for high-dose IVIg; 20% (6/30 cases) for plasmapheresis; 10/31 (32%) for corticosteroids, and 17/47 (36%) for immunosuppressive agents or chemotherapy. However, Tiede et al reported successful treatment in 8 out of 10 cases of AVWS in association with lymphoproliferative disorders with higher doses of VWF/FVIII concentrates.[15]

Although AVWS often responds poorly to the standard treatments for inherited VWD, some patients with AVWS do respond well to high doses of IVIG (1 to 2 g/kg body weight) within 2 to 4 days of therapy.[7] A good response can be anticipated in patients with AVWS who have an IgG monoclonal paraprotein, whereas those who do not have an IgG monoclonal paraprotein are much less likely to respond. The correction of the VWF and FVIII deficiencies in patients with AVWS who respond to IVIG is transient and typically lasts for 15 to 21 days. In these patients, larger VWF multimers reappear 24 hours after IVIG and normal levels of VWF and FVIII are typically reached approximately 48 hours after treatment.[7] This normalization is followed by a progressive disappearance of the large and intermediate VWF multimers and FVIII during the following weeks. Although AVWS cannot be cured by IVIG therapy, the duration of the treatment effect is sufficient for surgical intervention in responsive patients. With higher daily doses of IVIG (1 g/kg body weight), the time to achieving adequate VWF and FVIII:C levels can be shortened to approximately 24 hours. Because IVIG prolongs the half-life of VWF in patients with AVWS and IgG monoclonal paraproteins, an initial IVIG infusion followed by VWF/FVIII concentrates is reasonable for urgent situations (e.g., life-threatening bleeding or urgent surgery necessitate rapid correction of the hemostatic defect). In patients with AVWS in association with an IgM monoclonal paraprotein, IVIG is without effect.[7] Silberstein et al reported successful responses to plasma exchange on 11 separate occasions in a patient with AVWS and Waldenström macroglobulinemia.[27] With successful treatment of the primary disease, the AVWS associated with some lymphoproliferative disorders can disappear, as reported for a case of non-Hodgkin lymphoma.[28]

Cardiovascular Diseases

The association of cardiovascular diseases with AVWS has been reported with an increasing frequency during the past 20 years: from 12% in the early literature (31/288), 21% in the ISTH-SSC registry (39/186), to 41% in the more recent reports of the German registry (344/840), as shown in ►**Table 4**. AVWS in patients with congenital heart disease was described in 1986 by Gill et al.[29] The association between aortic stenosis and gastrointestinal bleeding was described earlier, in 1958, as Heyde syndrome.[30] AVWS associated with aortic stenosis has now been reported by many others,[31–43] and the underlying pathophysiological mechanisms is presumed to be the loss of the large VWF multimers from the enhanced shear stress (induced by disturbed flow through the stenotic valve), leading to increased VWF cleavage by ADAMTS13. In the ISTH-SSC registry, the underlying cardiovascular conditions reported to be associated with AVWS have included congenital cardiac defects, aortic stenosis, angiodysplasia, atrial septal defects, mitral valve prolapse, and gastrointestinal angiodysplasia (►**Table 4**). Of patients with these defects and AVWS, 77% were classified as bleeders.

In a recent retrospective study by Tiede et al, the underlying conditions associated with AVWS included aortic valve stenosis, aortic valve replacement, aortic and mitral valve replacement, and cardiac devices.[15] These authors reported that among the 16 patients with AVWS associated with cardiovascular disease, 10 had spontaneous bleeding (five severe), commonly epistaxis, gum bleeding, and gastrointestinal bleedings (three severe) and 11 had experienced provoked bleeding episodes (nine severe), mostly postoperative bleeding (seven severe) and bleeding after tooth extractions (two severe). During the 2-year follow-up of these patients, 50% remained alive, but none had died because of bleeding. The risk of new bleedings was 19% per year and 34% had required surgical procedures within 1 year after diagnosis. The increased shear stress that arises as a result of these cardiovascular disorders can induce two chronic changes in VWF with opposite effects. On the one hand, there is an increased concentration of VWF in the circulation, with a secondary increase of FVIII that may increase the risk of thrombosis. On the other hand, there is also a loss of large VWF multimers, induced by abnormal high shear stress, that is thought to cause bleeding by impairing platelet adhesion and aggregation. Although the defect in VWF-dependent platelet function can be silent, it often becomes apparent when patients acquire additional defects of hemostasis and/or are challenged by surgery or dental extractions. This clinical situation occurs in patients who require oral anticoagulation after heart valve replacement or after experiencing venous thrombosis, unexpectedly develop life-threatening cerebral hemorrhage shortly after the start of anticoagulation. At the same time, the FVIII levels in such patients are an established risk of venous thrombosis, whereas high VWF levels are a risk factor for arterial thromboembolic complications.

