ABSTRACT FORM ECAT SYMPOSIUM 15 – 16 SEPTEMBER 2022

Name and affiliations:

Prof. Dr H.C.J. Eikenboom, Department of Internal Medicine, Division of Thrombosis and Hemostasis, Leiden University Medical Center

Title:

Low Von Willebrand Factor and diagnostic threshold

Abstract:

Von Willebrand disease (VWD) is the most frequent inherited bleeding disorder characterized by defective platelet adhesion and aggregation due to a deficiency or functional defect of von Willebrand factor (VWF). VWD is characterized by mucosa-associated bleeding and bleeding after surgery and trauma. The diagnosis of VWD is based on a personal or family history of bleeding and laboratory abnormalities of VWF. VWD is classified in three types: type 1 characterized by quantitative deficiency of VWF (70 to 80% of cases), type 2 by dysfunctional VWF (20% of cases), and type 3 by a virtual absence of VWF (very rare). The prevalence of VWD has been estimated from population studies to be around 1%, however based on patients registered at specialized centers the prevalence of clinically relevant VWD is closer to 1 per 10,000. The prevalence is however strongly dependent on the applied diagnostic VWF cut-off level that may very among studies and guidelines between 30 and 50 IU/dL.

The diagnosis and classification is usually straightforward for types 2 and 3 VWD and the phenotypic diagnosis can usually be confirmed at the genetic level. However, in the case of type 1 VWD, with mild quantitative deficiency of VWF, the diagnosis is often difficult. All functional and structural VWF parameters are essentially normal in type 1 VWD and in line with the level of reduction of the VWF antigen. So, the only diagnostic test is actually the VWF antigen level, but it is difficult to determine an unambiguous cut-off level for VWF. There is not a specific level below which bleeding symptoms are consistently present. There may be major clinical variation regarding the bleeding symptoms and associated VWF levels. The VWF levels may increase with age, are dependent on ABO blood type, and may vary with the presence of co-morbidities. The bleeding phenotype may also be modified by additional mild platelet-function defects. All these issues complicate a straightforward diagnosis of type 1 VWD.

When VWF levels are below 30 IU/dL, usually also VWF mutations can be identified. However, when levels are between 30-50 IU/dL often no genetic defects can be identified within the VWF gene. Leading to the question whether these are actually reflecting disease or just variations in population distribution. In recent years persons with VWF levels between 30 and 50 IU/dL have been indicated as having “low VWF” or “possible type 1 VWD”. The recent ASH ISTH NHF WFH 2021 guidelines on the diagnosis of VWD made the following recommendation: The panel recommends a VWF level of <30 IU/dL regardless of bleeding, and for patients with abnormal bleeding, a VWF level of <50 IU/dL to confirm the diagnosis of type 1 VWD. Furthermore, the guideline committee suggested not to use ABO-specific reference ranges and that the testing should be performed when patients are at a baseline state of health to avoid increased levels due to acute-phase response.

For research a specific cut-off may be useful for categorization of patients and comparison of groups. However, the VWF level is a continuous variable that in clinical practice will always need to be considered in conjunction with the clinical bleeding symptoms. New assays that better reflect the actual bleeding phenotype of the patient are needed to solve this diagnostic dilemma.