Review Article

Acquired von Willebrand Syndrome: A Comprehensive Review and a Nordic Perspective

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ABSTRACT

Acquired von Willebrand syndrome (AVWS) is a rare condition characterized by an acquired functional and/or absolute deficiency of the von Willebrand factor (VWF) protein. The absence of widely accepted diagnostic criteria has hampered accurate estimates of incidence and prevalence, which are largely currently unknown. As bleeding symptoms are not included in the most widely used definitions, AVWS should be managed as a risk factor for bleeding, rather than a specific disease entity. The diagnostic workup is cumbersome, involving measurement of both VWF antigen, VWF glycoprotein Ib binding activity, VWF collagen binding activity, and, preferentially, also VWF multimer analyses. Moreover, since the presence of bleeding symptoms is not required for diagnosis, the condition is probably underdiagnosed. In contrast to acquired hemophilia, AVWS is seldom caused by the presence of specific antibodies, but rather secondary to another disorder, most commonly lymphoproliferative, myeloproliferative, cardiovascular, and autoimmune disorders. Pathogenesis of AVWS varies according to the underlying disorder and includes nonspecific adsorption of VWF to antibodies, adsorption onto surfaces of neoplastic cells, mechanical injury, or VWF proteolysis. Treatment includes treating the underlying cause as well as stopping acute bleeds. Here, we present a comprehensive review of what is currently known regarding demographics, diagnostics, and clinical presentation of the syndrome. Since no prospective treatment studies have been performed, treatment choices must be based on data from registries and case reports that are also summarized. Moreover, we present treatment experiences of previously unpublished Nordic cases.

Keywords acquired coagulation disorders, inhibitors, bleeding, management, VWF

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Acquired von Willebrand syndrome (AVWS) is a rare bleeding disorder that presents unique diagnostic and clinical challenges. Unlike inherited forms of the disease, AVWS often remains undiagnosed, as not all patients exhibit overt bleeding symptoms, even though they may be at significant risk of bleeding complications. The diagnostic process for AVWS can be challenging, requiring a thorough evaluation to differentiate it from other bleeding disorders. This review focuses on the treatment of AVWS from a Nordic perspective, with particular attention to hematologic diseases that commonly underlie this acquired condition. It emphasizes the complexity of diagnosing and managing AVWS, as well as the importance of early suspicion in patients at risk.

Epidemiology

AVWS is a rare but probably underdiagnosed bleeding disorder characterized by an acquired deficiency or structural change of the von Willebrand factor (VWF) protein. The true prevalence is unknown and yet to be formally established. AVWS was first described in 1968 in a young man also diagnosed with systemic lupus erythematosus (SLE).[1] The first reported case in Sweden was 10 years later in a 67-year-old man with multiple myeloma.[2] Since then, over 700 cases have been reported in the literature, but there are yet no broadly accepted diagnostic criteria. Most studies use a definition requiring levels of either plasma VWF antigen (VWF:Ag) or VWF activity using a glycoprotein Ib binding assay (VWF:GPIbB) below the normal range in the absence of evidence to suggest congenital von Willebrand disease (VWD)[3]; however, reduced levels of VWF collagen binding activity (VWF:CB) as well as abnormal values of VWF:GPIbB/Ag and VWF:CB/Ag ratios (ratio < 0.6) may be included in the definition of the syndrome.[4] VWF-activity in this manuscript usually refers to platelet-dependent activity, mainly VWF:GPIbM or VWF:GPIbR, since VWF:RCo has been replaced in the Nordics, in alignment with recent guidelines. However, VWF-activity can also describe VWF collagen binding and VWF FVIII binding. In AVWS, VWF-activity as platelet-

dependent activity and collagen binding activity usually align, and VWF activity/Ag ratios for both will be normal in AVWS of a type 1 VWD-like defect, and both will be low in a type 2 VWD-like defect.[5] The more recently published studies on AVWS associated with myeloproliferative disorders use four diagnostic criteria: VWF-activity level below the lower reference limit, VWF-activity/VWF-Ag ratio < 0.7, often no personal or family history of bleeding disorders, and no long-term history of frequent or abnormally prolonged episodes of bleeding.[6–8] Importantly, present bleeding symptoms are not included in the most recent diagnostic criteria. There is an increased attention to AVWS and its association with cardiovascular disorders and with the use of circulatory support devices.[9] AVWS is generally associated with an underlying disorder, and according to the 2000 report from the International Society on Thrombosis and Haemostasis (ISTH) registry of AVWS, lymphoproliferative disorders (48%), followed by cardiovascular (21%) and myeloproliferative (15%) disorders, are the most common underlying causes. Solid tumors and autoimmunity are reported at a frequency of 5 and 2% in AVWS, respectively. AVWS occurs in all age groups according to the underlying disorder, but is most frequent among the elderly. The median age of 62 years (range: 2–96) with a similar distribution between males and females was reported by the ISTH AVWS registry.[10]

Pathophysiology

AVWD is an acquired bleeding disorder of multifactorial etiology.[11] The symptoms are often reversible if the underlying cause is removed. Differentiating acquired from congenital VWD requires the same test panel and is important since management differs, but AVWS might be overlooked in patients with VWF antigen and activity levels above the cut-off for VWD.[12]

There are several mechanisms involved in the pathogenesis of AVWS.[12–15] These cause quantitative and qualitative defects in VWF with four major different subtype patterns dependent on the underlying cause of the condition. The most common mechanism is described first:

1. Adsorption of VWF onto cell surfaces (myelo- and lymphoproliferative neoplasms, thrombocytosis).

Increased platelet count is the major pathophysiological explanation for increased VWF binding to cell surfaces, resulting in consumption of large VWF multimers. Increased viscosity might also lead to high shear stress and accelerated proteolysis in this patient category.

Expected laboratory phenotype: type 2 being the dominant subtype with loss of high molecular weight VWF multimers (HMWM).

2. Mechanical destruction of VWF (congenital or acquired heart defects, such as aortic stenosis, left ventricular assist devices [LVAD], and extracorporeal membrane oxygenation [ECMO] devices). Shear stress-induced loss of HMWM VWF is the major mechanism in the case of stenotic valves and device-related AVWS. Also, proteolysis of VWF occurs as it passes through a stenotic valve, or platelet activation, resulting in adsorption of HMWM, which are possible mechanisms that reduces VWF activity more than the VWF antigen levels. In aortic stenosis, there is a correlation between in vivo shear stress and the loss of multimers.

Expected laboratory phenotype: type 2 subtype with loss of HMWM.

3. Autoantibody-mediated VWF clearance (i.e., autoimmune disorders, monoclonal gammopathy of undetermined significance [MGUS], multiple myeloma, lymphoproliferative neoplasms).

Autoantibodies, predominantly of the IgG subclass, might bind to the functional epitopes of VWF and neutralize its activity. Epitopes against collagen binding and platelet GPIb receptor have been described, preventing VWF from binding to collagen or platelets, respectively. Alternatively, IgM antibodies may form immune complexes with VWF and thereby accelerate its clearance. VWF antigen, VWF activity, and FVIII are reduced.

Expected laboratory phenotype: type 1, 2, or 3 subtype.

4. Moderate to mildly reduced VWF synthesis or secretion may occur in hypothyroidism. This form of AVWS is reversible after treatment of the hormonal dysfunction[16,17] and of limited clinical importance.

Expected laboratory phenotype: type 1 subtype predominant.

Take Home Messages

- There are several mechanisms involved in the pathogenesis of AVWS that cause quantitative and qualitative defects in VWF.
- The subtype patterns are dependent on the underlying cause of the condition, but type 2 is the most common.

Laboratory Diagnosis

Test Panel

Essentially, the same tests used to initially diagnose or rule out VWD are also used to detect AVWS (**Table 1**), including FVIII:C. The laboratory diagnosis of a type 2 AVWS is primarily characterized by low VWF activity in comparison to the amount of VWF antigen. A selective decrease in VWF activity indicates loss of HMWM (the most active VWF molecules) or, more rarely, the presence of inhibitory antibodies. The activity of VWF should be measured with tests that can demonstrate the ability of VWF to bind to both the platelet receptor GPIb and to collagen.[18] Although VWF:RCo methods are still used elsewhere, they are no longer recommended in guidelines[5] and are no longer available in laboratories in the Nordic countries.

