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Acquired Von Willebrand Syndrome (AVWS) in cardiovascular disease: a state of the art review for clinicians

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Abstract

Von Willebrand Factor (vWF) is a large glycoprotein with a broad range of physiological and pathological functions in health and disease. While vWF is critical for normal hemostasis, vascular integrity and repair, quantitative and qualitative abnormalities in the molecule can predispose to serious bleeding and thrombosis. The heritable form of von Willebrand Disease was first described nearly a century ago, but more recently, recognition of an acquired condition known as acquired von Willebrand Syndrome (AVWF) has emerged in persons with hematological, endocrine and cardiovascular diseases, disorders and conditions. An in-depth understanding of the causes, diagnostic approach and management of AVWS is important for practicing clinicians.

Keywords

Von Willebrand Factor; Acquired Von Willebrand Syndrome

Introduction

Von Willebrand Disease (VWD), a heritable, autosomal dominant disease is the most common hemostatic disorder in the United States affecting one out of every 100 persons (1% of the overall population); however, many people do not experience bleeding. In fact, the bleeding phenotype occurs in every 1 per 10,000 persons. VWD was first described in 1924 by a Finnish physician Erik Adolf von Willebrand who characterized 66 family members of a 5 year old girl with a propensity for bleeding and 2 years later reported a previously undescribed bleeding disorder that differed from hemophilia [1]. By contrast, acquired Von Willebrand Syndrome (AVWS) is a comparatively new condition in the fields of cardiology, vascular medicine and hematology of varied etiology characterized by changes either in the overall amount or in the structure and function of von Willebrand Factor. These latter changes form the basis for its highly heterogeneous phenotypic expression of disease and clinical manifestations to include bleeding, thrombosis and non-

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physiologic angiogenesis. Herein, we offer a contemporary review of AVWS, providing insights for the pathophysiology, diagnosis, management and remaining questions that will require a coordinated and concerted investigation to unlock the mysteries that impede transformational progress and ultimately impact patient care.

Von Willebrand factor: the basics

Von Willebrand Factor (vWF) is a glycoprotein ranging in size from 600,000 to 20 million Da that participates actively in platelet adhesion to either injured or disrupted vascular surfaces, activation and high-shear state platelet aggregation [2]. The vWF gene is located on the short arm p of chromosome 12 (12p13.2) with 52 exons that span 178 kbp.

vWF is synthesized in megakaryocytes and endothelial cells and follows several distinct pathways of secretion from vascular endothelial cells and platelets. The first represents a constitutive pathway linked directly to synthesis. The second is a regulated pathway involving storage of mature molecules for release following stimulation by one or more mediators, including histamine, leukotriene D4, platelet-activating factor, vascular permeability factor, the terminal component of complement, epinephrine, fluid mechanical forces, factor Vila, thrombin, and fibrin [3]. In addition, Weibel–Palade bodies (containing vWF) are rapidly translocated to the cell surface of platelets following activation [4].

The association of vWF with the luminal surface of endothelial cells may be mediated by vitronectin receptors αVβ3, GPIb, or a constituent of the Weibel–Palade body itself. The nature (or stimulus) of release also carries important functional ramifications. Thrombin stimulates the appearance of high-molecular weight multimers (HMWM) of vWF with increased functionality. Because vWF is stored in both endothelial cells and platelets, released in response to their activation, and participate in site-specific thrombosis and hemostasis it may represent a multidimensional biomarker of underlying pathological events [5].

Von Willebrand factor: structure and function

The pre–pro-vWF molecule consists of a 22-amino acid signal peptide, a 741 amino acid pro-peptide, and a 2050 amino acid mature subunit. The pro-vWF monomer is composed of 4 distinct domains (A–D) as follows: NH_2–D1–D2–D'–D3–A1–A2–A3–D4–B1–B2–B3–C1–C2–CK–COOH. vWF multimers are formed by C- and N-terminal intermolecular disulphide bonds, with the largest multimers exceeding 2×10^4 kDa and having the greatest adhesive activity. During synthesis, vWF undergoes extensive post-translational modification resulting in the addition of 12 N-linked and 10 O-linked glycosylation sites per mature monomer. Furthermore, the pro-peptide also contains four potential N-linked glycosylation sites whose function is not fully known. In total, carbohydrate accounts for approximately 20% of the molecular weight of vWF [4] (Fig. 1).

Mature vWF enters the plasma as a series of oligomers containing a variable number of subunits, ranging from a minimum of 2 to a maximum of ~ 40, with the largest HMWM having molecular weights, as previously mentioned, in excess of 20,000 kDa.

Following exocytosis, vWF unfolds into ultra-long strings with vWF “docking” on vascular endothelial cells to facilitate adhesion to platelets. Accordingly, vWF stored within Weibel–Palade bodies of endothelial cells is composed of the largest multimeric species, ultra-large vWF (UL–vWF), that are not typically observed in normal plasma because of ADAMTS-13 (a disintegrin-like and metalloprotease with thrombospondin type 1 motif, member 13) cleavage at the time of secretion. vWF multimers and the vWF pro-peptide are secreted together in 1:1 stoichiometric amounts, but the pro-peptide dissociates from vWF multimers and circulates independently as a noncovalent homodimer with a half-life of ~ 2 h [6].

Each monomer of vWF has functional domains that are important for primary hemostasis and pathological thrombosis-domain Al binds platelet glycoprotein Ibα receptors; domain A3 binds to collagen on damaged blood vessels; and domain A2 cleaves HMWM into smaller fragments [7, 8]. The cleavage process is important to avoid unregulated thrombosis since HMWM are highly active and propagate platelet thrombus formation through activation, adhesion and aggregation of platelets. Under conditions of normal blood flow, HMWM are folded and inactive, but under conditions of shear stress as occurs with vascular injury, intravascular shunts and either intra- or extra-corporeal high flow conditions, the molecule is stretched, activates and establishes a template for thrombus formation at sites of injury. As a regulatory mechanism, stretching of vWF unfolds the tertiary structure of the protein to induce a conformational change in the A2 domain that predisposes HWWMs to cleavage into smaller multimers or monomers with reduced thrombogenicity.

