HHS Public Access

Author manuscript

J Thromb Haemost. Author manuscript; available in PMC 2017 August 30.

Published in final edited form as:

J Thromb Haemost. 2015 July ; 13(7): 1345–1350. doi:10.1111/jth.12964.

Platelet-dependent von Willebrand factor activity. Nomenclature and methodology: communication from the SSC of the ISTH

I. BODÓ[*], **J. EIKENBOOM**[†], **R. MONTGOMERY**[‡], **J. PATZKE**[§], **R. SCHNEPPENHEIM**[¶], and **J. DI PAOLA**[**] **ON BEHALF OF THE SUBCOMMITTEE ON VON WILLEBRAND FACTOR**

[*]Department of Hematology and Stem Cell Transplantation, St László Hospital, Budapest, Hungary [†]Department of Thrombosis and Hemostasis, Leiden University Medical School, Leiden, the Netherlands [‡]Department of Pediatrics – MFRC, Medical College of Wisconsin, Milwaukee, WI, USA [§]Department of Assay Development, Siemens Healthcare Diagnostic Products GmbH, Marburg [¶]Department of Pediatric Hematology and Oncology, University Medical Center Hamburg-Eppendorf, Hamburg, Germany [**]Pediatrics/Genetics, University of Colorado Denver, Aurora, CO, USA

von Willebrand disease (VWD) is the most common bleeding disorder in man [1]. Measuring VWF functional activity is critical for making the correct diagnosis and classification. Traditionally considered the ‘gold standard’ for evaluating platelet-dependent VWF function, the ristocetin cofactor activity (VWF:RCo) assay was developed after the discovery of platelet aggregation by ristocetin [2–6].

Imprecision and insensitivity of the VWF:RCo assay led to the development of new assays. Some of the issues related to VWF activity testing have recently been reviewed [7–11]. Because it is critical that users of these various assays recognize differences between details of functions being measured, a new nomenclature was developed by the VWF Subcommittee of the Standardization and Scientific Committee (SSC) of the International Society for Thrombosis and Haemostasis (ISTH). The guiding principles in developing a practical and accurate nomenclature included simplicity, consistency and accuracy. The result of this effort reached consensus and was formally approved by the VWF Subcommittee at the Milwaukee SSC Meeting on 23 June 2014 (Table 1).

Correspondence: Imre Bodó, Department of Hematology and Stem Cell Transplantation, St László Hospital, 5-7 Albert Flórián út, Budapest HU-1097, Hungary. Tel.: +1 6786720602; fax: +36 14558252. bodoimre@freemail.hu.

Addendum

I. Bodó prepared the manuscript and chaired the *ad hoc* VWF Activity Nomenclature Committee. J. Eikenboom, R. Montgomery, J. Patzke, R. Schneppenheim and J. Di Paola actively participated in developing the best nomenclature and they all critically reviewed and revised the manuscript, significantly contributing to the final version. J. Eikenboom and J. Di Paola, as former and current chairmen of the ISTH SSC von Willebrand Subcommittee, were responsible for initiating and concluding the Nomenclature Committee task.

Disclosure of Conflict of Interests

J. Patzke discloses that he is an employee of Siemens Healthcare Diagnostics GmbH. J. Patzke and R. Schneppenheim hold a patent ‘Method for determining von Willebrand factor activity in the absence of ristocetin and for determining the ADAMTS-13 protease’. R. Montgomery discloses a patent licensed to GTI and that GTI-Immunocor has licensed a ristocetin-free assay from the Blood Center of Wisconson and the Medical College of Wisconsin. All other authors state that they have no conflict of interest.

Supporting Information

Additional Supporting Information may be found in the online version of this article

Ristocetin cofactor activity (VWF:RCo) assays

All VWF:RCo assays have in common the use of (i) intact (native, formalin-fixed or reconstituted lyophilized) platelets and (ii) ristocetin.

First-generation (manual) VWF:RCo assay

The original description [4] of the test used glass slides for the reaction. Although still used in some laboratories, this method is laborious, subjective and operator dependent.