A reduced VWF activity can be confirmed by a specific analysis of the molecular size distribution of VWF (i.e., the VWF multimer pattern), which can be defined with different size ranges (low, intermediate, and high). Ratios of VWF activity/antigen are useful when the results of the various tests are evaluated. It is not possible to set a specific cut-off value that can detect AVWS with any great certainty, but a low ratio, <0.7, is a strong indication that VWF activity is selectively reduced in comparison to the antigen level, even if the absolute VWF activity is not low enough

Table 1 Confirmatory test procedures in acquired von Willebrand syndrome

Measurand	Test name (abbreviation)	What is measured and how	Expected changes in AVWS
First line of confirmatory test procedures			
Coagulant activity of FVIII	FVIII:C	The functional activity of FVIII. Can be measured with a one-stage clotting assay (i.e., APTT-based) or with a chromogenic substrate assay	The activity is correlated with the VWF level. AVWS will usually not have a direct influence on the FVIII activity
VWF antigen	VWF:Ag	The mass concentration of VWF in plasma (irrespective of molecular size). VWF:Ag is usually measured with a latex immunoassay or with a chemiluminescence-based method	Most often, the least affected VWF parameter, but it depends on the pathophysiology of AVWS. Thus, VWF:Ag can be low (reduced biosynthesis or increased clearance), normal, and even high in some conditions (acute phase condition)
VWF binding capacity for (recombinant) GPIb	VWF:RCo or VWF:GPIbR or VWF: GPIbM	Measures the ability of VWF to interact with the platelet receptor GPIb. The activity is measured by agglutination of platelets (VWF:RCo), or beads coupled to recombinant GPIb (VWF:GPIbR). With the VWF:GPIbR assay, the wild-type GPIb protein is used, and the agglutination takes place in the presence of ristocetin. VWF:GPIb can also be measured by a chemiluminescence-based method. VWF:GPIbM utilizes recombinant mutated GPIb (gain-of-function) that are able to interact with VWF without ristocetin	Usually disproportionately low compared with VWF antigen (ratio < 0.7). Inhibitory antibodies may have a selective effect on only one of these VWF activity assays
VWF binding capacity for collagen	VWF:CB	Measures the ability of VWF to interact with collagen. The most common assay type is based on the enzyme-linked immunosorbent assay (ELISA), but a bead-based chemiluminescence-based assay is available. Different assays may contain different types of collagen, which differ in specific VWF binding activities	Usually disproportionately low compared with VWF antigen (ratio < 0.7). Inhibitory antibodies may have a selective effect on only some VWF activity assays
Second line of confirmatory tests			
VWF multimer size distribution	VWF multimer	The assay is based on the separation of VWF protein size by agarose gel electrophoresis. The protein bands (multimer pattern) are then visualized by immunoblotting procedures or direct visualization on the gel. Time-consuming and laborious assay, not readily available. There are several different in-house methods and one commercial semi-automated system available	Sensitive to loss of bands of specific sizes and for various structural abnormalities of the VWF multimers. AVWS will most often result in loss of the VWF multimers of the largest molecular sizes. More rarely, the multimer pattern is normal, which may be seen in AVWS caused by decreased biosynthesis
VWF propeptide antigen	VWFpp	A marker of VWF biosynthesis is measured with ELISA. An increased clearance of VWF is seen as an increased VWF propeptide to VWF antigen ratio	With few exceptions, the VWFpp/VWF:Ag ratio is markedly higher in most types of AVWS (higher than what can be seen in type 2 VWD and most type 1 VWD except type 1C/Vicenza). Thus, the VWFpp assay may be helpful to discriminate between AVWS (and type 1C/Vicenza) from most other VWD types
Inhibitory antibodies against VWF	anti-VWF antibodies (VWF inhibitor)	Measures antibodies that neutralize one or more of the VWF activities (inhibitors). Inhibitory antibodies are most often detected with a standard Bethesda mixing procedure, where the patient's plasma is mixed with a normal plasma with a known concentration of VWF activity. After mixing, the VWF activity is measured, and the degree of inhibition is calculated. It is important to measure both GPIb-binding activity and collagen-binding activity, as some antibodies only inhibit one of these activities. There are also other mixing protocols that are better to use if the patient sample contains endogenous VWF activity	Unlike other acquired coagulopathies, an autoimmune AVWS is quite rare. Antibodies against VWF form antibody-VWF complexes that may be rapidly cleared from the circulation. When the antibodies are directed against VWF epitopes important for the VWF functions, they can be detected by decreased VWF activities and low VWF activity/antigen ratios

Abbreviations: APTT, activated partial thromboplastin time; AVWS, acquired von Willebrand syndrome; FVIII, factor VIII; FVIII:C, factor VIII coagulant activity; VWF, von Willebrand factor; VWF:RCo, von Willebrand factor ristocetin cofactor activity.

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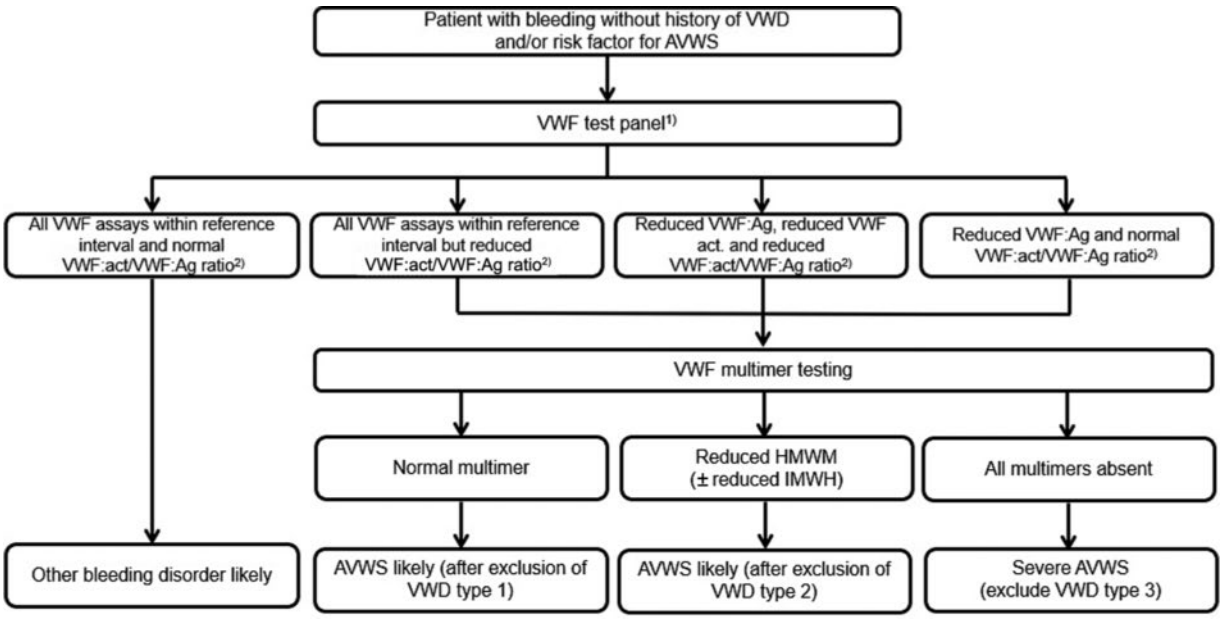

Fig. 1 Diagnostic algorithm for AVWS. The figure only illustrates the confirmatory tests used in the investigation of AVWS. Appropriate initial tests (e.g., activated partial thromboplastin time (APTT), prothrombin time (PT)/international normalized ratio (INR), platelets, blood count, C-reactive protein (CRP), etc. must always precede a more specific investigation of increased bleeding tendency. The detection of anti-VWF antibodies is not indicated in the figure. Autoimmune AVWS and other causes of AVWS may have similar symptoms and laboratory findings, and the initiation of an investigation with anti-VWF assays must be taken in close context with the patient's history. Antibodies are more likely to occur in patients with various hematological disorders and carcinoma, and less likely in patients with cardiovascular-related AVWS (including stenosis and implanted circulatory devices). HMWM, high molecular weight multimers; IMWH, intermediate molecular weight multimers.
[1]Basic test panel is FVIII:C, VWF:Ag, VWF:RCo or VWF:GPIbR or VWF:GPIbM, and VWF:CB (see **Table 1**). VWF: act indicates any of the platelet-GPIb-dependent (VWF:RCo or VWF:GPIbR or VWF:GPIbM) and the collagen-binding (VWF:CB) activity tests.
[2]Low levels of VWF activity compared with VWF antigen are currently the most accurate test for most variants of AVWS. A threshold value of < 0.7 can be used as an indicator for a selective loss of HMWM or the presence of inhibitory VWF antibodies.

to indicate a form of VWD.[12,19] Thus, a low VWF activity/antigen ratio may suggest a qualitative VWF defect similar to type 2 VWD and further evaluation with VWF multimer analysis or, if autoimmunity may be involved, the analysis of anti-VWF antibodies (**Fig. 1**). AVWS variants that produce a typical quantitative defect (impaired biosynthesis) are similar to type 1 VWD, where all VWF tests are reduced to approximately the same degree, VWF activity to antigen ratios are above 0.7, and the VWF multimer pattern is normal. This heterogeneity shows the importance of always evaluating the laboratory results against the patient's clinical picture.

