# von Willebrand Disease
## Diagnostic Strategies and Treatment Options

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**KEYWORDS**

• von Willebrand disease • von Willebrand factor • Mucocutaneous bleeding

**KEY POINTS**

- von Willebrand disease (VWD) is one of the most common inherited bleeding disorders.
- The clinical diagnosis of von Willebrand disease is usually made through the combination of clinical symptoms of mucocutaneous bleeding and laboratory-based evidence of von Willebrand factor (VWF) deficiency or dysfunction.
- Clinical subtypes of VWD are important to distinguish because they may have therapeutic implications.
- Treatment of VWD is designed to increase or replace circulating VWF, along with adjunctive therapies.

### INTRODUCTION

First described by Erik von Willebrand[1] in a Scandinavian family in 1926, von Willebrand disease (VWD) is an inherited bleeding disorder with a reported symptomatic prevalence of 1 in 10,000. VWD affects individuals of all races and can have clinical implications from childhood, when it is usually first discovered, to adulthood, when management of comorbid conditions is complicated by the bleeding tendency. VWD is classically manifested by a predisposition to mucocutaneous bleeding (MCB); this leads to increased risks of postoperative blood loss; significant epistaxis; oral bleeding; and, in women, menorrhagia. Although rare, life-threatening bleeding can occur. VWD is characterized by a deficiency, either quantitative (type 1, type 3) or qualitative (type 2), of von Willebrand factor (VWF).[2] The diagnosis and treatment of VWD requires the understanding of the necessary functions of VWF in promoting

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hemostasis and a familiarity with the clinical assays and treatments necessary to correct the bleeding diathesis seen in VWD.

## STRUCTURE AND FUNCTION OF VON WILLEBRAND FACTOR

VWF is a plasma glycoprotein that plays critical roles in promoting hemostasis by mediating the binding of platelets to collagen, mostly through its interaction with platelet glycoprotein (GPI)-1bα at sites of vessel injury and by stabilizing factor VIII (FVIII) from clearance in the circulation. VWF is the product of the *VWF* gene located in the short arm of chromosome 22. VWF contains a 22 amino acid signal peptide, followed by a 741 amino acid propeptide (commonly referred to as the D1-D2 domains) to ultimately generate a 2050 amino acid mature protein. The propeptide is critical for protein maturation and assembly; it is cleaved and released in equimolar amounts to the mature protein.[3] VWF is primarily synthesized in endothelial cells and megakaryocytes, and is stored in platelet alpha granules and Weibel-Palade bodies in endothelial cells. In terms of protein structure, the classic domain structure of the mature protein is D′-D3-A1-A2-A3-D4-B1-B2-B3-C1-C2-CK, although recent revisions have further segmented the protein into far more domains based on recent findings and correlation to function.[4] The different domains of VWF equip it with its varied functions in vivo. Collagen binding is primarily mediated by the A1 and A3 domains; platelet-binding function is primarily mediated by the A1 and C1-C2 domains, and FVIII binding is primarily mediated by the D′D3 domain.[4]

VWF has a unique ability to multimerize, in which individual VWF monomers undergo tail-to-tail dimerization in the C-terminus in the endoplasmic reticulum before N-terminal linkage via disulfide bonds at cysteine residues in the Golgi network.[5] This remarkable capability allows VWF to form a range of complexes, from individual monomers to large multimeric structures. This concept is critically important to the understanding of VWD because its multimeric structure is correlated with function, whereby increased large multimeric structure of VWD correspond with increased hemostatic ability. Abnormalities in multimer structure can lead to a qualitative defect in VWF (see later discussion). The primary modulator of VWF is ADAMTS13 (a disintegrin and metalloproteinase with a thrombospondin type-1 motif, member 13), which cleaves VWF at the A2 domain when VWF is unraveled under flow conditions. This can result in a change in multimeric distribution and may lead to an increased risk of bleeding with increased ADAMTS13 activity or conversely a predisposition to thrombosis if there is inhibition of ADAMTS13 function via autoantibodies, as seen in thrombotic thrombocytopenia purpura.[6,7]

## CLINICAL DIAGNOSTIC CRITERIA FOR VON WILLEBRAND DISEASE

The diagnosis of VWD is made by the combination of (1) signs or symptoms of clinical bleeding and (2) laboratory-based evidence of quantitative or qualitative deficiencies of VWF. VWD is commonly diagnosed in childhood or adolescence, especially for adolescent girls because VWD can lead to significant menorrhagia. However, it is not uncommon for individuals to go many years before diagnosis, thus there should be a high index of suspicion even in adults who present with symptoms of bleeding. MCB is the most common type of clinical bleeding, often manifesting as epistaxis, oral bleeding, purpura, petechiae, menorrhagia, and gastrointestinal bleeding. To standardize the reporting and consideration of varied bleeding symptoms, the International Society of Thrombosis and Haemostasis (ISTH) subcommittee on VWF has published generalized guidelines on bleeding symptoms to be reviewed when considering the diagnosis of VWD.[8] Further research has led to the development of validated