Second-generation (semi-automated) VWF:RCo assay

In the second-generation assays, VWF:RCo was adapted to traditional aggregometers, and commercial reagents became available. The reaction velocity (slope of the aggregation curve) is compared to the calibrator. Used in many laboratories throughout the world, this semi-automated VWF:RCo assay continues to be plagued with technical issues as it is insensitive (limit of detection, LOD: > 10–20 IU dL^{-1}) and imprecise (coefficient of variation [CV], up to 20–30%) [12].

Third-generation (fully automated) VWF:RCo assay

The VWF:RCo assay was successfully adapted to automated coagulometers with the advantage of improved precision and higher throughputs. Currently, most coagulation laboratories use one of the published protocols listed in Table S1.

Fourth-generation (modified fully automated) VWF:RCo assay

Recently, building on prior experience to improve assay characteristics [13], a set of modifications to the original automated assay was reported to markedly improve sensitivity (LOD, 3 IU dL^{-1}) with a CV of 6–9% (Table S1, bottom row) [14,15].

VWF:RCo flow cytometry methods

A sensitive flow cytometry analysis [16–19] has not gained wide acceptance because of the requirement for equipment and expertise not commonly available in hemostasis laboratories.

Advantages and disadvantages of the VWF:RCo assay

For decades, the VWF:RCo assay represented the gold standard for measuring VWF activity; therefore, much experience was accumulated. Furthermore, most data correlating VWF levels and treatment with desmopressin or VWF concentrates relate to VWF:RCo [5,20,21]. However, the disadvantages of the VWF:RCo assays are numerous. The tests have poor sensitivity [12], which prevents measuring VWF activity < 10 IU dL^{-1}, making it difficult to characterize patients with *severe VWD*. Additionally, because the VWF:RCo/VWF:Ag ratio is critical for the current classification, this poor sensitivity may lead to potential misdiagnoses. First and second-generation assays were also time consuming and poorly standardized.

The high coefficient of variation [12] may lead to false diagnoses in the *moderately reduced VWF* range. Potential sources of error include instability and batch-to-batch variability of

ristocetin or of the platelet reagent (whether locally prepared or commercially lyophilized) and some intrinsic instability of the assay system.

An additional disadvantage comes from the fact that VWF:RCo actually measures two parameters, (i) binding of ristocetin to VWF and (ii) binding of ristocetin-'activated' VWF to test platelets (i.e. activity is triggered by an artifact, because, although believed to induce conformational changes resembling the physiological activation of VWF brought about by immobilization on the collagen-rich subendothelial surface exposed to high shear stress [22,23], ristocetin itself is not a physiological activator of VWF). Two sequence variants, p.P1467S and the H-allele of a common polymorphism p.D1472H, in the ristocetin binding region of the A1 domain (exon 28) [19,24], cause spuriously decreased VWF:RCo levels. The H-allele of the p.D1472H polymorphism is common in the African American population and results in a decreased VWF:RCo/VWF:Ag ratio [24]. These low VWF activities do not correlate with bleeding symptoms but reflect an assay artifact. For these reasons, the time-honored notion that VWF:RCo is indispensable is rapidly changing [7–9,25].

Ristocetin-triggered GPIb binding (VWF:GPIbR) assays

Vanhoorelbeke, Deckmyn and colleagues developed a platelet-free ELISA test using a recombinant GPIb fragment captured by a monoclonal antibody coated onto ELISA plates [26] with much improved LOD and CV [27–29] (Table S2). Subsequently, the same principle was used to develop latex or magnetic particle-enhanced automated assays. Correlation with the classic VWF:RCo test is reported to be excellent, proving the validity of the concept (Table S2). However, it is important to note that these assays use different reagents for capturing the GPIb fragment as well as different recombinant or plasma-derived fragments (Table S2). The source and concentration of ristocetin are also variable. Finally, the epitope specificity of the monoclonal antibody capturing GPIb is critical [27]. Nevertheless, proper automated applications of the assay principle allow for precise and sensitive detection of VWF activity [25,30–33].