In recent years, analysis of VWF propeptide (VWF:pp) has shown potential to distinguish between VWD and AVWS.[20] The propetide is a large polypeptide (100 kDa) generated in connection with the release of VWF in plasma, and its concentration can be measured by a specific immunoassay. By calculating the VWF:pp/VWF:Ag ratio, it is possible to facilitate the identification of patients with a reduced half-life of VWF. Unfortunately, the VWF:pp test is currently only available in a few laboratories in the Nordic countries.

VWF Multimers

The physiological activity of VWF correlates with multimer size, the largest multimers being the most potent VWF molecules in terms of receptor (GpIb) and collagen binding.

VWF multimer analysis is a method that evaluates the multimer pattern in plasma. Generally, VWF multimers are divided into: low molecular weight multimers (LMWM), intermediate molecular weight multimers (IMWM), and high molecular weight multimers (HMWM). Of greatest interest is to look at the high and intermediate multimers, which may be selectively missing in qualitative VWD or AVWS. VWF multimer analysis is not widely available, but samples are most commonly sent to the few laboratories that perform either an in-house or a commercial semiautomated method.

Detection of Anti-VWF Antibodies

Antibodies against VWF are a rare cause of AVWS, and these can be identified as inhibitory or noninhibitory antibodies, depending on the test method. An inhibitor is a polyclonal high-affinity immunoglobulin, usually of isotype G (IgG) antibody, which specifically neutralizes the activity of the target factor. Thus, inhibitors against VWF can be detected as the capacity to neutralize the platelet GPIb-binding (VWF:GPIbM or VWF:GPIbR) and/or collagen-binding (VWF:CB) activities. The test procedure to detect inhibitory antibodies is most often based on the Bethesda mixing study protocol, similar to the inhibitor testing of acquired hemophilia A.[21,22] By definition, a residual activity of 50% equals 1 Bethesda unit (BU). The Bethesda protocol is considered positive when the calculated titer is > 0.5 BU/mL and works best when the patient's plasma contains no or very little endogenous VWF activity. Variants of the Bethesda protocol

have been described that account for situations when patient plasma contains significant VWF activity.[23,24]

Noninhibitory anti-VWF antibodies are detected by immunological assays. A common procedure is the enzyme-linked immunosorbent assay (ELISA), where pure VWF antigen is adsorbed to the plastic surface of the wells in microplates.[24,25] The protocol allows for isotype-specific assays. Variants of the immunoassays exist and can be based on simpler immunoblotting or more advanced multiplexing and fluorescent immunoassay systems. The immunoassay detects both inhibitory and noninhibitory antibodies, but it is the only assay that can detect antibodies against VWF that do not result in reduced VWF activities. The rationale for the noninhibitory assay is to identify antibodies that cause AVWS through accelerated VWF clearance. Such antibodies are seldom idiopathic and have mainly been associated with hematological diseases. The tests used to detect anti-VWF antibodies are based on various in-house methods, and the immunological assays are not readily available.

Pitfalls and Challenges in the Laboratory Diagnostics

The diagnosis of AVWS is complex and requires extensive laboratory evaluation due to the heterogeneity of the disease. Furthermore, clear preanalytical guidance regarding blood sampling, handling, and transportation should be provided.[18,26] Early diagnosis might be difficult, and AVWS is often overlooked in patients with VWF antigen and activity levels above the cut-off for VWD (typically around 50 U/dL), emphasizing the importance of VWF activity/Ag ratios, and if available, multimer analysis in all patients with suspected disease. The laboratory phenotype may vary between the different causes of AVWS. Although most patients exhibit a type 2 VWD pattern, type 1 as well as type 3 patterns may be seen. Sometimes, differentiation from inherited VWD is difficult in young adults and children with AVWS. Indeed, type 1 VWF deficiency is typical in hypothyroidism due to decreased synthesis of the VWF protein. In children with Wilms tumor, AVWS is characterized by undetectable or very low levels of both VWF antigen and activity, a moderate deficiency of factor FVIII coagulant activity (FVIII:C), and a normal VWF multimer pattern consistent with AVWS type 1 or lack of VWF consistent with AVWS type 3.[27] Therefore, interdisciplinary collaboration and complex laboratory evaluations are of paramount importance for the early recognition of AVWS and the selection of appropriate clinical management protocols.

Finally, there is no definitive association between any assay abnormality and bleeding symptoms. The VWF activity is usually less impaired in LVAD-related VWD than in congenital VWD (2A or 2B), but the loss of HMWM is the diagnostic hallmark of AVWS in LVAD.[15] However, not all LVAD patients with the loss of HMWM bleed. In summary, the interpretation and implementation of novel VWF assay tools calls upon active interaction between clinicians and the laboratory and tailored diagnostic work-up for certain patient groups.

Take Home Messages

- In principle, the same selection of tests is used to detect AVWS as used to diagnose hereditary VWD.
- In suspected autoimmunity, the test battery can be supplemented with assays to analyze inhibitory as well as noninhibitory anti-VWF antibodies.
- Analysis of VWF activity/Ag ratios and multimer patterns may be extra instructive because patients with AVWS sometimes exceed the cut-offs used in hereditary VWD for VWF antigen and activity tests.

Clinical Presentations

The clinical findings of AVWS are similar to those of congenital VWD,[28] with the exception that they usually occur late in life, typically with an acute onset of mucocutaneous bleeds in a person without a family history of bleeding symptoms and no history of prolonged bleeding in previous hemostatic challenge procedures.[29] Mucocutaneous bleeding, mainly from gastrointestinal (GI) or genitourinary tracts, is the most commonly reported bleeding site, followed by severe bleeding after tooth extraction and profuse and frequently relapsed nose bleedings.[30] The severity of bleeds depends on the underlying cause of AVWS and the degree of VWF functional deficiency.[29]

Underlying Disorders

1. Hematologic disorders:

Lymphoproliferative Disorders (LPD)

LPD is the largest group of underlying disorders associated with AVWS, accounting for approximately 50% of the reported cases of AVWS, with mild-to-life-threatening bleeding tendency. These can be further subdivided into lymphocytoid and plasmacytoid disorders, depending on the underlying cell line.

Waldenstrom Macroglobulinemia (WM)

In a French cohort, AVWS-WM was the most common (58%) underlying cause of AVWS out of the lymphoproliferative disorders, whereas in the ISTH registry, MGUS was the predominant LPD diagnosis.[10] In one study, AVWS occurred in 15% of patients with WM and usually presented in patients with elevated IgM levels (30–60 g/L).[31] Bleeding usually resolves with WM-treatment.[32]

Monoclonal Gammopathy of Undetermined Significance (MGUS)

MGUS was the most common LPD as the underlying cause of AVWS in the ISTH registry.[10] In a review from 2021 including 137 patients, bleeding severity ranged from no bleeding (16.1%) to minor bleeding (46.4%) and major bleeding (37.5%). In 90% of cases, low FVIII:C and VWF activity levels, with a pattern similar to type 2A VWD, were detected.[33]

Multiple Myeloma (MM)

AVWS seems to be relatively common in MM; in a study from Thübingen, Germany, including 164 patients with MM/plasma cell disease, 68 had bleeding symptoms (52.4%), 29 (33.7%) had low VWF laboratory test results, and in 16 patients (9.7%), VWF

multimeric analysis showed a relative decrease in the large VWF multimers.[34]

According to the ISTH registry on AVWS, the disorder is also associated with chronic lymphocytic leukemia (CLL), 3%, hairy cell leukemia (HCL), and non-Hodgkin lymphoma (NHL) 4%.[10,35,36]