Regulation of Von Willebrand factor

vWF is dynamically regulated by fluid shear stress which promotes aggregation of multiple vWF units and, at the same time, reduces multimer size using force-dependent cleavage by proteases, notably ADAMTS13, also known as vWF-cleaving protease (vWF-CP) [9]. When vWF is exposed to tensile forces, it has a tendency to unfold and become elongated, asymmetric protein, unfolding the A2 domain in the process as well, which can then be cleaved by ADAMTS13 [10]. Shear stress above 60 dyne/cm^2 is typically necessary to initiate vWF structural changes [11, 12]. Unlike the vWF-A1 and A3 domains, the vWF-A2 domain is more susceptible to conformation changes and cleavage by ADAMTS13 since the disulfide bridge in this domain is located between vicinal cysteines at the C-terminus compared to a disulfide bridge that lies between the N- and C-terminus of A1- and A3-domains making them more resilient to degradation.

Multimeric vWF is the largest protein in blood with a contour length of up to 250 μm. In addition, vWF stored within platelets and endothelial cells is often longer than the protein found within circulating blood. The binding of platelets to collagen is augmented by high shear rate that, in turn, leads to a conformational change in vWF- both at a dimeric level (unfolding to expose binding domains) and a multimeric level (stretching of the protein into a long chain). The unfolding and stretching of vWF is enhanced in high shear stress environments as a result of margination of platelets and platelet micro-particles toward the vessel wall-in large part by erythrocytes that migrate to the center the vessel due to hydrodynamic interactions and the interaction of non-spherical and deformable objects underflow conditions [13]. Accordingly, both margination and stretching must occur prior to

adhesion and the functional properties of vWF are highly dependent on shear rate and the concentration erythrocytes. (These important conditions will be highlighted in a section to follow).

Under inflammatory conditions there is a substantial amount of signaling between platelets, coagulation proteins and vascular endothelial cells. A key component of the pro-inflammatory crosstalk may be dependent on platelets and the effect of activation-dependent micro-vesicle release on leukocyte migration. Platelets can actively participate in deposition of granular contents from leukocytes and endothelial cells. These events are mediated by chemokines, such as CCL5 (RANTES) and CXCL4 (platelet factor 4) [14] and collectively represent an attractive target for pharmacological inhibition (discussed in a subsequent section).

Von Willebrand factor release

Platelet α-granules release vWF upon activation; however, endothelial cells combine basal or constitutively and regulated release of Weibel–Palade Body contents [15–17].Basal exocytosis or release of Weibel–Palade Body-anchored vWF bundles recruit platelets, while a more robust release occurs following chemical or mechanical endothelial stimulation.

Von Willebrand factor clearance

vWF is similar to other plasma proteins with a relatively short circulating half-life ranging from 6 to 24 h [18, 19]) and a strong potential for physical changes (oxidation, proteolysis, glycation), which can alter its functional properties. The main determinant for this wide variation has been attributed to glycosylation patterns. In particular, the presence of blood group ABO (H) structures. Individuals with blood group non-O display a longer vWF half-life after desmopressin administration than individuals with blood group O, which may explain the average 25% higher vWF levels in individuals with blood group non-O [20, 21]).

The available evidence suggests that a majority of vWF is cleared by an active regulatory mechanism involving the liver, spleen and vascular endothelial cells- [22] with the former being determined by its co-localization with macrophages [23] Macrophages can internalize proteins randomly via receptor-independent micropinocytosis or receptor-specific endocytosis involving sialo glycoprotein receptors [24], lipoprotein receptor LRP1, Siglec-5, a receptor present on macrophages that specifically interacts with sialic acid residues [25] or CLEC4.

Von Willebrand factor and platelet aggregate stability

The extracellular domain of glycoprotein (GP) Ibα serves as a primary vWF receptor that triggers shear stress-dependent platelet aggregation. Its intracellular domain associates with actin-binding protein-280 (filamin 1a) that binds directly to filamentous actin, thereby linking the membrane skeleton to GPIbα.There is a significant increase in the amounts of actin that co-immunoprecipitate with GPIbα as platelets aggregate in response to shear stress. Monoclonal antibody blockade of vWF binding to GPIbα inhibits shear stress-induced platelet aggregation and actins association with GPIbα. Pretreatment of platelets

with CyD causes inhibition of actin binding to GPIbα in shear-activated platelets and increases the rate and magnitude of platelet disaggregation. These findings suggest that shear stress causes changes in the association between GPIbα and the actin-based membrane skeleton. The increased interaction between GPIbα and the actin-based membrane skeleton results from shear-induced vWF binding to GPIbα and is considered mechano-protective as it controls shear-induced aggregation of activated platelets [26].

Platelet aggregates induced by normal plasma or HMWMs of vWF (e.g. Humate-P) dissociate by 50% within 15-25 min following dilution. By contrast, aggregates formed in the presence of endothelial microparticles (EMP) persist two-to-threefold times longer with the same treatment, indicating greater stability. Addition of EMP to plasma from patients with severe VWD restores ristocetin-induced platelet aggregation. It is believed that EMP carry ultra-large vWF multimers, promote platelet aggregation, and increase the stability of the aggregates formed. Thus, thrombosis occurring at sites of profound vessel wall and vascular endothelial cell injury may be more resistant to platelet disaggregation and other regulatory mechanisms [27]

Von Willebrand factor and platelet binding to sites of vascular injury

The adhesion of platelets to sites of vascular injury is critically dependent on the binding of vWF to the platelet surface glycoprotein complexes, GP Ib-V-IX and GP IIb-IIIa (integrin αII- β3). There is evidence that the binding of vWF to these receptors is not only essential for stable platelet adhesion but is also important for the transduction of activation signals required for changes in platelet morphology, granule secretion, and stable platelet aggregation. The adhesion of platelets to vWF results in a dramatic actin filament reorganization, and the cytoskeletal recruitment of various structural proteins (e.g. talin and integrin αIIb-β3) and signaling enzymes (e.g. pp60c-src, focal adhesion kinase (FAK), phosphatidylinositol 3-kinase (PI 3-kinase), and protein-tyrosine phosphatase (PTP)-1B). The cytoskeletal translocation of signaling enzymes in vWF-stimulated platelets is abolished by pretreating platelets with an anti-GP Ib-V-IX antibody [28].