Gain-of-function mutant GPIb binding (VWF:GPIbM) assays

The newest VWF activity assays use recombinant gain-of-function mutant GPIb fragments, allowing spontaneous binding of VWF to the mutant GPIb without ristocetin (Table S3). The binding is optimized when any two of three specific mutations are introduced [34]. Recent published data support the concept that the VWF:GPIbM assays are consistently correlated with the standard VWF: RCo assay [25,35–37]. These assays are precise [35], sensitive [35,38,39] and not subject to the falsely low values seen with the p.P1467S and p.D1472H polymorphisms [34]. Additionally, with ELISA applications of these new assays it may be possible to differentiate between VWD type 2A and 2B [34,40,41]. These assays have been referred to as 'VWF Ac' or 'INNOVANCE VWF Ac'. The more descriptive 'VWF:GPIbM' is the preferred name.

Monoclonal antibody binding-based VWF activity (VWF: Ab)

The original ELISA assay used the monoclonal antibody REF-VIII:R/2, which is directed against a VWF epitope involved in VWF-GPIb binding [42–44]. The commercial latex-enhanced automated immunoturbidimetric assay (LIA) version is marketed as 'VWF activity' assay, abbreviated as *VWF:Act*. As the assay does not provide information about the function of VWF being measured, it is preferable to use the more descriptive VWF:Ab term.

The LIA (HemosIL VWF activity) performed better than the ELISA [45,46] in discriminating VWD subtypes and showed good correlation with VWF:RCo [47–51]. Advantages of the HemosIL VWF:Ab test are several, including the fact that it is user-friendly, applicable to several platforms, and thus, feasible for routine laboratories [48,49]. However, because the VWF:Ab assay reports the binding of the VWF A1 domain to a mAb and not to GPIb, it is unclear to what extent this antibody is able to accurately mimic the GPIb binding surface [50]. Some VWD type 2M mutations (e.g. p.G1324A) are not detected by the assay [51] and it is not clear to what extent the assay is sensitive to the loss of HMW multimers [47,48]. Furthermore, the VWF:Ab assay did not resolve the problem with the lower limit of detection because linearity is reported [47] to be acceptable only above 12.5 IU dL^{-1}. In addition, the current package insert indicates that the LOD is 19 IU dL^{-1}. Taken together, the good overall correlation with the VWF:RCo assay probably gives this assay a role in the routine screening of VWF patients, when combined with other tests. However, the VWF:Ab test cannot be recommended as a replacement for the VWF:RCo assay.

An assay using a similar principle uses a llama nanobody that recognizes the active conformation of VWF, allowing the detection of constitutionally active VWF in VWD type 2B and thrombotic thrombocytopenic purpura (TTP) [52], but does not measure VWF activity and is not discussed further in this review.

In summary, the past several years have seen a remarkable (r)evolution of assays measuring platelet-dependent VWF activities. The original manual and semi-automated methods have mostly been replaced by automated techniques with higher precision. In the most recent applications described here, the platelets have been substituted by recombinant GPIb fragments immobilized on ELISA wells or latex particles, allowing accurate measurement of VWF activity in the very low (< 1–10 IU dL^{-1}) range. Further innovation has led to the newest generation of accurate and sensitive ristocetin-free assays, which prevent the problems that plagued the ristocetin-based assays, including false-positive results in certain populations.