Amyloidosis (AL)

AL is a rare disease of abnormal protein deposition in tissues and organs. In 2007, Boston Medical Centre reported four patients with bleeding diathesis in amyloidosis caused by AVWS with partial or total absence of HMW multimers, with improvement of symptoms after treatment of amyloidosis.[37]

Myeloproliferative Neoplasms (MPNs)

The prevalence of AVWS in MPNs is high; in 2015, Mital et al described three cohorts, one with essential thrombocythemia (ET; 170 patients), one with polycythemia vera (PV; 142 patients), and one with myelofibrosis (32 patients), with prevalence of AVWS of 20, 12, and 16%, respectively. In a later, slightly smaller study of 116 patients with ET and 57 patients with PV, the prevalence was 55 and 49%, respectively,[38–41] and in a Korean study from 2023, the prevalence of AVWS in ET was 41 and 18% in PV.[8] However, these patients do not always bleed; in fact, in the ISTH registry, less than half of the patients with AVWS and a MPN (48%) were classified as bleeders.[10] MPN-associated AVWS has primarily been linked to platelet counts $> 1{,}000 \times 10^9$/L, where abnormal binding of the VWF HMW multimers to the platelet GpIb receptor is thought to be the primary underlying mechanism.[3,4] The most usual finding will thus be a phenotype resembling VWD type 2A with VWF:activity/Ag < 0.7 and absence of HMW multimers. In addition, normalization of the platelet count has been shown to restore VWF multimeric composition.[6,7] Therefore, most guidelines advise testing for AVWS in patients with a platelet count higher than $1{,}000 \times 10^9$/L.[7–9] However, AVWS has also been described in patients with platelet count $< 1{,}000 \times 1010$, indicating the presence of alternative mechanisms such as direct action of the JAK-2 V617F mutation[1,4,42] or the presence of antibodies, which either interfere with VWF activity or enhance its clearance.[3,4,11] Treatment of these patients is complicated by the fact that concomitant thrombosis is frequent in this group of diseases,[43,44] which is described to be associated with the presence of the JAK-2 V617F mutation.

Chronic Myeloid Leukemia (CML)

A study from Dresden reported that out of a cohort of 146 children with CML, 55% had thrombocytosis (platelet count $> 500 \times 10^9$/L), 12% of these had bleeding, compared with 6% in patients with regular platelet count. Retina bleeding, menorrhagia, bleeding after tooth extraction, and multiple hematomas were reported. In the four patients that were investigated, there was a loss of HMW multimers in plasma, which recovered after specific treatment and normalization of platelet counts.[45]

2. Solid tumors:

AVWS can occur in patients with solid tumors, primarily Wilms' tumor. In a prospective, single-center study of 50 consecutive children newly diagnosed with Wilms tumor, the incidence of AVWS was found to be 4/50 (8%) as determined by coagulation test screening. Two patients were diagnosed with AVWS type 2, two with AVWS type 3, and none of the patients presented with bleeding symptoms.[46] A retrospective study identified a prolonged activated partial thromboplastin time (APTT), presumably due to lowered FVIII:C, in 19/47 patients with Wilms tumor, and 2/19 fulfilled diagnostic criteria for AVWS.[47] Several other case reports have described bleeding diathesis at the time of diagnosis and during surgery.[48–55] In all cases, laboratory values and clinical bleeding symptoms resolved following chemotherapy and/or surgery.

There are also sporadic reports of AVWS diagnosed in patients with peripheral neuroectodermal tumor,[56] adrenal cortical carcinoma,[57] hepatocellular carcinoma,[58] clear cell renal cell carcinoma,[59] epithelial myoepithelial carcinoma of the parotid salivary gland[60] and Ewing sarcoma.[61]

3. Cardiovascular diseases:

Edward Heyde first described the association of aortic stenosis and recurrent gastrointestinal bleeding in 1958, and in 1992, it was proposed that the lack of HMWM of VWF leading to AVWS and gastrointestinal angiodysplasia was the cause of the bleeding.[62,63] Since then, AVWS has been reported in a variety of cardiovascular diseases, mainly in association with high shear rates and stress.

Congenital Heart Diseases (CHD)

AVWS has been described in congenital heart diseases (CHD) with vascular lesions at a prevalence of 9 to 50%. In 2014, a comparative study of 50 children with stenotic and nonstenotic CHD reported that 50% of patients in the stenotic group lacked HMWM of VWF, which was resolved following intervention or surgery. However, none had bleeding complications.[64] Another 2014 study of 192 adults with CHD identified laboratory evidence of AVWS in 20.8% of subjects, most commonly in complex CHD and Eisenmenger syndrome.[65] In a 2016 study of 60 children with congenital pulmonary or aortic stenosis, AVWS was identified in 9 and 14%, respectively, but only 2 (28%) of those had bleeding symptoms.[66] Finally, a 2023 study of 65 newborns and infants undergoing cardiac surgery reported intraoperative AVWS in 37% with associated increased use of hemostatic aids.[67] Currently, the association between laboratory diagnosis of AVWS in CHD and bleeding complications is not well established, especially in these often complex diseases.

Aortic Stenosis

Following Heyde's original report, the triad of aortic stenosis, bleeding from gastrointestinal angiodysplasia, and AVWS was designated as Heyde's syndrome. In these usually elderly patients, repeated bleeding episodes lead to refractory anemia, red blood cell transfusions, decreased quality of life, and increased morbidity and mortality. A pivotal study in 2003 of 42 patients reported bleeding in 21% of patients with severe aortic stenosis and reduced VWF HMWM in 79%. These resolved within 1 day following surgical treatment.[68] Likewise, in a 2015 study of 31 patients with severe aortic stenosis, 68%

had reduced VWF HMWM, 39% were severely anemic, and 13% had gastrointestinal angiodysplasia.[69] These studies suggest that the prevalence of AVWS in severe aortic stenosis is more common than usually considered. However, not all patients with reduced VWF HMWM bleed, and there are other causes for gastrointestinal angiodysplasia than AVWS in patients with aortic stenosis. Decreased gastrointestinal perfusion can cause hypoxia-induced dilation of the blood vessels and increased intraluminal pressure, which causes smooth muscle relaxation and dilatation of vessels. Both mechanisms can lead to angiodysplasia.[70]

Hypertrophic Obstructive Cardiomyopathy

In hypertrophic obstructive cardiomyopathy, the obstructed outflow tract of the left ventricle can lead to AVWS and gastrointestinal bleeding as described in a case series of 77 patients in 2015.[71] In this cohort, 36% had bleeding, and 78% had abnormal VWF multimers. Both AVWS and the bleeding symptoms resolved following surgical treatment.

Mitral Regurgitation

Data on AVWS in mitral regurgitation is limited, and the incidence is unknown. The available literature suggests that bleeding symptoms and associated anemia are less frequent in mitral regurgitation than in aortic stenosis, supported by clinical experiences.[72] A study in 2014 discovered lowered VWF HMWM in patients with mild, moderate, and severe mitral regurgitation at rates of 8, 64, and 85%, respectively, with bleeding symptoms in 17% and gastrointestinal angiodysplasia in 13%.[73] Surgical repair led to restoration of VWF HMWM. In contrast, a 2021 study of 85 patients discovered abnormal VWF activity to antigen ratios, but VWF levels were unaffected by transcatheter mitral valve repair and were not associated with bleeding symptoms.[74] Finally, a study of 84 patients in 2024 reported loss of VWF HMWM in 69% and VWF multimers were restored following surgeries, but bleeding history was positive in only 8%.[72]

Left Ventricular Assist Device (LVAD) and Extracorporeal Membrane Oxygenation (ECMO)

LVAD are used for circulatory support in patients with end-stage heart failure as a bridge to transplantation or as a destination therapy. ECMO devices are temporary mechanical circulatory support systems with simultaneous extracorporeal gas exchange for acute cardiorespiratory failure. In both LVAD and ECMO-treated patients, risk for severe bleeds is significantly increased by various mechanisms, including anticoagulation therapy, platelet dysfunction, hyperfibrinolysis, coagulation factor consumption, and the high shear rates created by the continuous flow across the devices.[75] Virtually all patients treated with LVAD or ECMO develop AVWS with the loss of VWF HMWM, but the clinical implications are not well established.