Von Willebrand factor and angiogenesis

vWF is critical for normal vascular homeostasis and integrity. Quantitative and qualitative abnormalities that characterize VWD have shown both in vitro and in vivo to cause enhanced vascularization that increases inversely with the overall degree of residual vWF activity [29]. The available evidence suggests that vWF binding to integrins and several components of Weibel-Palade bodies found within vascular endothelial cells, such as angiopoietin-2 and galectin-3, all converge to regulate vascular endothelial growth factor (VEGF) signaling. HMWMs of vWF are the most important regulators of angiogenesis. The early work of Zimmerman [30] suggests that vWF is in fact a marker of angiogenesis.

Von Willebrand disease classification

Von Willebrand disease (VWD) is the most common heritable bleeding disorder in the general population with the most common sites of bleeding being the mucocutaneous,

gastrointestinal, genitourinary, intra-articular and intracranial. It is typically divided into types 1, 2 and 3 with several sub-types [31, 32].

Type 1 VWD

Type 1 VWD is an inherited bleeding disorder due to quantitative deficiency of vWF. The diagnosis is based on criteria for symptoms of significant mucocutaneous bleeding, laboratory tests compatible with vWF deficiency and inheritance suggested by a positive family history for VWD or a documented vWF mutation, all of which must be satisfied. Laboratory test results are compatible with type 1 VWD if the levels of both vWF:RCo (ristocetin co-factor) activity and vWF:Ag (antigen) are > 2 SD below the population mean and ABO type adjusted mean on > 2 separate determinations. The plasma vWF multimer distribution is typically normal [33, 34].

Type 2 VWD

Type 2 VWD (15-30% of cases) is a qualitative defect of vWF and the bleeding tendency can vary between individuals. Four subtypes exist: 2A, 2B, 2 M, and 2 N. These subtypes depend on the presence and functionality of the associated vWF multimers.

Type 2A

vWF is quantitatively normal but qualitatively defective. The ability of the defective vWF to coalesce and form HMWM is impaired, resulting in a decreased quantity of HMWM and low vWF:RCo activity. vWF antigen (vWF:Ag) level is either low or normal.

Type 2B

This is a gain-of-function defect in vWF. The ability of the qualitatively defective vWF to bind platelet GP1b is markedly enhanced, leading to its spontaneous binding to platelets and subsequent rapid clearance of bound platelets and of HMWM. Thrombocytopenia may occur and HMWM are either reduced or absent from the circulation.

Type 2 M

Type 2 M VWD is a qualitative defect of vWF characterized by its decreased ability to bind to the platelet GPIb receptor and a concomitant impaired ability to form HMWM. The vWF antigen levels are normal. The vWF: RCo activity is decreased and HMWM are present in the circulation.

Type 2 N

This is a deficiency of the binding of vWF to coagulation factor VIII. vWF antigen levels are normal and the vWF: RCo activity is normal. By contrast, coagulation factor VIII levels are markedly decreased.

Type 3 VWD

Type 3 VWD is considered rare, representing < 5% of all VWD cases, and reflecting an incidence of ~ 1–2 persons per million of population. It may represent a much higher

proportion of VWD cases in developing countries-possibly up to 60% of identified cases [35].

Acquired Von Willebrand Syndrome

A variety of pathogenic mechanisms have been proposed to cause structural or functional disturbances of vWF. These include autoantibodies, either interfering with platelet or collagen binding or increasing vWF clearance from the plasma. Underlying diseases and conditions include myeloproliferative and lymphoproliferative diseases and malignancy. Sequestration of HMWM has been demonstrated in patients with hematologic disorders because of adsorption to myeloma cells or platelets, but also in reactive thrombocytosis. Proteolytic cleavage has also been described in patients with pancreatitis, liver cirrhosis and leukemia. In hypothyroidism, AVWS may be the end-result of decreased synthesis of otherwise normal vWF [34, 36]. Patients with AVWS have a bleeding phenotype; however, in some instances, a thrombosis phenotype or a concomitant predisposition to both thrombosis and bleeding is observed.

The heterogeneity of AVWS makes it particularly challenging for clinicians to diagnose and treat. In addition, and unlike the heritable forms of VWD, AVWS does not fit neatly into any of the existing classifications or subclassifications. As we will describe, AVWS has laboratory and phenotypic features of type 2A VWD; however, there is a difference between an inability to form vWF HMWM and, for instance, shear-induced cleavage of previously formed HMWM with a wide range of resulting vWF monomers, multimer lengths, fragments and their respective functionality.

Acquired Von Willebrand Syndrome is not the same as Type 2A Von Willebrand Disease

While AVWS has frequently been referred to (or sub-classified) as Type 2A VWD, there are distinct features for each [37]. The multimeric phenotype of classic Type 2 VWD not only includes a HMWM deficiency (or absence), but a decrease in intermediate-molecular weight multimers and an inner triplet band pattern on high-resolution gel analysis. In addition, collagen binding activity and vWF-RCo activity is variably decreased in some forms of AVWS, including left ventricular device-related AVWS. Overall, vWF activity is comparatively less affected in LVAD patients where only a moderate reduction in HMWM is observed and occasionally the vWF: CB/vWF:Ag or vWF:RCo/vWF:Ag ratio is within the normal range (≥ 0.7). In addition, vWFAg is typically normal, but can be markedly reduced in AVWS and reduced, albeit mildly in most cases of Type 2A VWD. Last, in LVAD-associated AVWS, HMWM decrease, while LMWM and vWF fragments (~ 225 D monomers) increase. Elevated levels of vWF fragments correlate with angiodysplasia-related bleeding. vWF functional discordance is observed in both; however, bleeding as a phenotype is more heterogeneous in AVWS than in Type 2A VWD.