While most welcome in the battery of tests for the diagnosis of VWD, the exact behavior of the particular assays is not clear at this time. Side-by-side comparison using healthy controls as well as pathological plasma samples (including VWD type 1, type 2 and type 3 patients) is urgently needed. An ongoing comparative study [53] is expected to provide useful information for clinicians and laboratory professionals alike, and will likely lead to gradual replacement of the older VWF:RCo assay. In addition to providing the technical details of the currently available assays, this short review provides the new nomenclature approved by

the ISTH VWF SSC to clearly distinguish various test principles, which is recommended for all future communications in the field.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

The following members of the *ad hoc* VWF Activity Nomenclature Committee contributed to this manuscript: Luciano Baronciani (Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, A. Bianchi Bonomi Hemophilia and Thrombosis Center, Milan, Italy), Ulrich Budde (Laboratory of Hemostasis, University Hospital Hamburg, Hamburg, Germany), Giancarlo Castaman (Careggi University Hospital, Center for Bleeding Disorders, Department of Heart and Vessels, Florence, Italy), Augusto B. Federici (Angelo Bianchi Bonomi Hemophilia and Thrombosis Centre, Milano, Italy), Kenneth D. Friedman (Medical College of Wisconsin, Department of Internal Medicine and Pathology, Milwaukee, WI, USA), Andrew Lawrie (Unversity College London, Haemostasis Research Unit, London, UK), Flora Peyvandi (Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, A. Bianchi Bonomi Hemophilia and Thrombosis Center, Milan, Italy, and Universitá degli Studi di Milano, Department of Pathophysiology and Transplantation, Milan, Italy), and J. Evan Sadler (Washington University School of Medicine, Departments of Medicine, and Biochemistry and Molecular Biophysics, St Louis, MO, USA). We are grateful to the members of the ISTH SSC VWF Subcommittee, S. Haberichter, D. Hampshire, P. James, K. Kokame, J. A. Kremer Hovinga Strebel, F. W. G. Leebeek and A. Tosetto, for their support and intellectual input during discussions of the nomenclature.

References

1. Rodeghiero F, Castaman G, Dini E. Epidemiological investigation of the prevalence of von Willebrand's disease. Blood. 1987; 69:454–9. [PubMed: 3492222]
2. Howard MA, Firkin BG. Ristocetin–a new tool in the investigation of platelet aggregation. Thromb Diath Haemorrh. 1971; 26:362–9. [PubMed: 5316292]
3. Weiss HJ, Hoyer LW, Rickles FR, Varma A, Rogers J. Quantitative assay of a plasma factor deficient in von Willebrand's disease that is necessary for platelet aggregation. Relationship to factor VIII procoagulant activity and antigen content. J Clin Invest. 1973; 52:2708–16. [PubMed: 4542944]
4. Allain JP, Cooper HA, Wagner RH, Brinkhous KM. Platelets fixed with paraformaldehyde: a new reagent for assay of von Willebrand factor and platelet aggregating factor. J Lab Clin Med. 1975; 85:318–28. [PubMed: 234499]
5. Nichols WL, Hultin MB, James AH, Manco-Johnson MJ, Montgomery RR, Ortel TL, Rick ME, Sadler JE, Weinstein M, Yawn BP. von Willebrand disease (VWD): evidence-based diagnosis and management guidelines, the National Heart, Lung, and Blood Institute (NHLBI) Expert Panel report (USA). Haemophilia. 2008; 14:171–232. [PubMed: 18315614]
6. Favaloro EJ. Laboratory identification of von Willebrand disease: technical and scientific perspectives. Semin Thromb Hemost. 2006; 32:456–71. [PubMed: 16862518]
7. Bolton-Maggs PH, Favaloro EJ, Hillarp A, Jennings I, Kohler HP. Difficulties and pitfalls in the laboratory diagnosis of bleeding disorders. Haemophilia. 2012; 18(Suppl 4):66–72. [PubMed: 22726086]
8. Lillicrap D. von Willebrand disease: advances in pathogenetic understanding, diagnosis, and therapy. Blood. 2013; 122:3735–40. [PubMed: 24065240]
9. Castaman G, Hillarp A, Goodeve A. Laboratory aspects of von Willebrand disease: test repertoire and options for activity assays and genetic analysis. Haemophilia. 2014; 20(Suppl 4):65–70.
10. Hayward CP, Moffat KA, Graf L. Technological advances in diagnostic testing for von Willebrand disease: new approaches and challenges. Int J Lab Hematol. 2014; 36:334–40. [PubMed: 24750680]
11. Pruthi RK. A practical approach to genetic testing for von Willebrand disease. Mayo Clin Proc. 2006; 81:679–91. [PubMed: 16706266]

