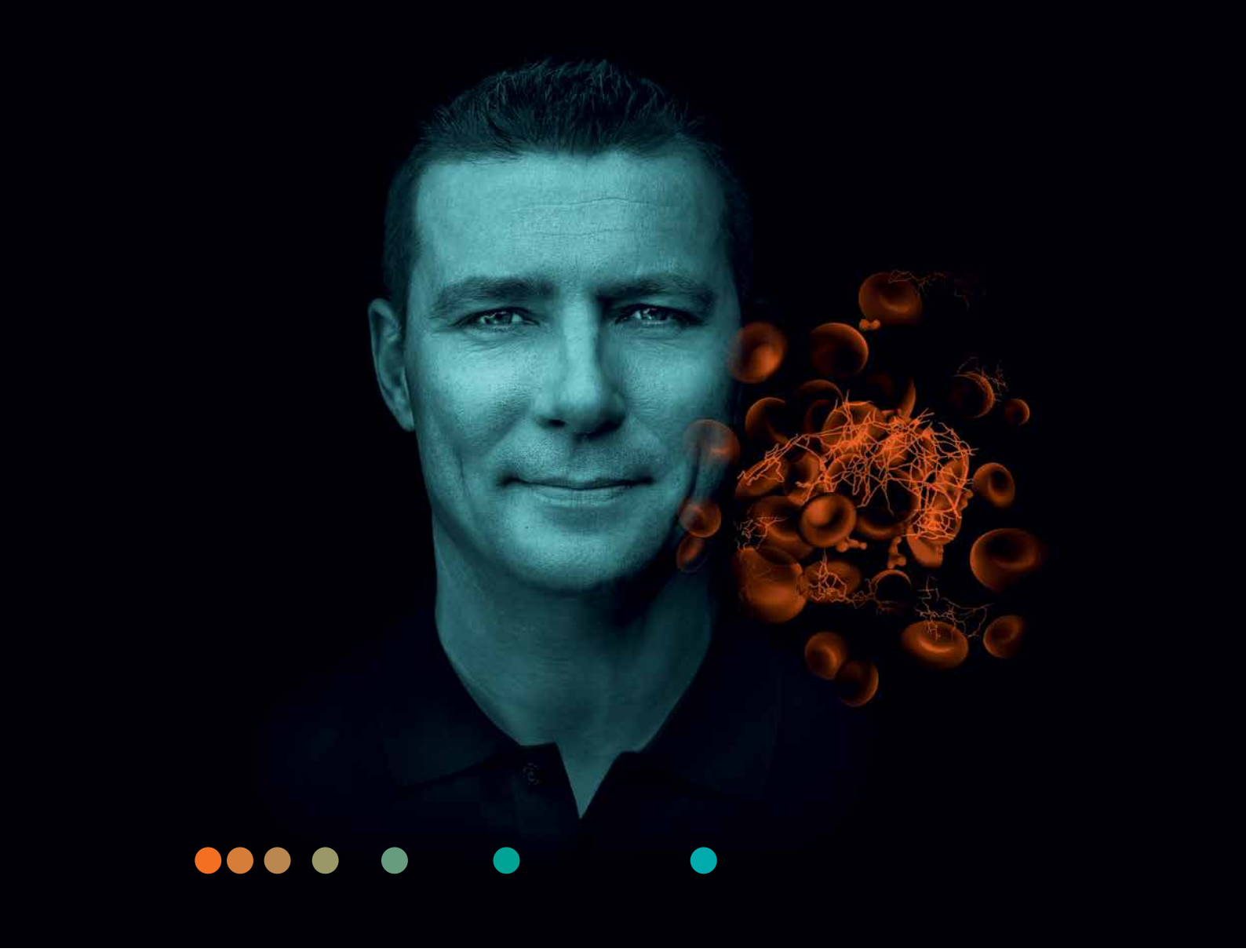


Von Willebrand disease

Bleeding risk assessment:
Evaluation of primary hemostasis is key

siemens-healthineers.com/hemostasis

SIEMENS
Healthineers

Von Willebrand disease: physiological causes and effects

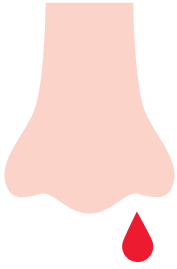
Disturbances in the primary hemostasis system are the major cause of bleeding events. Patients with these disturbances are at increased risk for severe bleeding, especially during surgical interventions. Careful evaluation of primary hemostasis, which is principally determined by platelet function and von Willebrand factor activity, is important to minimize adverse outcomes in these patients.

Von Willebrand factor (VWF) is a multimeric, high-molecular glycoprotein involved in primary hemostasis, supporting platelet adhesion and aggregation under high-shear stress at the site of injury. Furthermore, VWF is the specific carrier protein of coagulation factor VIII, protecting factor VIII against inactivation and rapid clearance.