Currently, the risk for gastrointestinal bleeding in LVAD patients has been estimated to be 18 to 27%, with arteriovenous malformations in 50% of those.[76,77] The pathophysiology behind these is not well defined, with some similarities to Heyde's syndrome. However, the VWF multimer alterations do not consistently predict the bleeding risk, suggesting that the pathophysiology is multifactorial.[78]

In ECMO-treated patients, bleeding complications such as intracranial, gastrointestinal, pulmonary, and cannular site bleeding are common.[79] While AVWS can be detected within 24 hours after starting ECMO, the acute bleeds are usually not related to AVWS. Mucosal and gastrointestinal bleeds usually occur later, and AVWS can contribute to the bleeding risk of these.

Hypothyroidism and Autoimmune Disorders

Hypothyroidism has been reported to cause AVWS, mainly by reduction of VWF secretion in the setting of low thyroid hormones but also by autoantibody-mediated mechanisms.[27,80] A 2014 study of 90 patients with hypothyroidism reported an AVWS prevalence of 29%, with mildly or moderately lowered VWF levels and minor bleeding symptoms in 22%.[17] The levels significantly increased after restoration of euthyroidism. In the clinical setting, the actual prevalence of symptomatic AVWS in hypothyroidism is considered low. Other immunological diseases associated with AVWS are SLE, connective tissue diseases, Scleroderma, Sjögrens syndrome, antiphospholipid syndrome, and graft versus host disease.[81]

Medications and Vaccines

Several medications have been identified as potential causes of AVWS, primarily anticonvulsants, but also certain antibiotics, hydroxyethyl starch (HES; a plasma expander), and immune checkpoint inhibitors. The anticonvulsant valproic acid has in several reports, including prospective studies of children, been demonstrated to cause a significant decrease in both VWF antigen and activity levels with preservation of the VWF multimeric structure, similar to congenital VWD type 1.[82–84] The proposed mechanism is reduced synthesis of VWF, and the decreased levels of VWF antigen and activity have not been found to be associated with serum valproic level. Although AVWS is detected in up to 67% of patients treated with valproic acid, its clinical significance remains uncertain, as patients do not typically experience bleeding symptoms.[83] However, bleeding may occur during surgery and trauma, and it is therefore recommended to measure VWF antigen and activity prior to surgery.

AVWS has been associated with the use of antibiotics and antifungal medication, due to increased proteolysis of VWF multimers. Cases of AVWS following the use of griseofulvin and ciprofloxacin spontaneously resolved upon discontinuation of the medication.[85,86]

Anti-PD-L1 immune checkpoint inhibitors have also been reported as the cause of AVWS in a patient with squamous cell carcinoma of the lung due to immunological mechanisms.[87]

Infusion of HES has been demonstrated in healthy volunteers to reduce levels of VWF activity,[88,89] and clinically significant cases of AVWS, including cases with fatal outcome following use of HES, have been reported.[90]

A single case of AVWS relapse has been reported following the Moderna SARS-CoV-2 vaccine, presumably on an autoimmune background.[91]

Management of AWS

Management of AWS has three targets: treatment of acute bleeds, prevention of surgical bleeding, and treatment of the underlying disorder to induce remission. There are few randomized studies to guide treatment decisions, and recommendations in this review are based on case series and the collective experience in the seven Nordic European hemophilia centers.

Treatment and Prevention of Bleeds

The severity of bleeding varies considerably among patients. Adequate VWF and FVIII levels can be obtained by either using desmopressin or a VWF/FVIII or VWF-containing concentrate, but the effect can be short-lived due to increased factor clearance.[19,42] Tranexamic acid should be used in conjunction. In case of acute bleeding, VWF/FVIII or VWF-containing concentrates are combined with other treatment modalities, including intravenous administration of high-dose immunoglobulin G (IVIG) or plasmapheresis to deplete autoantibodies and to achieve longer factor half-life.[33] Recombinant activated factor VII (rFVIIa) has been effective in some cases that were resistant to desmopressin or VWF/FVIII concentrates.[19,92]

VWF/FVIII and VWF Concentrates

Plasma-derived and recombinant VWF products are currently available. Three plasma-derived concentrates containing VWF have been used in AVWS in the Nordics. The choice between VWF replacement therapies (FVIII/VWF 1:1, 1:2, 0:1) is made based on local practices and the clinical and laboratory assessment, including considerations for thrombosis risk. The half-life of infused VWF is often significantly shorter in AVWS than in inherited VWD, thus requiring higher doses of VWF/FVIII concentrate to ensure adequate hemostatic levels.[42] Efficacy should be evaluated for each patient by pre- and serial postinfusion FVIII and VWF activity measurements. Postinfusion factor levels should be measured initially at 1 to 4 and 8 to 12 hours, and subsequently every 12 to 24 hours depending on the patient's clinical status. The goal is to maintain FVIII and VWF activity levels between 50 to 100 IU/dL for 3 to 10 days for serious bleeding or major surgery.

In our Nordic practice, we use starting doses between 40 and 100 VWF IU/kg of body weight, depending on the severity of bleeding and the patient's residual factor activity, in an attempt to reach desired VWF levels of 50 to 100 IU/dL. Subsequent doses will depend on the response of the patient. In a patient with a normal half-life, subsequent doses of 20 to 40 VWF IU/kg every 12 hours are usually sufficient. As the half-life of VWF can be short, especially in patients with underlying MGUS or neutralizing inhibitors, increased doses or more frequent administration may be necessary in AVWS.[42]

The success of treatment with factor concentrates is dependent, above all, on the underlying disorder associated with AVWS and the severity and location of the bleed. The overall clinical response has varied between 40 and 80% according to different studies. Tiede et al[30] reported on 25 patients with AVWS who were treated with VWF/FVIII concentrate for an acute bleeding episode or surgical procedures. Doses were given as a single dose or once daily for minor bleeds or interventions in four patients or repeated at 3 to 12-hour intervals in 21 patients. The median starting dose was 43 FVIII IU/kg. Clinical response was achieved in 80% of patients. In the ISTH registry, VWF/FVIII concentrates were used in 115/186 patients with AVWS (62%), with doses ranging between 30 and 100 VWF:RCo IU/kg. Favorable clinical response was demonstrated in approximately 40% of cases.[10]

High-dose continuous infusion of plasma-derived VWF/FVIII concentrate may be necessary in the acute setting of refractory AVWS to overcome inhibition and/or enhanced clearance of VWF. This approach, with doses varying between 2 and 15 VWF IU/kg/hour, was effective in the management of major surgeries or acute bleeds in a few patients.[93–95] Recombinant VWF (rVWF) is a high-molecular-weight VWF concentrate without FVIII. Due to its ultra-large multimer content, it may be better suited to treat AVWS, represented by severe loss of large VWF multimers. Furthermore, rVWF has a longer plasma half-life than plasma-derived VWF and may be safer in patients with higher FVIII levels and, therefore, at risk of developing thrombosis. So far, there are only a few reports on the use of rVWF in AVWS. rVWF was successful in the perioperative management of a pediatric patient and in an adult patient with a VWF-specific IgM antibody, resulting in a sufficient increase of VWF activity and cessation of bleeding. In contrast, rVWF showed only a suboptimal response in a patient with an inhibitory antibody.[96]

Monitoring of VWF Replacement Therapy

Effective management requires close laboratory monitoring to balance hemostatic efficacy with thrombotic safety. During major bleeding or surgery, replacement therapy should maintain VWF activity and FVIII:C $>$ 50 IU/dL, ideally 50 to 100 IU/dL throughout the bleeding or perioperative period. Because FVIII:C may rise excessively, frequent monitoring (typically every 12–24 hours during the acute phase) is essential to prevent levels $>$ 200 IU/dL, which substantially increase thrombotic risk. Dosing should be adjusted to maintain hemostasis while avoiding FVIII accumulation. Close surveillance is especially important in elderly patients and those with cardiovascular comorbidities, where thrombotic risk is elevated.