12. Favaloro EJ, Koutts J. Laboratory assays for von Willebrand factor: relative contribution to the diagnosis of von Willebrand's disease. Pathology. 1997; 29:385–91. [PubMed: 9423220]
13. Rodeghiero F, Castaman G. Calibration of lyophilized standards for ristocetin cofactor activity of von Willebrand Factor (vWF) requires vWF-deficient plasma as diluent for dose–response curves. Thromb Haemost. 1987; 58:978–81. [PubMed: 3502200]
14. Favaloro EJ, Mohammed S, McDonald J. Validation of improved performance characteristics for the automated von Willebrand factor ristocetin cofactor activity assay. J Thromb Haemost. 2010; 8:2842–4. [PubMed: 20961398]
15. Hillarp A, Stadler M, Haderer C, Weinberger J, Kessler CM, Romisch J. Improved performance characteristics of the von Willebrand factor ristocetin cofactor activity assay using a novel automated assay protocol. J Thromb Haemost. 2010; 8:2216–23. [PubMed: 20727070]
16. Chen D, Daigh CA, Hendricksen JI, Pruthi RK, Nichols WL, Heit JA, Owen WG. A highly-sensitive plasma von Willebrand factor ristocetin cofactor (VWF:RCo) activity assay by flow cytometry. J Thromb Haemost. 2008; 6:323–30. [PubMed: 18031294]
17. Lindahl TL, Fagerberg IH, Larsson A. A new flow cytometric method for measurement of von Willebrand factor activity. Scand J Clin Lab Invest. 2003; 63:217–23. [PubMed: 12817908]
18. Giannini S, Mezzasoma AM, Leone M, Gresele P. Laboratory diagnosis and monitoring of desmopressin treatment of von Willebrand's disease by flow cytometry. Haematologica. 2007; 92:1647–54. [PubMed: 18055988]
19. Flood VH, Friedman KD, Gill JC, Morateck PA, Wren JS, Scott JP, Montgomery RR. Limitations of the ristocetin cofactor assay in measurement of von Willebrand factor function. J Thromb Haemost. 2009; 7:1832–9. [PubMed: 19694940]
20. Patzke J, Schneppenheim R. Laboratory diagnosis of von Willebrand disease. Hamostaseologie. 2010; 30:203–6. [PubMed: 21057713]
21. Favaloro EJ. Diagnosis and classification of von Willebrand disease: a review of the differential utility of various functional von Willebrand factor assays. Blood Coagul Fibrinolysis. 2011; 22:553–64. [PubMed: 21885953]
22. Scott JP, Montgomery RR, Retzinger GS. Dimeric ristocetin flocculates proteins, binds to platelets, and mediates von Willebrand factor-dependent agglutination of platelets. J Biol Chem. 1991; 266:8149–55. [PubMed: 2022635]
23. Weiss HJ, Rogers J, Brand H. Defective ristocetin-induced platelet aggregation in von Willebrand's disease and its correction by factor VIII. J Clin Invest. 1973; 52:2697–707. [PubMed: 4201262]
24. Flood VH, Gill JC, Morateck PA, Christopherson PA, Friedman KD, Haberichter SL, Branchford BR, Hoffmann RG, Abshire TC, Di Paola JA, Hoots WK, Leissinger C, Lusher JM, Ragni MV, Shapiro AD, Montgomery RR. Common VWF exon 28 polymorphisms in African Americans affecting the VWF activity assay by ristocetin cofactor. Blood. 2010; 116:280–6. [PubMed: 20231421]
25. de Maistre E, Volot F, Mourey G, Aho LS, Ternisien C, Briquel ME, Bertrand MA, Tardy B, Frotscher B, Nguyen P, Dumont L, Vandroux D, Hezard N, Trossaert M. Performance of two new automated assays for measuring von Willebrand activity: HemosIL AcuStar and Innovance. Thromb Haemost. 2014; 112:825–30. [PubMed: 25103956]
26. Vanhoorelbeke K, Cauwenberghs N, Vauterin S, Schlammadinger A, Mazurier C, Deckmyn H. A reliable and reproducible ELISA method to measure ristocetin cofactor activity of von Willebrand factor. Thromb Haemost. 2000; 83:107–13. [PubMed: 10669163]
27. Vanhoorelbeke K, Pareyn I, Schlammadinger A, Vauterin S, Hoylaerts MF, Arnout J, Deckmyn H. Plasma glycocalicin as a source of GPIbalpha in the von Willebrand factor ristocetin cofactor ELISA. Thromb Haemost. 2005; 93:165–71. [PubMed: 15630508]
28. Vanhoorelbeke K, Cauwenberghs N, Vandecasteele G, Vauterin S, Deckmyn H. A Reliable von Willebrand factor: ristocetin cofactor enzyme-linked immunosorbent assay to differentiate between type 1 and type 2 von Willebrand disease. Semin Thromb Hemost. 2002; 28:161–6. [PubMed: 11992239]
29. Federici AB, Canciani MT, Forza I, Mannucci PM, Marchese P, Ware J, Ruggeri ZM. A sensitive ristocetin co-factor activity assay with recombinant glycoprotein Ibalpha for the diagnosis of