Prevalence of AVWS in Cardiovascular Disease

AVWS has been described is a number of cardiovascular diseases and conditions. In most instances, high blood shear rates and stress are present.

Congenital heart disease—The incidence of AVWS in patients with congenital heart disease ranges from 1–2% up to as high as 20–30% according to the complexity of disease and conditions that include high-shear blood flow as might be seen with Eisenmenger's syndrome [38]. In a study of children with either congenital pulmonic or aortic stenosis, there was a history of bleeding in 9% and 18%, respectively. Seven of the 60 children (12%) had laboratory findings consistent with a diagnosis of AVWS, and two of these (28%) had a history of bleeding [39].

Aortic Stenosis—Aortic stenosis is a common valve anomaly among adults worldwide, stemming from either rheumatic or non-rheumatic disease- the latter being much more common and typically the result of a bicuspid aortic valve or progressive calcification associated with aging. In 1958, Edward Heyde described an association between aortic stenosis and chronic gastrointestinal bleeding [40]. Warkentin [41] and colleagues proposed the role of an acquired coagulopathy in patients with severe aortic stenosis with depletion of vWF HMWM in the pathogenesis of Heyde Syndrome-often with concomitant angiodysplasia.

A seminal study of patients with aortic stenosis and AVWS was reported in 2003 [42]. Platelet-function abnormalities under conditions of high shear stress, decreased vWF:RCo activity, a reduction of vWF HMWM or a combination of these was present in 67 to 92 percent of patients with severe aortic stenosis and correlated significantly with the severity of valve stenosis. Primary hemostatic abnormalities were completely corrected on the first day after surgery, but tended to recur at 6 months, especially when there was a mismatch between patient and prosthesis i.e. under-sized.

Transcatheter Aortic Valve Replacement: Transcatheter Aortic Valve Replacement (TAVR) has emerged as a treatment for patients with severe aortic stenosis. Moderate to severe paravalvular leak (PVL) after TAVR remains a strong predictor of morbidity and mortality. However, it has been challenging to establish a unifying stratification for the severity of PVL with different imaging modalities. In both animal models and humans undergoing TAVR, PVL maintains high shear forces, preventing the recovery of vWF HMW multimers [43]. Accordingly, monitoring HMW vWF multimer recovery after TAVR may offer a readily available diagnostic tool to gauge the severity of PVL. The CT-ADP test is highly sensitive to defects in vWF HMW multimers. The loss of HMW multimers reduces the hemostatic competence of vWF and causes a prolongation of the CT-ADP. Ven Belle et al. reported that a vWF: HMW multimer ratio of ≥ 0.8 had a negative predictive value of 98.7% with an AUC of 0.94 and a value of CT-ADP of ≤ 180 s had an AUC of 0.93. They reported that among patients undergoing TAVR, mortality at 1 year was twice as high among those with more-than-mild PVL compared to those without a PVL and both the final CT-ADP and the final vWF: HMW-multimer ratio were better predictors of 1-year mortality than parameters determined by TEE [44].

Aortic Insufficiency and Mitral Insufficiency—AVWS has been reported in patients with aortic insufficiency and mitral insufficiency, including from mitral valve prolapse [45]. The incidence is variable and a reporting bias may contribute to reported rates of 15–20%.

Hypertrophic Cardiomyopathy—A report of five patients with symptomatic obstructive hypertrophic cardiomyopathy, spontaneous gastrointestinal, mucosal and excessive postsurgical bleeding and AVWS was published in 2011. Each patient underwent surgical septal myectomy with resolution of AVWS [46].

Ventricular Septal Defects—There have been reports of AVWS in patients with congenital ventricular septal defects with resolution following corrective surgery [47].

Acquired VWS and Cardiovascular Complications

Diseases, disorders and conditions characterized by high blood shear stress and proteolysis of vWF can, in some circumstances, cause increased vWF and factor VIII levels, thereby paradoxically increasing the risk of venous and arterial thromboembolic conditions [48], including myocardial infarction (MI) and ischemic stroke (IS). Several potential mechanisms have been proposed, including a relative increase in vWF as compared to ADAMTS13 level. An elevated vWF level may confer as much as a three-to-four-fold higher relative risk of ischemic stroke as compared to patients with lower levels of vWF [49]. Other studies have reported a concentration-dependent increased relative-risk of ischemic stroke, approaching seven-fold and for MI to be as high as four-to-five fold with increasing levels of vWF. Turbulent flow at sites of critical coronary stenosis may cause a local imbalance between vWF and ADAMTS13 (increased vWF/ADAMTS13 ratio in coronary flow) [50]. Heightened platelet activation stemming from platelet GPIbα may also contribute to a thrombotic phenotype. The incidence of MI or IS in patients with AVWS has not been well-defined and is likely under-recognized and diagnosed.

Mechanical circulatory support devices (described in detail in a subsequent section) may contribute to the development of thrombosis not only by contact of their artificial surfaces with blood but also through hydrodynamic forces [51]. This degree of high shear stress induces the transition of vWF from a globular state to an extended chain conformation, potentially facilitating its interaction with platelets. Hydrodynamic forces may also indirectly contribute to the development of thrombosis through the destruction of red blood cells. Hemolysis is associated with platelet activation and several mechanisms involving free Hb may account for this, including direct platelet activation, the production of reactive oxygen species and the scavenging of nitric oxide [52].

Using in vitro conditions representative of those occurring on the surface of extracorporeal membrane oxygenation devices, Da et al. [53] demonstrated that free Hb binds directly to vWF, thereby increasing the affinity of the vWF A1 domain for the glycoprotein Ib (GPIb) receptor on the surface of platelets. The active form of vWF bound to vimentin, and the purified A2 domain blocked that binding. The interaction of a gain-of-function A1A2A3 mutant with platelets was reduced using anti-vimentin antibody. The increased interaction between platelets and vWF facilitates binding of platelets to insolubilized fibrinogen or to components of the extracellular matrix such as collagen. This qualitative and quantitative alteration of platelet binding and aggregation induced by free Hb may contribute to the development of thrombi in mechanical circulatory devices despite anticoagulation with unfractionated heparin.