Deamino D-arginine Vasopressin or Desmopressin (DDAVP)

DDAVP is administered when VWF concentrates are not immediately available or for minor bleeds. DDAVP stimulates the release of VWF from endothelial cells by acting on the V2 receptor and also by increasing endogenous levels of FVIII.[97] DDAVP can be used for the treatment of bleeds in patients in whom the administration leads to normal or at least $>$ 50 IU/dL VWF activity and FVIII:C levels. The initial dose of 0.3 μg/kg should be administered intravenously. The levels should increase at least two- to threefold and remain at least above 50 IU/dL 4 hours post-DDAVP. VWF and FVIII activity levels should be closely monitored after DDAVP to maintain levels that are sufficient to prevent or treat bleeds. Dosing can be repeated in 12 to 24 hours for two to three times until tachyphylaxis may limit the response. The rationale for the use of DDAVP is that it can cause a transient release of ultrahigh molecular weight multimers and may be more readily

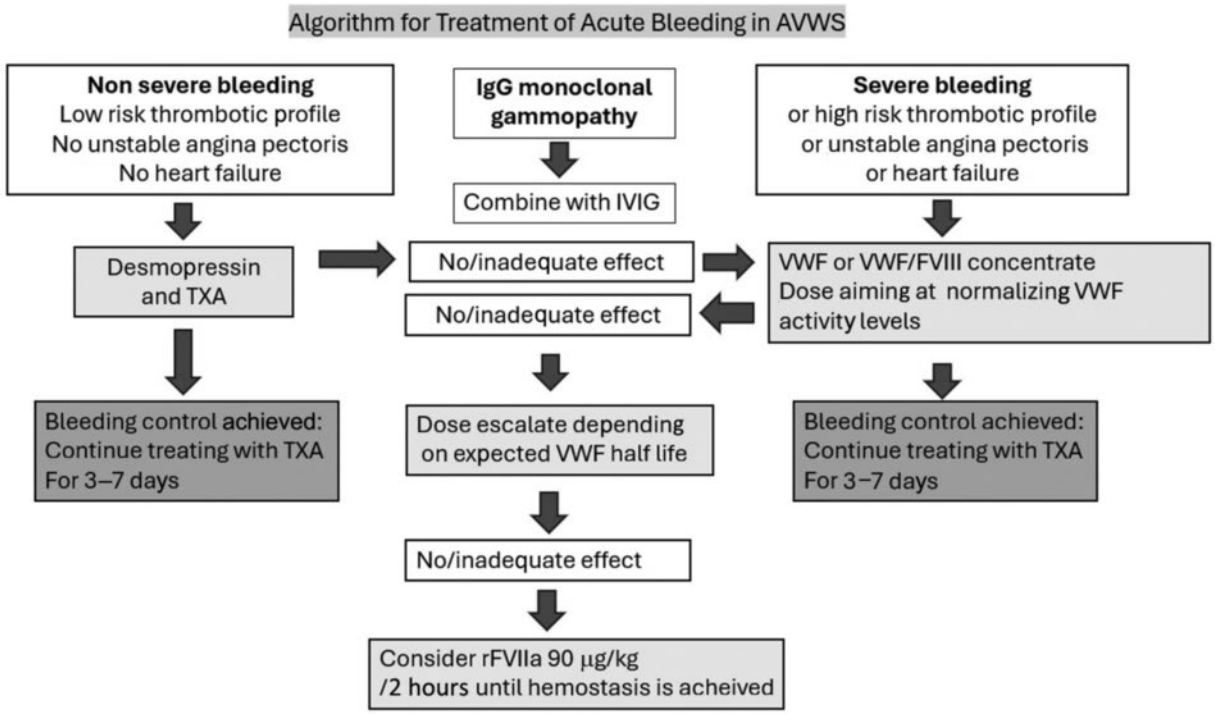

Fig. 2 Algorithm for treatment of acute bleeding in AVWS. The figure illustrates a proposed algorithm where thrombotic risk, presence of contraindications for desmopressin, severity of bleeds, and presence of IgG MGUS will guide treatment decisions in the acute phase. AVWS, acquired von Willebrand syndrome; FVIII, factor VIII; IVIG, intravenous immunoglobulin; rFVIIa, recombinant activated factor VII; TXA, tranexamic acid; VWF, von Willebrand factor.

available in emergency situations than VWF concentrates. However, in connection with life-threatening and other severe bleeds, a VWF/FVIII concentrate should be administered as the first-line treatment (**Fig. 2**).

The overall success rate with DDAVP is approximately 30% according to the underlying cause associated with AVWS. The ISTH registry reported lower clinical efficacy in cardiovascular disorders (10%) and myeloproliferative neoplasms (21%), and higher success rates in autoimmune (33%), lymphoproliferative (44%), and neoplastic (75%) disorders.[10,19,98] Patients with AVWS with anti-VWF inhibitors are likely to have bleeding problems and might be resistant to treatment of underlying diseases and/or therapy with DDAVP. Indeed, a short plasma half-life of VWF following DDAVP administration was reported in AVWS associated with lymphoproliferative disorders and MGUS due to the presence of anti-VWF antibodies.[92] A transient effect of DDAVP was also observed in patients with myeloproliferative neoplasms.

Emicizumab

Emicizumab (Hemlibra) is a subcutaneous, bispecific monoclonal antibody that mimics activated factor VIII by bridging FIXa and FX, thereby promoting thrombin generation independently of VWF. Although not established for AVWS, it represents a potential option for patients with severe, refractory bleeding in whom VWF replacement is ineffective due to rapid clearance or inhibitors, such as in monoclonal gammopathy-associated cases.

Current evidence remains scarce but encouraging. The first reported case of emicizumab use in AVWS[99] described a 70-year-old woman with rheumatoid arthritis-associated AVWS and recurrent gastrointestinal bleeding unresponsive to VWF replacement. Treatment with emicizumab 1.5 mg/kg weekly (no loading) led to complete cessation of bleeding and improved hemoglobin levels over 6 months, despite persistently low VWF and FVIII levels—consistent with its VWF-independent mechanism.

A scoping review on the of off-label emicizumab use in type 3 VWD—particularly in patients with VWF inhibitors, where conventional rFVIII or rFVIIa therapy imposes a high treatment burden—reported favorable hemostatic outcomes with reduced bleeding and treatment burden, using standard hemophilia A regimens (3 mg/kg weekly × 4, then 1.5 mg/kg weekly, 3 mg/kg every 2 weeks, or 6 mg/kg every 4 weeks).[100] The authors suggested that a similar approach may be beneficial in AVWS with rapid VWF clearance or inhibitors. A recent case report further discusses emicizumab as a rational, VWF-independent treatment option for refractory bleeding, particularly in cases of rapid VWF clearance or inhibitors, but emphasizes its off-label use restricted to expert centers.[101]

Overall, emicizumab may be considered in selected refractory AVWS cases with rapid VWF clearance or inhibitors. Use is off-label and should be guided by specialized hematology expertise under close monitoring and with careful assessment of benefits and risks. Laboratory monitoring must account for FVIII assay interference, and combination with high-dose activated prothrombin complex concentrate should be avoided because of thrombosis risk; rFVIIa may be used if additional hemostatic support is required. Prospective studies are needed to define its safety and efficacy in AVWS.

Antifibrinolytic Therapy and Topical Agents

Bleeding can also be treated with antifibrinolytic agents, especially bleeding from mucosal sites such as epistaxis, dental bleeding, or heavy menstrual bleeding. Tranexamic acid (TXA) is a synthetic antifibrinolytic agent that works by inhibiting the activation of plasminogen to plasmin, thus preventing fibrinolysis and stabilizing blood clots and reducing bleeding. TXA is dosed orally at 1 to 1.5 g two to three times per day, or in acute settings intravenously at 10 to 15 mg/kg every 8 hours.

In the context of AVWS, tranexamic acid can be used as an adjunctive treatment in combination with VWF concentrates or DDAVP to manage bleeding episodes, especially mucocutaneous bleeding, such as epistaxis, gastrointestinal bleeding, and menorrhagia. TXA is also useful prophylactically to reduce bleeding risk during and after surgical procedures.[42] TXA is generally well-tolerated. However, TXA is contraindicated in upper urinary tract bleeds due to the risk of obstruction.