Because the mechanism of AVWS associated with cardiovascular disorders is related to the loss of HMW multimers, it

is not surprising that inhibitors have been detected only in a minority of patients: Tiede et al detected inhibitors in 2/27 samples tested (7%)[15]; and in the ISTH-SSC registry, they were detected in 2/39 tested (5%).

Data from the ISTH-SSC registry showed that many of the available treatment options for AVWS are generally unsuccessful for AVWS associated with cardiovascular disease as the proportion responding to treatment were as follows: 3/30 (10%) for desmopressin; 4/30 (13%) for VWF/FVIII concentrates; 2/25 (8%) for corticosteroids; with no responses to IVIG (10 patients) and plasmapheresis (2 patients).[10] In contrast to the registry data, Tiede et al reported a treatment success rate of 70% among ten patients with AVWS associated with cardiovascular disease with VWF/FVIII concentrates[15]: the increased rate of efficacy with VWF/FVIII concentrates is probably related to the higher (80 to 100 U/Kg) doses and/or intensive regimens used. Desmopressin has theoretical advantages over VWF/FVIII concentrates for such patients in that the secretion of endogenous ultralarge multimers, and their immediate availability at the site of bleeding would be expected to improve local hemostasis more than exogenous VWF/FVIII concentrates that lack ultralarge VWF multimers. Nevertheless, VWF/FVIII concentrates have been proven effective in many patients, especially when they are used at higher dosage and/or when are given more frequently.

Thrombocythemia and Other Myeloproliferative Neoplasms

Patients with AVWS associated with essential thrombocythemia and other myeloproliferative neoplasms (MPNs) constitute a significant proportion of the patients described in the ISTH-SSC registry (29/186, 15%) and other literature (48/288, 18%) (►**Table 4**). Tiede et al reported just 1/35 (3%) patient.[15] In the study of Mohri et al,[3] among 125 patients with MPNs, 14 (11%) showed AVWS and 2 of them were classified as active bleeders (14%). Among the 99 patients with AVWS reported by Sanchez-Luceros et al,[44] MPN was found in 75%. In the German registry, AVWS was found in 286/840 (34%) of patients with MPNs. VWF abnormalities in MPNs have been investigated in several studies.[44–56]

Most patients investigated in these studies were not actively bleeding and were tested mainly to confirm the diagnosis or to plan therapy for surgery or trauma, which explains the relatively high prevalence of AVWS compared with other studies. Thrombosis and bleeding, in some instances occurring simultaneously in a patient, are frequent complications of MPNs. The sites and intensity of bleeding symptoms mimic those seen in inherited VWD.[15,17] Gastrointestinal bleeding followed by soft tissue bleeding and intra- or postoperative bleedings are the most common symptoms among patients with AVWS associated with MPNs. Whether a given patient suffers from thromboembolism or bleeding is strongly dependent on the platelet count. At platelet counts ranging from 400 to less than $1{,}000 \times 10^9$/L, thromboembolism is the more common complication, whereas bleeding clearly predominates with platelet counts above $2{,}000 \times 10^9$/L. Between 1,000 and $2{,}000 \times 10^9$/L, both complications may occur and even simultaneously.[15,17] In the data from the ISTH-SSC registry, less than half of the patients with AVWS and a MPN (48%) were classified as bleeders.

The large multimers nearly always show an absolute or relative reduction in such patients, mimicking the findings in congenital type 2A VWD: in medium-resolution gels, some samples of patients with AVWS show changes to the "subbanding pattern" similar to congenital type 2A VWD caused by increased proteolysis of VWF.[45–48] There is now evidence that this change to multimer banding in some patients with AVWS and MPNs also reflects enhanced proteolysis of VWF.[51]

Inhibitors against VWF are uncommon in AVWS associated with MPNs, with the study of Mohri et al[3] reporting inhibitors in 1/14 (7%) and the ISTH-SSC registry reporting inhibitors in 1/26 (4%). MPN rarely occurs in children, but it may be complicated with thrombotic and hemorrhagic events, like MPNs in adults. Data from the ISTH-SSC registry showed relatively poor responses to all treatment options for most patients with AVWS and MPNs: 3/14 (21%) responded to desmopressin; 2/14 (14%) responded to VWF/FVIII concentrates, and 5/14 (36%) responded to immunosuppressants or chemotherapy. The treatment with VWF/FVIII concentrates and desmopressin infusion usually rapidly stops the bleeding complications. Normalization of VWF in persons with MPNs may, however, result in thromboembolic complications. Moreover, the newly secreted or infused normal VWF is altered rapidly, like endogenous VWF. Therefore the correction from treatments lasts for much shorter times than treatment for congenital VWD. If severe bleeding complications occur in patients with MPNs and AVWS, cytoreduction with hydroxyurea, anagrelide, or interferon α is indicated. Typically, after normalization of the platelet count, the VWF normalizes and the hemorrhagic diathesis disappears.[45–48]