patients with low von Willebrand factor levels. Haematologica. 2004; 89:77–85. [PubMed: 14754609]

30. Costa-Pinto J, Perez-Rodriguez A, del C Goméz-del-Castillo M, Loures E, Rodriguez-Trillo A, Batlle J, Lopez-Fernandez MF. Diagnosis of inherited von Willebrand disease: comparison of two methodologies and analysis of the discrepancies. Haemophilia. 2014; 20:559–67. [PubMed: 25077350]
31. Stufano F, Lawrie AS, La Marca S, Berbenni C, Baronciani L, Peyvandi F. A two-centre comparative evaluation of new automated assays for von Willebrand factor ristocetin cofactor activity and antigen. Haemophilia. 2014; 20:147–53. [PubMed: 24028703]
32. Cabrera N, Moret A, Caunedo P, Cid AR, Vila V, Espana F, Aznar JA. Comparison of a new chemiluminescent immunoassay for von Willebrand factor activity with the ristocetin cofactor-induced platelet agglutination method. Haemophilia. 2013; 19:920–5. [PubMed: 23730809]
33. Verfaillie CJ, De Witte E, Devreese KM. Validation of a new panel of automated chemiluminescence assays for von Willebrand factor antigen and activity in the screening for von Willebrand disease. Int J Lab Hematol. 2013; 35:555–65. [PubMed: 23551532]
34. Flood VH, Gill JC, Morateck PA, Christopherson PA, Friedman KD, Haberichter SL, Hoffmann RG, Montgomery RR. Gain-of-function GPIb ELISA assay for VWF activity in the Zimmerman Program for the Molecular and Clinical Biology of VWD. Blood. 2011; 117:e67–74. [PubMed: 21148813]
35. Patzke J, Budde U, Huber A, Mendez A, Muth H, Obser T, Peerschke E, Wilkens M, Schneppenheim R. Performance evaluation and multicentre study of a von Willebrand factor activity assay based on GPIb binding in the absence of ristocetin. Blood Coagul Fibrinolysis. 2014; 25:860–70. [PubMed: 25192242]
36. Lawrie AS, Stufano F, Canciani MT, Mackie IJ, Machin SJ, Peyvandi F. A comparative evaluation of a new automated assay for von Willebrand factor activity. Haemophilia. 2013; 19:338–42. [PubMed: 23205618]
37. Geisen U, Zieger B, Nakamura L, Weis A, Heinz J, Michiels JJ, Heilmann C. Comparison of von Willebrand factor (VWF) activity VWF: Ac with VWF ristocetin cofactor activity VWF:RCo. Thromb Res. 2014; 134:246–50. [PubMed: 24891215]
38. Graf L, Moffat KA, Carlino SA, Chan AK, Iorio A, Giulivi A, Hayward CP. Evaluation of an automated method for measuring von Willebrand factor activity in clinical samples without ristocetin. Int J Lab Hematol. 2014; 36:341–51. [PubMed: 24750681]
39. Patzke J, Muth H, Wilkens M, Schneppenheim R. Performance of a new automated von Willebrand factor activity assay based in GPIbα binding. J Thromb Haemost. 2011; 9:671. Abstract P-WE-479.
40. ISTH. SSC Subcommittee minutes 2014: von Willebrand factor. International Society on Thrombosis and Haemostasis; 2014. http://c.ymcdn.com/sites/www.isth.org/resource/resmgr/yearly_subcommittee_minutes/all_subcommittee,_standing_c.pdf
41. Stufano F, Baronciani L, Pagliari MT, Franchi F, Cozzi G, Garcia Oya I, Peyvandi F. Diagnosis of type 2B von Willebrand disease (VWD) using an alternative assay to ristocetin induced platelet agglutination (RIPA). Thromb Res. 2014; 134:OC-156.
42. Goodall AH, Jarvis J, Chand S, Rawlings E, O'Brien DP, McGraw A, Hutton R, Tuddenham EG. An immunoradiometric assay for human factor VIII/von Willebrand factor (VIII:vWF) using a monoclonal antibody that defines a functional epitope. Br J Haematol. 1985; 59:565–77. [PubMed: 2580547]
43. Chand S, McCraw A, Hutton R, Tuddenham EG, Goodall AH. A two-site, monoclonal antibody-based immunoassay for von Willebrand factor–demonstration that vWF function resides in a conformational epitope. Thromb Haemost. 1986; 55:318–24. [PubMed: 2428124]
44. Murdock PJ, Woodhams BJ, Matthews KB, Pasi KJ, Goodall AH. von Willebrand factor activity detected in a monoclonal antibody-based ELISA: an alternative to the ristocetin cofactor platelet agglutination assay for diagnostic use. Thromb Haemost. 1997; 78:1272–7. [PubMed: 9364997]
45. Laffan M, Brown SA, Collins PW, Cumming AM, Hill FG, Keeling D, Peake IR, Pasi KJ. The diagnosis of von Willebrand disease: a guideline from the UK Haemophilia Centre Doctors' Organization. Haemophilia. 2004; 10:199–217. [PubMed: 15086318]

