von Willebrand Disease: 100 Years of Progress and New Horizons

Author:	Helena Bradbury, EMJ, London, UK

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THE 2026 ANNUAL Congress of the European Association for Haemophilia and Allied Disorders (EAHAD) placed special emphasis on the centenary of von Willebrand disease (VWD), first described in 1926 by Erik von Willebrand. This milestone provided an opportunity to reflect on a century of scientific progress and clinical advancement.

The Arosenius Lecture, dedicated to fostering innovation in haemophilia research and care, commemorated this anniversary by tracing the historical evolution of the disease, reviewing key developments in its diagnosis and management, and exploring future directions in research and treatment.

PAST, PROGRESS, AND PATH FORWARD

James O'Donnell, Consultant Haematologist at the National Coagulation Centre, St James's Hospital, Dublin, Ireland, opened his lecture by reflecting on the historical foundations of VWD. First described in 1926 in a 5-year-old girl, VWD is now recognised as the most common inherited bleeding disorder, affecting approximately 1% of the general population.[1] Clinically, it is characterised by mucocutaneous bleeding symptoms, including epistaxis, gingival bleeding, easy bruising, menorrhagia, and prolonged bleeding following trauma, dental procedures, or surgery. O'Donnell emphasised that, beyond improved clinical recognition, significant advances have been made in understanding the complex biology of the disease. Under physiological conditions, von Willebrand factor (VWF) biosynthesis is largely confined to endothelial cells and megakaryocytes. The VWF monomer consists of 2,050 amino acids, while its propeptide comprises 741 amino acids, reflecting the structural and functional complexity that underpins its critical role in haemostasis.

O'Donnell then discussed in detail the biosynthesis of VWF, explaining that monomer formation occurs within endothelial cells, where VWF is synthesised as a 250 kDa precursor monomer.[2] Within the endoplasmic reticulum, C-terminal disulphide bonds form, resulting in dimerisation. These dimers are subsequently transported to the Golgi apparatus, where N-terminal disulphide bonds facilitate multimerisation. The mature VWF is ultimately secreted into the plasma as a heterogeneous array of multimers, each composed of approximately 40–100 monomeric subunits.

"I think it's very important to remember, and something that's often forgotten, is that VWF actually exists *in vivo* as several discrete pools," noted O'Donnell. He went on to outline the four principal VWF pools currently recognised.[3] First, heterogeneous multimeric VWF is secreted from endothelial cells and circulates freely in the plasma. Second, high molecular weight VWF multimers are stored within Weibel–Palade bodies, specialised, rod-shaped secretory organelles unique to endothelial cells that serve as storage sites for VWF

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and P-selectin. Third, high molecular weight VWF multimers are also contained within platelet α-granules, accounting for approximately 15% of the total VWF present in platelet-rich plasma. Finally, a small proportion of VWF remains bound within the extracellular matrix of the vessel wall following endothelial secretion.[3]

OVERVIEW OF THE COAGULATION CASCADE AND DYSREGULATION IN VON WILLEBRAND DISEASE

So, what is the function of VWF? As described by O'Donnell, VWF primarily acts as a carrier protein for Factor VIII, stabilising it in the circulation and protecting it from proteolysis and premature clearance. In the event of vascular injury, subendothelial collagen is exposed, triggering the release of VWF from endothelial cells. VWF binds to collagen and recruits platelets to the site of injury, facilitating platelet adhesion and aggregation to form the initial platelet plug, an essential step in primary haemostasis.

Secondary haemostasis involves activation of the coagulation cascade through the intrinsic and extrinsic pathways. The intrinsic pathway includes Factors XII, IX, and VIII, ultimately leading to activation of Factor X. The extrinsic pathway is initiated by tissue factor and Factor VII, which also activate Factor X. Both pathways converge on the common pathway, where activated Factor X, in the presence of calcium and Factor V, converts prothrombin (Factor II) into thrombin. Thrombin then cleaves fibrinogen (Factor I) to form fibrin, an elastic, fibrous protein that stabilises the clot. VWD predominantly affects primary haemostasis by impairing platelet adhesion and aggregation. However, it also influences secondary haemostasis through reduced stabilisation of Factor VIII, thereby linking defects in VWF to abnormalities in both platelet function and coagulation.[4]

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WHERE ARE WE IN 2026 WITH VON WILLEBRAND DISEASE?