Perturbed Angiogenesis—Bleeding associated with angiodysplasia is common among patients with VWD and AVWS (summarized above). Because vWF is considered a negative regulator of angiogenesis, studies of vascular endothelial cell out-growth have been undertaken to better determine the responsible mechanisms of angiodysplasia [54]. While variability across VWD subtypes occurs, vascular endothelial cells from patients with Type 2A VWD display the greatest proliferative activity as well as heightened migration and angiopoietin gene expression and protein secretion.

Bartoli [55] and colleagues collected paired samples form 35 patients with continuous flow LVADs. In all patients, there was a loss of HMWM and a concomitant increase in vWF fragments. Human endothelial cells exposed to plasma from patients with LVADs showed abnormal angiogenesis with reduced tubal length and migration.

Acquired VWS and Mechanical Circulatory Support Devices

Mechanical circulatory support (MCS) devices, including veno-arterial extra-corporeal membrane oxygenation (ECMO) and LVADs are increasingly used as a bridge to heart transplant or destination therapy in patients with advanced heart failure. Several devices have been used over the two past decades (Table 1). The employment of veno-venous (VV) ECMO for respiratory support has also increased substantially for respiratory failure. As mechanical support device use increases with expanding indications, the occurrence of complications is also expected to increase. LVADs and ECMO are associated with a significant risk of major bleeding, not fully explained by anticoagulant or antiplatelet therapy. Gastrointestinal (GI) and muco-cutaneous are the most common sites; however, mediastinum/thorax and intracranial bleeding can also occur. The incidence of GI bleeding increased significantly, from 0.068 episodes per patient year (EPPY) for pulsatile LVADs to 0.63 EPPY for continuous-flow LVAD.

Pump thrombosis (PT) also occurs in patients following LVAD implantation. The rate of PT at 3 months post-HeartMate II implantation was originally reported in INTERMACs to be 2.2% before March 2011 (a period from 2004–2013), followed by an increase to 8.4% after March 2011 (a period from 2011–2013)- an observation believed to be related to inadequate systemic anticoagulation [56] While the concomitant risk of bleeding and thrombosis has been viewed by some in the field as an unexpected paradox, others have carefully considered potential explanations, including common coexisting or even biologically related mechanisms. In fact, both thrombosis and bleeding may be related to changes in vWF.

Von Willebrand factor kinetics in patients with mechanical circulatory support devices—vWF has primarily two crucial functions in hemostasis including facilitating platelet adhesion at vascular injury sites and platelet aggregation along with being a carrier of coagulation factor VIII. Pathological arterial blood flow creates fluid shear stresses and high shear rates. Increased shear rates exceeding 10,000 s^{-1} in LVADs cause vWF-mediated activation-independent platelet adhesion and aggregation, followed by stable aggregation.In addition, shear-induced erythrocyte lysis causes the release of free hemoglobin, that in turn, augments platelet adhesion and micro-thrombus formation on extracellular matrix in a glycoprotein GP Ib-IX-V and vWF-dependent manner [53]. Free-hemoglobin has also been

reported to sterically hinder ADAMTS-13–vWF interaction [57]. Free HB upregulates reactive oxygen species that, in turn, increase vascular tone, activate platelets, cause endothelial dysfunction and prompt coagulation and inflammation. Carbon monoxide and iron are released with the breakdown of HB and both contribute to coagulation and hypo-fibrinolysis [58]. Abnormal elevations of blood carboxy-hemoglobin have been observed in patients on LVAD support and bind to HB group(s) on plasmin and α2-anti-plasmin and decrease plasmin activity and enhance α2-anti-plasmin activity, thereby limiting fibrinolysis [59]. Collectively, these processes increase the risk of thrombosis.

AVWS is a well-described in LVAD patients [60] and patients on ECMO [61] In fact, a majority of patients treated with MCS develop AVWS with loss of HMWM. AVWS has also been described with micro-axial circulatory support devices (Impella™).

The most striking change in the physiology of circulating blood brought about by implantation of an LVAD is the conversion of normal pulsatile flow to continuous flow. As previously mentioned, there is an elevation of shear rate and stress within the device; however, the same is true in the systemic circulation as well [62]. An increase in shear stress above 8–10 Pa can result in the application of forces > ~ 10–15 pN (picoNewton = 10 – 12 N), which has been shown to alter the structure of vWF-specifically, unwinding the complex protein and exposing the A2 domain cleavage site to and enhancing vWF binding to platelets. Stretching forces are applied when vWF multimers form a “bridge” between two platelets that are traveling and rolling together in a shear field. Binding to the surface of a single platelet should not significantly increase the tension on vWF [63] but the peak force on two platelets held together by vWF is predicted to exceed 450 pN at a shear stress of 10 Pa. This force is enough to unfold many structural proteins and probably unfolds vWF domain A2, facilitating the cleavage of its Tyr 1605-Met 1606 bond by ADAMTS13. In this state, the force applied to a vWF at a given shear rate would be 2- to 3- orders of magnitude greater than the force applied to free vWF in solution. This specific force estimate may explain why vWF cleavage by ADAMTS-13 is enhanced when vWF multimers are platelet-bound.

The most common cause of GI bleeding in LVAD patients is the development of arteriovenous malformations (AVMs). The underlying pathophysiology is not fully known; however, the following explanations have been considered: 1) high intraluminal pressure causes reflective and localized smooth muscle relaxation and arterio-venular dilation [64] and 2) intestinal hypoperfusion resulting from reduced pulse pressure leads to regional hypoxia, synthesis and release of VEGF with vascular growth, proliferation, dilation and subsequent angiodysplasia. While the association of AVM with GI bleeding following LVAD implantation has some similarities to Heyde’s Syndrome described in patients with severe valve stenosis (summarized previously), the pathophysiology may be distinct. In AVWS, like in Heyde’s syndrome, changes in vWF, specifically the observed changes in multimers, vWF activity and vWF antigen do not consistently correspond or accurately predict the risk for GI bleeding.