Von Willebrand disease (VWD), a dysfunction of primary hemostasis caused by quantitative or qualitative deficiency of von Willebrand factor, is the most common hereditary bleeding disorder. Leading symptoms of VWD include nosebleeds, menorrhagia, and bleeding after tooth extraction. In contrast, strong elevated VWF levels due to endothelial activation or dysfunction are frequently associated with cardiovascular disease and the risk for future ischemic heart disease or stroke.

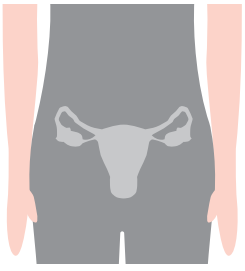
Von Willebrand disease is present in roughly 1% of the general population. In patients undergoing surgery, a correct diagnosis allows targeted prophylactic treatment of the identified bleeding risk with the potential to significantly reduce the need for blood transfusions.[1]

Leading symptoms of VWD



Nosebleeds

Bleeding after tooth extraction



Menorrhagia

Distribution of VWF levels

A wide range of VWF levels is seen in the general population. There are several genes that affect VWF levels, with the major genetic influence coming from the ABO blood-group gene. Individuals with blood group O have 15–25% lower VWF levels than individuals with non-O blood group. However, a substantial fraction of the variation in VWF is not heritable and is related to inflammatory activity. VWF shows a fast and strong increase with acute phase reaction, which complicates the detection of mild VWD in the presence of stress or inflammation.[2]

NHLBI interpretation guide for VWF levels[2]

50–200% VWF	Normal VWF
30–50% VWF	Low VWF; probably modestly increased bleeding risk
<30% VWF	Decreased VWF; increased bleeding tendency; presence of VWF mutations likely

Subtypes of von Willebrand disease[2]

The most common type is VWF with quantitative defects, but a normal distribution of multimers.

VWD Type 1	Reduction of VWF defined; antigen and activity are in the same range due to decreased synthesis or increased degradation
VWD Type 3	Complete absence of VWF multimers (<5%)

Qualitative defects of VWF are less common.

VWD Type 2A	Selective reduction in or deficiency of large VWF multimers and reduction of platelet-dependent function
VWD Type 2B	Characterized by a strong affinity of VWF to GPIb, usually in conjunction with a low platelet count and reduced VWF activity
VWD Type 2M	Low platelet-dependent function of the VWF with large multimers present
VWD Type 2N	The FVIII binding site of VWF is defective; FVIII cannot bind and thus FVIII cannot be protected from premature degradation; clinical symptoms such as with hemophilia A

Management of VWD

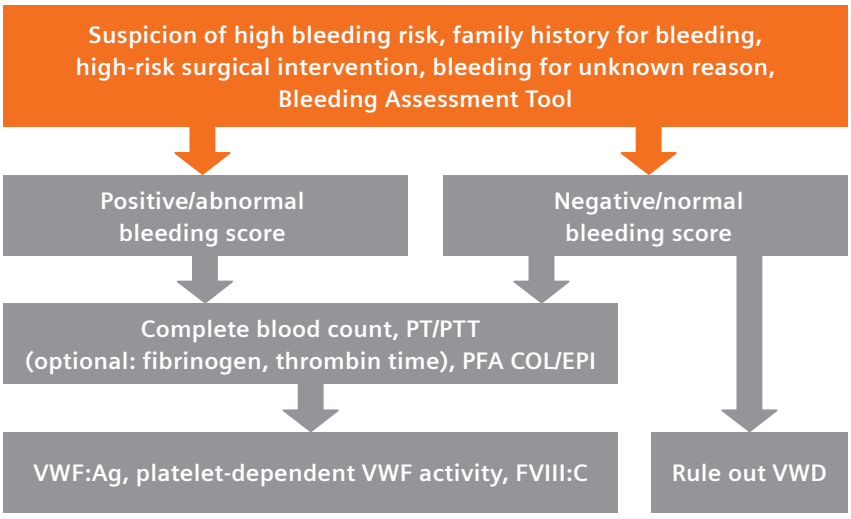
To prevent or control bleeding in VWD patients, two major strategies are available. The first option is to increase plasma VWF concentration by stimulation and release of endogenous VWF stores in platelet and endothelial cells through application of desmopressin. This approach works well in most VWD type 1 patients and certain type 2 patients.

Replacement of VWF is the second alternative. Several human, plasma-derived VWF concentrates are available for therapy of those patients with insufficient response to desmopressin. However, before therapy can be started, a thorough anamnesis including appropriate lab testing is required.