Recombinant Activated Factor VII (rFVIIa)

Recombinant activated factor VII may be considered only as a last-resort, off-label therapy for life-threatening bleeding unresponsive to all other modalities, including VWF concentrates, desmopressin, IVIG, or immunosuppression. While rFVIIa can transiently enhance thrombin generation independent of VWF, it does not correct the underlying VWF/FVIII defect. Its use also carries a significant risk of thrombosis, particularly in elderly or comorbid patients. Accordingly, administration should be restricted to expert hematology centers, under close clinical and laboratory supervision, and reserved for cases where conventional therapies have failed.

rFVIIa is usually administered with a dose of 90 µg/kg with repetitive doses in cases of extreme or life-threatening bleeding that cannot be controlled by other means.[102–104]

Intravenous Immunoglobulin (IVIG)

Administration of high-dose IVIG may prolong the half-life of VWF by interfering with FC-receptor-mediated clearance of antibody-VWF complexes. The standard dose is 1 g/kg intravenously for 2 consecutive days (total dose 2 g/kg). The effect is not immediate; it takes 48 to 72 hours before VWF levels rise, necessitating concurrent use of VWF concentrates for acute bleeding control. IVIG is effective in AVWS due to anti-VWF autoantibodies, especially in AWVS associated with monoclonal IgG-gammopathy such as MGUS and MM, where IVIG should be considered as part of the first-line treatment in case of bleeding. However, IVIG will not work if the antibody is of the IgM isotype, and in case of acute bleeds, plasmaspheres may be considered.

Take Home Message

A suggested treatment algorithm for acute bleeds is given in **Fig. 2**.

Treatment of the Underlying Disorder

Several recent reviews guide management of AWS in cardiac disease, which will resolve with valve replacement or weaning from the device,[105–107] and will not be covered in detail in this review. (**Table 2**)

Table 2 Treatment algorithm based on etiology in patients with acquired von Willebrand syndrome with bleeding symptoms

	Myeloproliferative neoplasms	IgG MGUS, smoldering myeloma, myelomatosis	IgM MGUS	Waldenström macroglobulinemia, CLL, lymphoma	Cardiovascular disease
Mechanism	Adsorptive[a] Shear stress and increased proteolysis[a] Autoantibody-mediated VWF clearance[a]	Adsorptive[a] Autoantibody-mediated VWF clearance[a]	Adsorptive[a] Autoantibody-mediated VWF clearance[a]	Adsorptive[a] Autoantibody-mediated VWF clearance[a]	Mechanical destruction[a] Shear stress and increased proteolysis[a]
1st line treatment	VWF or VWF/FVIII concentrate in combination with cytoreduction	IVIG and Desmopressin/TXA or VWF or VWF/FVIII concentrate in combination with antimyeloma treatment	Desmopressin/TXA or VWF or VWF/FVIII concentrate.	IVIG and desmopressin/TXA or VWF or VWF/FVIII concentrate in combination with rituximab or immunochemotherapy	VWF or VWF/FVIII concentrate. Treatment of the cause (e.g., surgery)
2nd line treatment	rFVIIa	rFVIIa	rFVIIa Plasmapheresis	rFVIIa	rFVIIa

Abbreviations: FVIII, factor FVIII; IVIG, intravenous immunoglobulin; rFVIIa, recombinant activated factor VII; TXA, tranexamic acid; VWF, von Willebrand factor.

Table 3 AVWS associated with plasmacyte-related disorders

PRD	*n*	Antineoplastic treatment and response
1st line		
IGA MGUS	1	Coticosteroids: no response
IGG SMM	1	Rituximab: no response
IGG MGUS	1	Glucocorticoids + cyclophosphamide: no response
IGG MGUS	1	Lenalidomide + dexamethasone: no response
IGG MGUS[a]	1	Thalidomid: no response
IGG SMM	1	Bortezomib/carfilzomib + daratumumab + cyclophosphamide + dexamethasone: no response
IGG MGUS	1	ASCT: overall response[b]
2nd line		
IGA MGUS	1	Rituximab: no response
IGG MGUS	1	Lenalidomide-dexamethasone: overall response
IGG MGUS	1	Bortezomib + dexamethason: overall response
IGG SMM	1	Bortezomib + dexamethasone: overall response
IGG SMM	1	Carfilzomib + daratumumab + cyclophosphamide + dexamethasone + lenalidomide: overall response
PRD treated due to AVWS and other criteria		
MM[a]	1	Melphalan + Prednisone + Bortezomib: overall response
MM IGA-LAMBDA	1	Melphalan + Prednisone + Bortezomib: overall response
MM IGG-KAPPA	1	Daratumumab + thalidomide + dexamethasone + ASCT: overall response

Abbreviations: ASCT, autologous stem cell transplantation; IGA, immunoglobulin A; IGG, immunoglobulin G; MGUS, monoclonal gammopathy of undetermined significance; MM, multiple myeloma; n, number of cases; PRD, plasmacyte-related disorders; SMM, smoldering multiple myeloma.
[a]Nordic cases not previously reported.
[b]Overall response is defined as normalization or improvement of von Willebrand tests or cessation of bleeding for 3 months or longer.[108,111,113–115]

Treatment of AVWS-MGUS

The presence of AVWS turns an underlying MGUS into monoclonal gammopathy of clinical significance,[108] and in patients with severe bleeding due to AVWS-MGUS, this is an indication for treatment targeting the otherwise indolent monoclonal gammopathy. In a review by Nicol et al of antineoplastic treatment of AVWS with underlying lymphoid neoplasms, including all reported cases up to May 2021, it was suggested that treatment should be stratified according to the underlying clonal cell line.[109] The review demonstrated a pattern, where AVWS related to underlying plasmocyte disorders had the highest overall response rate (ORR) to anti-myeloma drugs, whereas AVWS related to otherwise indolent lymphocyte disorders had higher ORR to immunosuppressive treatments, and the response of AVWS matched the response of the underlying disorder. Treatment of AVWS-MGUS according to the underlying cell line is described in the following paragraphs.

Treatment of AVWS in Plasmocyte-Related Disorders (PRD)

In the review by Nicol et al from 2021, AWS with underlying non-IgM MGUS, smoldering multiple myeloma (SMM), or overt multiple myeloma (MM), anti-myeloma drugs provided a response of AWS in 71.4% of cases (20/28).[109] The proteasome inhibitor bortezomib (nine cases) was effective in 66.7%, and thalidomide (one case) and lenalidomide (two cases) were effective in 100%. In contrast, immunotherapy or immunochemotherapy with steroids, rituximab, melphalan, cyclophosphamide, or combinations only induced responses in 30% (3/10). A systematic literature search of AVWS in plasmocyte-related disorders since 2021 retrieved reports of a further 19 cases of antineoplastic treatment, presented in **Table 3**, including not previously reported Nordic cases.[110–114] Three more cases of AWS in plasmocyte-related disorders treated with bortezomib have been reported, effective in combination with dexamethasone or prednisolone-melphalan.[110,112] Thalidomide monotherapy has been ineffective in one case, and lenalidomide-dexamethasone has been effective in one of two cases (as well as in multidrug combinations).[110,111,113] Immunosuppressive drugs alone were ineffective in four cases.[110–112] See **Table 3** for details. This is in concordance with the findings of Nicol et al, and antimyeloma drugs should be considered when treatment is indicated in AVWS associated with IgG MGUS or SMM.

Treatment of AVWS in Lymphocyte-Related Disorders

The lymphocyte-related disorders commonly associated with AWS are Waldenströms macroglobulinemia (WM), chronic lymphocytic leukemia/lymphoma (CLL), and marginal zone lymphoma (MALT). Nicol et al reviewed 43 cases, where immunosuppression with rituximab resulted in an ORR of 60% (three-fifths) and immunochemotherapy an ORR of 66 to 75%, corresponding to the response of

Table 4 Acquired von Willebrand syndrome associated with lymphocyte-related disorders

LRD	*n*	Antineoplastic treatment and response
1st line		
MALT	1	Corticosteroids: no response
CLL	1	Chemotherapy: overall response[b]
CLL[a]	1	Rituximab: response?
CLL and SMM	1	Rituximab: overall response
WM	1	Chlorambucil + rituximab: no response
WM	1	Rituximab + cyclophosphamide + dexamethasone: overall response
WM	2	Rituximab + cyclophosphamide + dexamethasone: overall response
WM	1	Rituximab + cyclophosphamide + dexamethasone: no response
WM	2	Bortezomib + cyclophosphamide + dexamethasone: overall response
WM	1	Bortezomib: no response
2nd line		
MALT and IGA MGUS	1	Rituximab: overall response
MALT	1	Rituximab: overall response
WM	2	Ibrutinib: overall response
WM	1	Ibrutinib: overall response
CLL and SMM	1	Obinotuzumab + venetoclax: overall response
WM	1	Obinotuzumab + idelalisib: overall response
CLL[a]	1	Thalidomid: no response

Abbreviations: CLL, chronic lymphatic leukemia; LRD, lymphocyte-related disorders; MALT, mucosa-associated lymphoid tissue; MGUS, monoclonal gammopathy of undetermined significance; n, number of cases; SMM, smoldering multiple myeloma; WM, Waldenström macroglobulinemia.
[a]Nordic cases not previously reported.
[b]Overall response is defined as normalization or improvement of von Willebrand tests or cessation of bleeding for 3 months or longer.[109,110,115–119]

the underlying lymphocyte disorder.[109] Some drugs or combinations have only been used in a single case, such as idelalisib and carfilzomib, both with positive overall response. Twelve more cases of AVWS in lymphocyte-related disorders reported since 2021 are shown in **Table 4**, demonstrating a similar pattern of response.[110,115–120] Rituximab monotherapy or immunochemotherapy was effective in a further six cases.[110,116,117,120] Ibrutinib has been reported effective and safe in two cases (as was obinutuzumab in combination with venetoclax or idelalisib.[116,117,119] Based on these data, when treatment is indicated in AVWS in lymphocyte-related disorders, rituximab monotherapy or immunochemotherapy can be effective.