Securing a diagnosis of acquired Von Willebrand Syndrome

The diagnosis of clinical VWD requires accurate testing for FVIII, vWFag, and typically several vWF activity assays, including vWF:RCo, vWF collagen binding (vWF: CB) and HMWM. Variation in HMWM is known to influence the results of these assays-specifically, a reduction in HMWM reduces the sensitivity of vWF: CB to the greatest degree and vWF: RCo activity to an intermediate degree [35].

In Type 2A VWD, there is a loss of vWF HMWM, mildly reduced vWFag and FVIII and a vWF functional discordance with vWF:RCo/vWFag or vWF:CB/vWFag < 0.7. Rare sub-types of VWD type 2A, including $2_A/II_C$, II_D and II_E, with gene mutations in the vWF pro-peptide or D3 or CK domains can be further differentiated by multimers patterns and shear-dependent polymer-platelet-aggregate formation, platelet binding and string formation [65]. Increased vWF pro-peptide to vWFag ratio may be helpful to distinguish AVWS from VWD, with ratios of 4.0 or higher (normal range 0.6–1.6) [66] (Table 2).

Treatment options

The management of patients with AVWS is based on the underlying disease, condition, device (if present) and pathological phenotype. Ischemic stroke and MI should be diagnosed employing contemporary blood biomarkers, electrocardiography and imaging. The initial treatment should proceed according to standards of care and best practice.

Thrombosis—Surgical management is the first choice for treatment of PT, however that may not be an option in patients who are poor surgical candidates due to other co-morbidities. Treatment for pump thrombosis varies on the type of device, with HMII patients experiencing significantly higher morbidity and mortality with thrombolysis than HVAD patients [67].

Bleeding—Traditionally, there have been different approaches that have been recommended for bleeding complications. The management strategies would need to be individualized weighing the risks of bleeding against thrombotic risks. The strategies include changes in the device setting including changing the speed or pulsatility. Other options would include local endoscopic therapies and pharmacologic management as outlined below. Endoscopic therapies are often used as a first line management of GI bleeding with good results, however given the recurrent nature of the bleeding in the setting of need for chronic anticoagulation, other therapy options are often required. Pharmacologic approach would include holding anticoagulation temporarily, attempt to lower the international normalized ratio, reduction in the antiplatelet therapy, thalidomide, Somatostatin analogues, desmopressin and vWF concentrate.

Changes in the pump speed in the continuous flow devices is recommended in the current guidelines (class IIb, level of evidence C) in patients with recurrent GI bleeding and AV malformations [68]. The correlation between speed and the percent of vWF HMWM was observed with HVAD devices but not as much with Heartmate II [59]. A recent study showed that reduced pulsatility in CF-LVADs led to an increase in bleeding complications. Those patients in the low pulsatility index group had a hazard ratio of 4.06 ($p = 0.04$) when

compared to the high pulsatility group [69]. Another study demonstrated that vWF defect under CF-MCS reflects the balance between degradation induced by high shear stress and the endothelial release triggered by the pulsatile flow [70]. Therefore, low pulsatility index is currently proposed to be related to increased risk of bleeding.

Initial trials for Heartmate II specified an INR goal of 2.0–3.0 with observed bleeding events. Prior evidence suggested that in patients with high risk of bleeding, the risk of lowering the target INR to 1.5–2.5 in addition to aspirin therapy appears to be small. More recent studies suggest INR values less than 2.0 increase the rate of thrombotic events occurring outside of the hospital among patients supported with CF-LVADs [71].

Thalidomide has been evaluated in several small studies; given its known anti-angiogenic properties and reports of efficacy in treating angiodysplasia related GI bleeding in other populations. There is a significant concern for thrombosis with the use of thalidomide especially with the mechanical device in place. Overall, the data regarding the use of thalidomide in LVAD patients is limited.

Octreotide is a somatostatin analog, which has been used in the management of GIB secondary to acquired angiodysplasia. The proposed mechanisms are decreased splanchnic blood flow, inhibition of VEGF reducing angiogenesis, increased vascular resistance and effect on platelet aggregation. Octreotide has been studied in several small trials showing mixed results. A recent multicenter retrospective study proposed that patients with continuous-flow left ventricular assist devices receiving secondary prophylaxis with octreotide had a significantly lower GI bleed recurrence compared with historical controls not treated with octreotide [72].

Desmopressin administration has been employed for the treatment of VWD for many years. It acts by releasing intact vWF from platelets and endothelial cells. While it has been anecdotally used for LVAD associated bleeding, no studies have formally investigated its role. There is a case report of using inhaled desmopressin in a patient with refractory gastrointestinal bleeding [73]. In general, DDAVP is of variable impact in the management of patients with Type 2 VWD.

Small studies have documented the use of Wilfactin®, vWF concentrate devoid of factor VIII, in a CF-LVAD patient with severe GI bleeding. Wilfactin® [74] is currently the only vWF plasma derived therapeutic concentrate almost devoid of FVIII that contains most of the HMWM found in normal plasma, and is used to treat patients with VWD leading to stabilization of hemoglobin and cessation of bleeding without thromboembolic complications. Recombinant human vWF (rvWF; vonicog alfa; Vonvendi®) is the only plasma-free and fVIII absent replacement product currently available. In addition, it contains ultra-HMWM and HMWM that could prove useful in managing “on-demand bleeding” in patients with AVWS.

While most clinicians consider therapeutic options when bleeding occurs, an optimal approach to the management of patients with AVWS would include a prophylactic or maintenance strategy to minimize the risk of bleeding. Prevention of Hemorrhage after Implantation of Mechanical Circulatory Support (PHAM) is a randomized control trial

currently underway to demonstrate the role of prophylactic treatment with vWF factor concentrate after implantation of continuous-flow left ventricular assist device (CF-LVAD). The study aims to enroll 156 adult patients with CF-LVAD who have functional defects of vWF measured between day 2 and day 4 after implantation. The primary outcome is percentage of patients with clinically significant bleeding within 3 months after implantation and the hypothesis is that prophylactic treatment with Wilfactin® after implantation of continuous-flow left ventricular assist device reduces the frequency of bleeding in comparison to the usual care. One would anticipate future studies of similar design with rvWF (Vonvendi®) as well.