Highlighting the scale of progress to date, O'Donnell noted that there are now more than 15,000 VWD-related publications indexed on PubMed. A major milestone was reached in 2021 with the publication of comprehensive, evidence-based guidelines developed collaboratively by the American Society of Hematology (ASH), the International Society on Thrombosis and Haemostasis (ISTH), the National Hemophilia Foundation (NHF), and the World Federation of Hemophilia (WFH).[5] These guidelines were grounded in a systematic review of the available evidence and represented an important step towards standardising diagnosis and management.

However, as O'Donnell emphasised, important limitations remain. Of the 11 diagnostic recommendations in the 2021 ASH guidelines,[5] nine were graded as conditional suggestions rather than strong recommendations. Similarly, all eight management recommendations were classified as suggestions, underscoring the continued reliance on low- to moderate-certainty evidence in many areas of VWD care. Looking ahead, several key research gaps persist. First, there is a need for a clearer definition of the clinical significance of mild-to-moderate reductions in plasma VWF levels (30–50 IU/dL). Second, further investigation is required to better understand the emerging non-haemostatic functions of VWF. Finally, the development of novel therapeutic strategies remains a priority to enhance and individualise the clinical management of VWD.

Expanding on this first research priority, O'Donnell referred to previous guideline recommendations stating that patients with a significant personal bleeding history and plasma VWF levels in the 30–50 IU/dL range should be classified as having "low VWF." This represents the most common diagnostic category within the VWD spectrum, estimated to affect more than 7.5 million individuals in the USA alone.[6]

He then drew attention to the Low Von Willebrand in Ireland Cohort Study (LoVIC), a prospective longitudinal cohort study that has generated several important publications in this field. Data from LoVIC have shown that a proportion of patients with mild-to-moderate reductions in VWF levels nonetheless experience clinically significant bleeding.[3] In a 2017 study, more than 70% of female participants had elevated bleeding assessment tool (BAT) scores.[7] Comparable findings were reported in the Zimmerman Program, where over 62% of individuals within the "low VWF" cohort demonstrated an increased ISTH BAT score.[8] However, this association has not been consistently observed across all populations. For example, a 2020 study found no significant increase in bleeding symptoms among children with mild-to-moderate reductions in VWF levels.[9]

Summarising these findings, O'Donnell concluded that a small, but clinically important, subset of patients with mild-to-moderate reductions in VWF levels exhibit a bleeding phenotype that remains unexplained.[10] He further highlighted the observed overlap between this subgroup and patients diagnosed with bleeding disorder of unknown cause, suggesting that as-yet unidentified genetic or biological modifiers may link the two conditions.