Treatment of AVWS Secondary to Myeloproliferative Neoplasms (MPNs)

In MPNs, the major morbidity is caused by increased risk of both arterial and venous thrombosis, and the goal of treatment is traditionally to reduce this risk.[121] However, several studies have shown that these patients have a higher frequency of bleeding than the normal population.[122] The most obvious reason is that the majority of patients are treated with aspirin and/or oral anticoagulants, but it has also been proposed that platelet hyperreactivity caused by the driver stem cell mutation will cause a secondary platelet storage pool defect and thus, reduced platelet function.[123] On top of this, some patients will develop AVWS, further ameliorating the primary hemostasis and, in severe cases, cause low levels of FVIII:C with inhibition of secondary hemostasis and extreme risk of bleeding. The management of MPN patients is therefore a delicate balance between the risk of thrombosis and bleeding.

Current Recommendations

AVWS is most often diagnosed in patients with high platelet counts,[38] and in some cases, bleeding is the first symptom that eventually leads to a MPN diagnosis. In patients with clinically relevant bleeding, treatment with cytoreductive drugs such as Hydroxy Urea and interferon-a is recommended together with VWF-containing factor concentrates, as well as platelet apheresis in extreme cases.[19,124] However, the evidence for this treatment is modest, with only one paper systematically evaluating cytotoxic treatment in Philadelphia chromosome-negative MPN-associated AVWS, involving three patients with PV and three patients with ET, with overall response in all but one patient. This patient with PV was diagnosed with an inhibitor, which might explain the lack of response.[125] For patients diagnosed with MPN-associated AVWS without bleeding symptoms, a wait-and-watch approach is generally recommended, but cytoreduction is recommended in cases with extreme thrombocytosis.[124]

Lessons Learned from Case Reports

Since the first report of MPN-associated AVWS, published in 1983, where AVWS was described in a patient with myelofibrosis,[126] a

Table 5 Response to treatment in patients with myeloproliferative neoplasia, synopsis of 31 case reports

Treatment	*n*	Result
Undefined cytoreductive treatment	7	Overall response in all 6/7
Hydroxy urea	9	Overall response in 7/9
Hydroxy urea and anagrelide	2	Overall response
Hydroxy urea and platelet apheresis	2	Overall response
Hydroxy urea and interferon-a	1	Overall response
Hydroxy urea, interferon-a, and platelet apheresis	1	Overall response
Hydroxy urea and operation of aortic stenosis	1	Overall response
Hydroxy urea and thyroxine		
Interferon-a 2b	2	Overall response
Interferon-a 2b and ranimustine	1	Overall response
Interferon-a 2b and cardiac surgery		
Platelet apheresis	1	Overall response
IVIG	1	Overall response
Symptomatic treatment of bleeds with VWF containing concentrates	1	Overall response
Desmopressin treatment at surgery	1	Overall response
Conservative treatment only	1	Overall response

Abbreviations: IVIG, intravenous immunoglobulin; VWF, von Willebrand factor.

literature search revealed 26 case reports describing the treatment of 30 patients with MPN-associated AVWS. In line with previous reports from cohorts and registries[10,38] most of the cases were diagnosed with ET (18/30, 60%), followed by PV (9/30, 30%), myelofibrosis (MF; 3/30, 10%), and one case with myelodysplastic syndrome (MDS)/MPN overlap syndrome with ring sideroblasts and thrombocytosis. Also, in line with previous reports, the presence of the JAK-2 V617F mutation seems to be associated with AVWS being present in 11/19 (58%) of cases where genetic analyses had been performed. Most patients were treated with hydroxyurea alone (nine cases) or in combination with angrelide (two cases), interferon-a (two cases), or platelet apheresis (three cases), with overall response in all but two patients treated with hydroxyurea only (**Table 5**). This case series includes three patients where AVWS, unexpectedly, was primarily associated with aortic stenosis and not with the underlying MPN diagnosis, whereof two were successfully treated with valve replacement.[127–129] One case was diagnosed with hypothyroidism, and VWF parameters corrected only after treatment with thyroxine.[130] In one patient with MPN-associated AVWS with a lack of VWF HMWM, the multimer pattern normalized after hydroxyurea treatment; however, VWF activity and antigen levels remained low. A genetic variant conferring a VWD type 1 phenotype was found; thus, challenging the statement that the diagnosis of AVWS must involve exclusion of the inherited form.[131]

AVWS Associated with MPN during Pregnancy

Two studies describe the outcome of AVWS diagnosed in patients with ET during pregnancy. In one study from 2020,[132] 17 pregnancies in nine ET patients were retrospectively analyzed. Two patients were diagnosed with AVWS, and acetyl salicylic acid was withheld, but no specific treatment was given. In a larger series, published in 2018,[6] 24 pregnancies in 18 patients with ET were described. In all pregnancies VWF:RCo/Ag ratio was < 0.7 in the first trimester; in 20 (83%), AVWS was diagnosed. In two patients with VWF:RCo $< 30\%$, acetyl salicylic acid was withheld until, after repeated testing at gestational weeks 14 to 16, VWF:RCo reached $> 30\%$. No evidence of AVWS was presented in any of the pregnancies in the third-trimester testing. In six (25%) pregnancies, women were prescribed cytoreductive therapy in the form of interferon-α throughout pregnancy, and in two of them, it was discontinued at the beginning of the third trimester.

Treatment of Cardiovascular Diseases Associated with AVWS

The long-term management of bleeding of AVWS in cardiovascular diseases involves treating the underlying cause, if possible. For aortic stenosis-associated AVWS, a recent meta-analysis including data of 1,354 patients reported recovery from AVWS in 86 to 92% and cessation of bleeding in 73% of patients following aortic valve replacement.[133] Surgical treatment in patients with hypertrophic obstructive cardiomyopathy and mitral regurgitation has also been a successful treatment strategy, but only in limited, mainly single-center case series studies.[71,73] Of note, current guidelines do not suggest interventional treatment of aortic stenosis or mitral regurgitation in patients with AVWS if the conventional criteria for treatment are not met.[134] In LVAD and ECMO-treated patients, multimers are restored immediately following the device explantation.[135]

Take Home Messages for Treatment

- Antimyeloma drugs should be considered when treatment is indicated in AVWS associated with IgG MGUS or SMM.

- Rituximab monotherapy or immunochemotherapy can be effective.
  When treatment is indicated in AVWS in lymphocyte-related disorders, WM, CLL, and MALT.
- Treatment of AVWS in MPN patients includes cytoreductive therapy and platelet apheresis
- If a patient with AVWS and MPN does not respond to MPN-directed therapy, alternative diagnoses such as MGUS, Heyde's syndrome, or hypothyroidism must be suspected.
- The treatment of cardiovascular diseases, AVWS is treating the underlying cause, especially in aortic stenosis and other valvular heart disease.
- For LVAD and ECMO-associated AVWS, the evidence supporting the use of VWF concentrates is poor, and the multifactorial pathophysiology of bleeds should be considered.

Conclusion

The main challenges in AVWS remain the lack of widely accepted criteria for diagnosis, hampering the possibility of estimating the incidence and prevalence of the syndrome. In addition, well-controlled prospective studies that can tell us what bleeding risk the diagnosis will confer are lacking, as well as what treatment modality is the most efficient. However, the updated data information from retrospective studies and case reports presented in this review may be a valuable tool when making treatment decisions as well as writing national and international guidelines.

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Statements and Additional Information

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