As our understanding of the biological pathways involved in the etiology of the complications increases, there is a potential for exciting new treatments for prevention and treatment of these complications.

Future directions

The available data suggest that the underlying pathophysiology of AVWS is cleavage of vWF HMWM under high shear stress conditions. Patients with a variety of cardiovascular disorders and conditions can develop AVWS; however, the most commonly observed in adult cardiology is aortic stenosis, MCS-particularly LVAD and TAVR with post-procedural PVL. The investigation of vWF HMWMdynamics and the interactions with platelets during and shortly after TAVR is an area of ongoing research designed to provide insight toward identifying the optimal antithrombotic strategy in patients undergoing TAVR.

While we acknowledge that further investigation of the cascade of events in each of the common scenarios identified above is needed, fundamentally there are a few basic approaches that could be undertaken with an eye toward intervention. The first is to reduce or eliminate the high shear stress environment. The second is to reduce the susceptibility of vWF to cleavage. The third is to attenuate the biological effects of cleaved vWF, including direct and indirect effects on the microvasculature and increased concentration of VEGF as the likely culprit for cellular proliferation and angiodysplasia.

vWF is cleaved by ADAMTS13 at the A2 domain (Fig. 2). Accordingly, a therapy designed to inhibit the binding or catalytic activity of ADAMTS13 could prevent cleavage and the resulting down-stream effects observed in AVWS. There are several challenges and considerations with such a strategy, including 1) vWF, under normal circumstances, is metabolized with a circulating half-life of 12-20 h, and 2) preventing either the binding or catalytic activity of ADAMTS13 could, in essence, cause an excess of vWF HMWM and provoke the equivalent of thrombotic thrombocytopenic purpura (TTP) - a highly prothrombotic disorder.

An ex-vivo study using donor whole blood exposed to LVAD-like supra-physiological shear stress showed that inhibition of ADAMTS-13 by doxycycline decreased vWF degradation and improved vWF function without hyperactivation of platelets [75]. In a similar manner, Rauch et al. have identified an antibody (mAb508) that was able to block the vWF–ADAMTS-13 interactions, resulting in an inhibition of 83 ± 8% when used at a maximum

dose [76]. Although very promising, before its effectiveness can be assessed in LVAD patients, additional research is required in order to determine both the safety and feasibility of these possible treatment options, taking into account the expected risk of thrombotic events.

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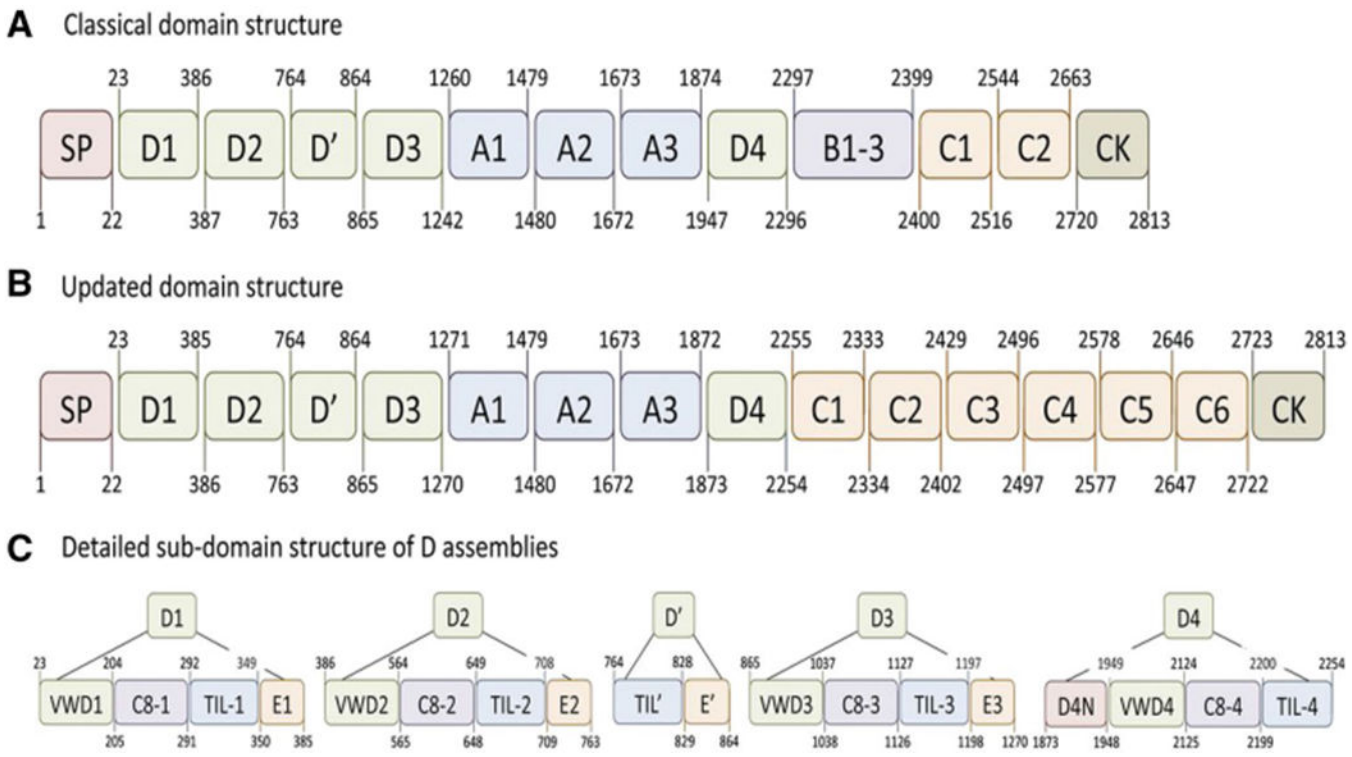

Fig. 1.