46. Favaloro EJ, Henniker A, Facey D, Hertzberg M. Discrimination of von Willebrands disease (VWD) subtypes: direct comparison of von Willebrand factor:collagen binding assay (VWF: CBA) with monoclonal antibody (MAB) based VWF-capture systems. Thromb Haemost. 2000; 84:541–7. [PubMed: 11057847]
47. De Vleeschauwer A, Devreese K. Comparison of a new automated von Willebrand factor activity assay with an aggregation von Willebrand ristocetin cofactor activity assay for the diagnosis of von Willebrand disease. Blood Coagul Fibrinolysis. 2006; 17:353–8. [PubMed: 16788311]
48. Sucker C, Senft B, Scharf RE, Zotz RB. Determination of von Willebrand factor activity: evaluation of the HaemosIL assay in comparison with established procedures. Clin Appl Thromb Hemost. 2006; 12:305–10. [PubMed: 16959683]
49. Salem RO, van Cott EM. A new automated screening assay for the diagnosis of von Willebrand disease. Am J Clin Pathol. 2007; 127:730–5. [PubMed: 17439831]
50. Pinol M, Sales M, Costa M, Tosetto A, Canciani MT, Federici AB. Evaluation of a new turbidimetric assay for von Willebrand factor activity useful in the general screening of von Willebrand disease. Haematologica. 2007; 92:712–3. [PubMed: 17488704]
51. Trossaert M, Ternisien C, Lefrancois A, Llopis L, Goudemand J, Sigaud M, Fouassier M, Caron C. Evaluation of an automated von Willebrand factor activity assay in von Willebrand disease. Clin Appl Thromb Hemost. 2011; 17:E25–9. [PubMed: 20724302]
52. Hulstein JJ, de Groot PG, Silence K, Veyradier A, Fijnheer R, Lenting PJ. A novel nanobody that detects the gain-of-function phenotype of von Willebrand factor in ADAMTS13 deficiency and von Willebrand disease type 2B. Blood. 2005; 106:3035–42. [PubMed: 16014562]
53. ISTH. SSC Subcommittee minutes 2011: von Willebrand factor. International Society on Thrombosis and Haemostasis; 2011. http://c.ymcdn.com/sites/www.isth.org/resource/resmgr/yearly_subcommittee_minutes/2011_minutes.pdf [Accessed 30 November 2014]
54. Bowyer AE, Shepherd F, Kitchen S, Makris M. A rapid, automated VWF ristocetin cofactor activity assay improves reliability in the diagnosis of von Willebrand disease. Thromb Res. 2011; 127:341–4. [PubMed: 21186048]
55. Lawrie AS, Mackie IJ, Machin SJ, Peyvandi F. Evaluation of an automated platelet-based assay of ristocetin cofactor activity. Haemophilia. 2011; 17:252–6. [PubMed: 21070498]