Other Neoplasms

AVWS is a rare complication of patients with solid tumors (►**Table 4**) that occurs in approximately 6% of AVWS patients reported in the literature (15/266) and in 5% reported in the ISTH-SSC registry (9/186). AVWS in cancer patients has been described most frequently in patients with Wilms' tumor (nephroblastoma), and the clinical features are not always benign.[57,58] In the German registry (Budde, personal data), there were only three patients with carcinomas and AVWS with mild symptoms (►**Table 4**). In the ISTH-SSC registry, 75% of the patients were classified as active bleeders and among the patients tested for an inhibitor, one of three (33%) had a circulating inhibitor detected. Data from the ISTH-SSC registry showed that most treatment options are quite successful for patients with cancer and AVWS: three fourths responded to desmopressin; all six patients treated with VWF/FVIII concentrates responded to treatment; two patients responded to treatment with IVIG; and one of two patients responded to immunosuppressive agents or chemotherapy.[10] Based on available reports, most patients with AVWS in association with Wilms' tumor do not bleed whereas about one third have only mild symptoms that can easily be controlled with desmopressin. In patients with solid tumors and carcinomas, mild symptoms also predominate and desmopressin is therefore the drug of choice. Although not many

cases have been reported, AVWS always disappeared following successful treatment of the primary disease.

Immunological Diseases

Although AVWS was first described in patients with SLE and autoantibodies to VWF, in the literature, only small numbers of cases of AVWS associated with immunological diseases have been described, usually in association with SLE (six patients), autoimmune diseases of another etiology (six patients), and very rarely with mixed connective tissue disease (one patient) and graft-versus-host disease (one patient) (►**Table 4**). Recently, additional cases were described.[59] In the ISTH-SSC registry, 75% of patients with AVWS associated with immunological disease were classified as active bleeders.[10] Although VWF is theoretically a target protein in immunological diseases, autoantibodies to VWF are rare and were detected in two out of eight patients in the registry (25%). ISTH-SSC registry data indicate that the treatment is often not very successful: one out of four patients was treatable with desmopressin (25%) and one out of two patients treated responded to IVIG (50%).[10] Whenever an autoantibody has been reported to induce AVWS, the symptoms have been severe. In these patients, VWF is very rapidly removed from the circulation and therapies such as desmopressin and IVIG frequently fail. Bleeding that cannot otherwise be controlled warrants consideration of rFVIIa, at the usual dose of 90 µg/kg body weight or higher.[17]

Acquired von Willebrand Syndrome in Patients with Other Diseases

Other miscellaneous conditions associated with AVWS are listed in ►**Table 4**, and several references provide data on such patients.[60–72] In the data from the ISTH-SSC registry, 57% of the patients were classified as bleeders and the risk of new bleeding episodes was 27%/year;[10] Notably, in 27% of the patients, surgical procedures were required within 1 year after diagnosis.[17] Because of the high risk of new bleeding episodes and the necessity to make plans for controlling bleeding with surgery for many patients in this group, it is important to establish their AVWS diagnosis.[17]

Current Issues and Future Perspectives on AVWS

Compared with acquired hemophilia, AVWS is remarkably heterogeneous and the pathogenic mechanisms remain undefined in many cases. An updated version of the International Registry on AVWS has been established on line (www.intreavws.com) and will be available by July, 2013 as an interactive AVWS registry to promote the registration of new cases and discussions with experts about appropriate diagnostic and therapeutic approaches within 24 to 48 hours of a case submission. The aim is to gain a better understanding of the basic mechanisms of AVWS (through the use of new assays), an improved understanding of the limits of standard therapies for AVWS, and the efficacy of novel and experimental therapeutic approaches for this syndrome. Experts on AVWS are encouraged to work with other physicians and specialists to design appropriate diagnostic screening algorithms for patients at risk of bleeding. The authors encourage individuals to submit new interesting cases to this online registry to promote this international, investigator-driven, prospective study on AVWS, which has been organized on behalf of the VWF SSC of the ISTH.

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