The structural domains of Von Willebrand Factor. Reproduced with permission from Lenting et al. [77]

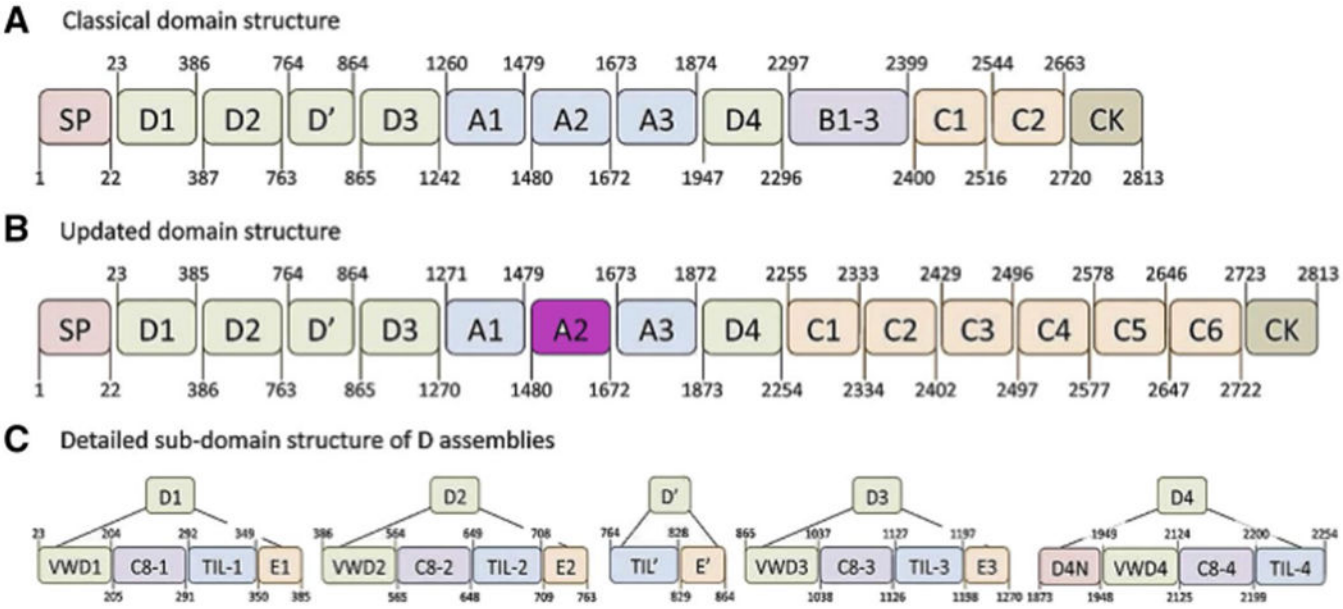

Fig. 2.

The cleavage of VWF takes place at the protein's A2 domain (highlighted in purple). This site could represent a potential target for future therapies designed with a goal to maintain a sufficient quantity or concentration of high molecular weight multimers, maintain VWF activity and reduce the generation of VWF fragments, thereby supporting hemostasis and preventing the over-expression of vascular growth factors that underlie perturbed angiogenesis and the development of gastro-intestinal angiodysplasias- a major source of serious bleeding. Reproduced with permission from Lenting et al. [77]

Table 1

The evolution of left ventricular assist devices

Type of LVAD	HeartMate II	HVAD	HeartMate 3
Design	Axial	Centrifugal	Centrifugal
Mechanical features	Mechanical pivot	Hydrodynamic	Magnetic
Thrombosis (per cent of patients)	10.7	6.4	0
Bleeding events (per person-year)	0.98	1.00	50 (33.1%)[a]
GI bleeding events (per person-year)	0.45	0.56	24 (15.9%)[a]

[a]Unable to calculate events per person-year as the trial follow up was only 6 months

LVAD Left ventricular assist device ; *HVAD* Hydrodynamic ventricular assist device

Table 2

Diagnostic Studies in VWD and AVWS 2018

Assay	Type 1	Type 2A	Type 2B	Type 2 M	Type 2 N	Type 3	AVWS	Reference Range
VWF:Ag	Low	Low	Low	Normal/low	Normal/Low	Und	Normal/low	50-240 IU/dl
VWF:GPIbM[a] or VWF:RCo[a]	Low	Very low	Very low	Low	Normal/low	Und	Low	50-240 IU/dl
VWF:GPIbM/Ag or VWF:RCo/VWF:Ag	Normal	Low	Low	Low	Normal	–	Normal/low	>0.6
VWF:CB	Low	Very low	Very low	Normal/low	Normal/low	Und	Low	50-240 IU/dl
VWF:CB/VWF:Ag	Normal	Low	Low	Normal/low	Normal	–	Normal/low	>0.6
FVIII:C	Normal/low	normal/low	Normal/low	normal/low	Very low	Very low	Normal	60-190 IU/dl
FVIII:C/VWF:Ag	Normal	Normal	Normal	Normal	Low	–	Normal/low	> 0.7
HMWM	Normal	Very low/und	Very low/und	Low	Low	Very low	Low	Normal distribution
VWF fragments	NP	NP	NP	NP	NP	NP	Present[+]	NP

AVWS Acquired Von Willebrand Syndrome

FVWII:C factor VIII; *VWF* von Willebrand factor; *VWF:Ag* VWF antigen; *VWF:CV* VWF collagen binding; *VWF:GPIbM* VWF binding to mutant (gain of function) GPIb; *VWF:RCo* VWF ristocetin cofactor activity; *HMWM* high molecular weight multimers; Und,undetectable; *NP* not present

[a]VWF:GPIbM has replaced the VWF:RCo in some centers, but VWF:RCo or any VWF platelet-dependent activity assay could be used here as well

[+]Particularly in patients with left Ventricular Assist Devices

Adapted from Keesler DA. Research and Practice in Thrombosis and Haemostasis 2018; 2: 34-41