56. Miller CH, Platt SJ, Daniele C, Kaczor D. Evaluation of two automated methods for measurement of the ristocetin cofactor activity of von Willebrand factor. Thromb Haemost. 2002; 88:56–9. [PubMed: 12152679]
57. Lattuada A, Preda L, Sacchi E, Gallo L, Federici AB, Rossi E. A rapid assay for ristocetin cofactor activity using an automated coagulometer (ACL 9000). Blood Coagul Fibrinolysis. 2004; 15:505–11. [PubMed: 15311161]
58. Redaelli R, Corno AR, Borroni L, Mostarda G, Nichelatti M, Morra E, Baudo F. von Willebrand factor ristocetin cofactor (VWF:RCo) assay: implementation on an automated coagulometer (ACL). J Thromb Haemost. 2005; 3:2684–8. [PubMed: 16359507]
59. Zhao Y, Gu Y, Ji S, Yang J, Yu Z, Ruan C. Development of an ELISA method for testing VWF ristocetin cofactor activity with improved sensitivity and reliability in the diagnosis of von Willebrand disease. Eur J Haematol. 2012; 88:439–45. [PubMed: 22268616]
60. Pinol M, Sanchez T, Sales M, Vanrusselt M, Arnout J. New automated ristocetin cofactor activity assay to distinguish type 1 and type 2 von Willebrand disease (VWD). J Thromb Haemost. 2009; 7 Abstract PP-Th-635.
61. Tous J, Barry RG, Arnout J, Vanrusselt M, Pascual Z. New automated chemiluminescent VWF:Ag and VWF:RCo assays: preliminary analytical and clinical performance. J Thromb Haemost. 2009; 7 Abstract PP-TH-625.
62. Schneppenheim R, Obser T, Budde U, Patzke J. Development of a new functional assay for von Willebrand factor binding to platelet GpIba that does not require Ristocetin. Hamostaseologie. 2010; 30:FC4-05.
63. Favaloro EJ, Mohammed S. Towards improved diagnosis of von Willebrand disease: comparative evaluations of several automated von Willebrand factor antigen and activity assays. Thromb Res. 2014; 134:1292–300. [PubMed: 25300811]

Table 1

Approved nomenclature for the various activities measured by current assay systems

Abbreviation for VWF activity	Description
VWF:RCo	Ristocetin cofactor activity: all assays that use platelets and ristocetin
VWF:GPIbR	All assays that are based on the ristocetin-induced binding of VWF to a recombinant WT GPIb fragment
VWF:GPIbM	All assays that are based on the spontaneous binding of VWF to a gain-of-function mutant GPIb fragment
VWF:Ab	All assays that are based on the binding of a monoclonal antibody (m*Ab*) to a VWF A1 domain epitope