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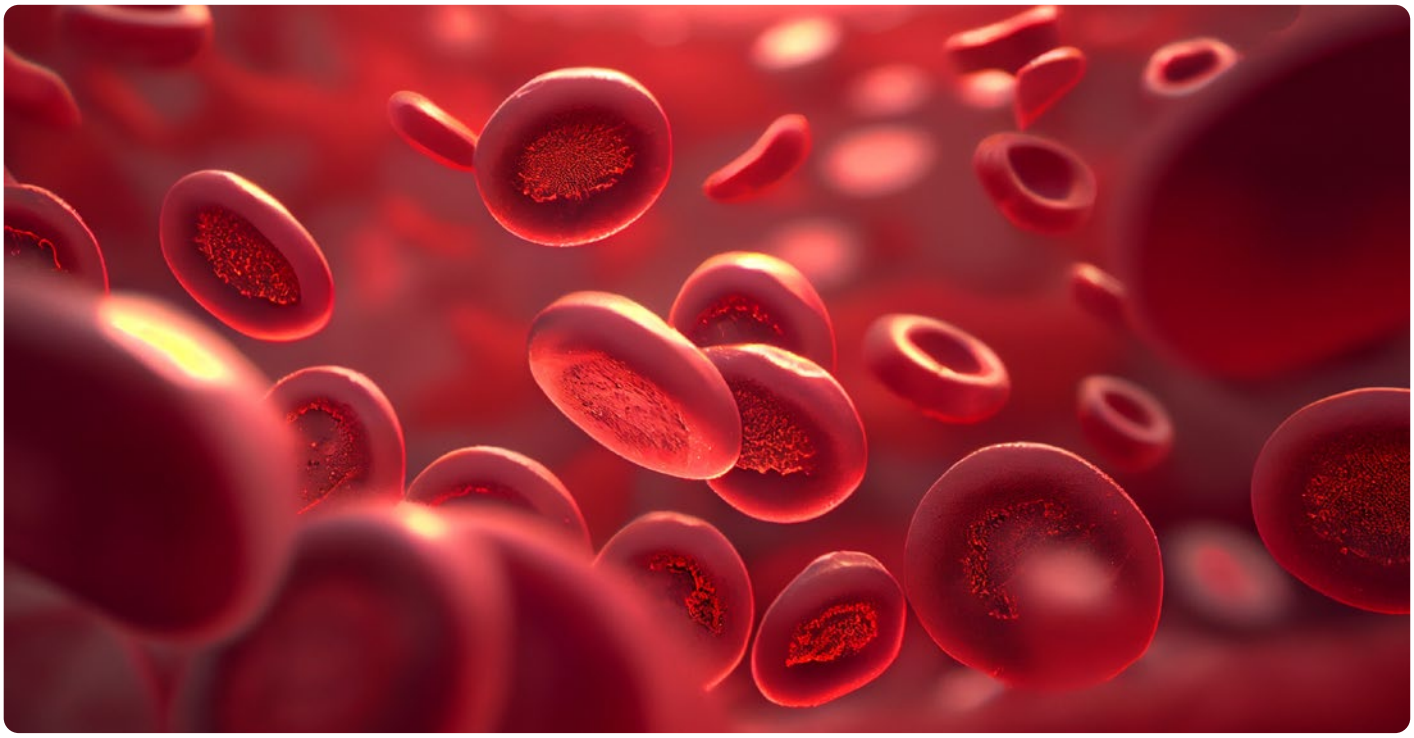

> **A deeper understanding of these interactions may help explain the bleeding phenotype observed in a subset of patients with "low VWF"**

EMERGING RESEARCH

So, what are the future research priorities in VWD? First, O'Donnell emphasised the need to define the pathogenic mechanisms responsible for VWD in families in whom no causative VWF sequence variant can be identified. Second, it remains crucial to understand why some individuals with mild-to-moderate reductions in plasma VWF levels experience significant bleeding, while others do not. Recent work has demonstrated that VWF interacts with a broad network of proteins, with more than 50 ligand-binding partners reported to date.[11] A deeper understanding of these interactions may help explain the bleeding phenotype observed in a subset of patients with "low VWF." These ligand interactions influence multiple aspects of VWF biology, including its biosynthesis, intracellular trafficking within endothelial cells, susceptibility to proteolysis in the circulation, and regulation of cellular clearance pathways.

Beyond haemostasis, emerging research has identified additional biological roles for VWF. It has been implicated in the regulation of angiogenesis,[12] while binding of growth factors to the VWF-A1 domain appears to contribute to wound-healing processes.[13] More recently, VWF has also been shown to play a role in modulating innate immune responses.[14]

O'Donnell also highlighted the significant clinical burden faced by women with low VWF, particularly heavy menstrual bleeding. Data from a 2017 study showed that 40% of affected women required time off work or school, 36% required iron therapy, 24% underwent dilatation and curettage, and 8% required hysterectomy, figures that underscore the substantial impact on quality of life.[7]

Finally, several novel therapeutic strategies are emerging in VWD, including a pegylated aptamer (rondoraptivon pegol, BT200), a bispecific nanobody (KB-V13A12), and a monovalent antibody (HMB-002), reflecting a shift towards more targeted and mechanism-based treatment approaches.

CONCLUSION

In conclusion, the Arosenius Lecture highlighted both the remarkable progress made in understanding VWD and the significant challenges that remain. A century after its first description, advances in molecular biology, clinical phenotyping, and evidence-based guidelines have transformed patient care. Yet important uncertainties persist, particularly regarding the mechanisms underlying "low VWF," variability in bleeding phenotype, and the broader biological roles of VWF beyond haemostasis. Emerging insights into VWF interactions and novel therapeutic strategies offer promising avenues for more personalised management. Ultimately, the next phase of research will be critical in translating biological discovery into improved outcomes for patients.

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