Diagnosis and monitoring of von Willebrand disease

To correctly diagnose cases involving a bleeding anamnesis or a family history of von Willebrand disease and subsequently monitor patient response to therapy, physicians require a specific test for von Willebrand factor. A functional assay is the preferred screening method for detecting quantitative as well as qualitative defects of von Willebrand factor.[3]

Patients suspected of VWD[3]



Subtyping of VWD by additional specialty assays

VWD subtype characteristics (modified from Reference 2)

Assay	Normal	Type 1	Type 2				Type 3
			2A	2B	2M	2N	
Screening tests							
PFA COL/EPI	N	N or↑	↑	↑	↑	N	↑↑↑
Platelet count	N	N	N	N or↓	N	N	N
VWF activity: • Platelet-dependent VWF activity	N	Borderline to ↓↓	↓ or ↓↓	↓↓	↓ or ↓↓	N or borderline	↓↓↓
Further VWF-related routine tests							
VWF Ag	N	Borderline to ↓↓	Borderline or↓	Borderline or↓	Borderline or↓	N or borderline	↓↓↓
FVIII:C	N	N or↓	N or↓	N or↓	N	↓↓	↓↓↓
VWF structure analysis							
VWF multimer analysis	Normal multimer distribution	Normal multimer distribution	Lack of HMWM	Lack of HMWM	Normal distribution	Normal multimer distribution	Absent
RIPA • High dose • Low dose	N NR	N or↓ NR	↓ NR	N ↑	↓ NR	N NR	NR NR

N = Normal
NR = No reaction

Excellent correlation to VWF:RCo method

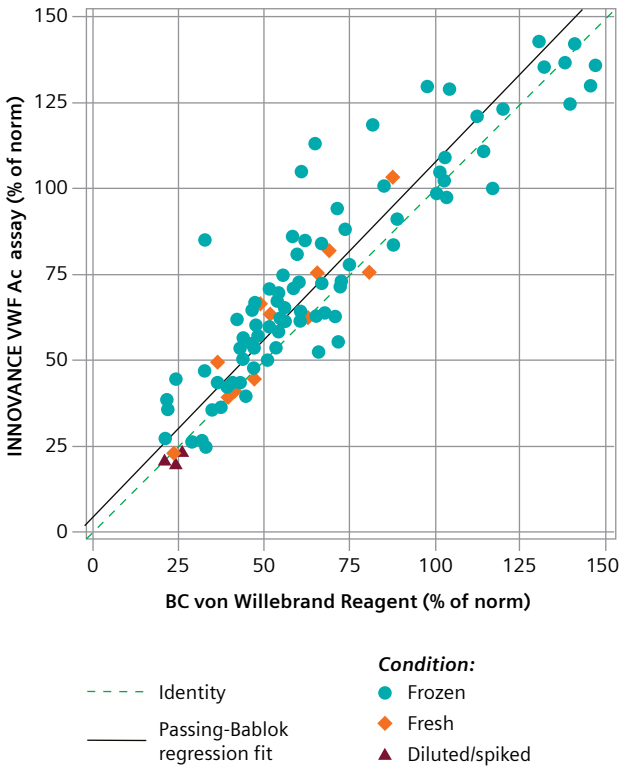
In the past, VWF:RCo assays such as BC von Willebrand Reagent were the recommended screening method for VWD. Ristocetin can also induce decapping of the A1 binding domain, the mechanism employed in VWF:RCo assays. However, ristocetin is an artificial substance, and in the presence of certain polymorphisms, false-low VWF levels may be measured that are not connected to bleeding risk.[4] In contrast to VWF:RCo assays, assays such as the INNOVANCE® VWF Ac assay directly determine real activity of VWF. Both assays show excellent correlation.

"The automated VWF:GPIbM has demonstrated excellent clinical performance and has been favored by experts as interchangeable with VWF:RCo."

Higgins, et al. Am J Hematol. 2019;94:496-503.[5]

Method comparison measured on BCS® XP System

Scatter plot including Passing-Bablock regression



Basics

Number of Samples (n)	102
Pearson Correlation Coefficient (r)	0.916
Coefficient of Determination (r^2)	0.839

Passing-Bablok Regression

	Parameter Estimate	95% Confidence Interval Lower Limit	95% Confidence Interval Upper Limit
Slope	1.037	0.959	1.137
Intercept	3.497	–2.893	8.257

A real functional assay for the automated determination of von Willebrand factor activity in human citrated plasma

INNOVANCE VWF Ac assay

The INNOVANCE VWF Ac assay is a turbidimetric latex-based assay that requires no stirring and allows testing on all Siemens Healthineers and Sysmex® automated coagulation instruments.*

- Excellent precision and lot-to-lot consistency.
- Provides the ability to measure samples from 4–600% of norm based on three different settings in single-determination.
- Reagents are liquid and ready to use.

"The INNOVANCE VWF Ac assay is reliable and precise with high sensitivity. The absence of ristocetin ensures result accuracy and minimizes the risk of misdiagnosis, especially in patients with a particular variant."

Professor Dr. Reinhard Schneppenheim, MD, PhD, Professor of Pediatrics, Department of Pediatric Hematology and Oncology, University Medical Center Hamburg-Eppendorf

Assay performance

15 µL
Required sample volume on CS-2500 and CS-5100 Systems

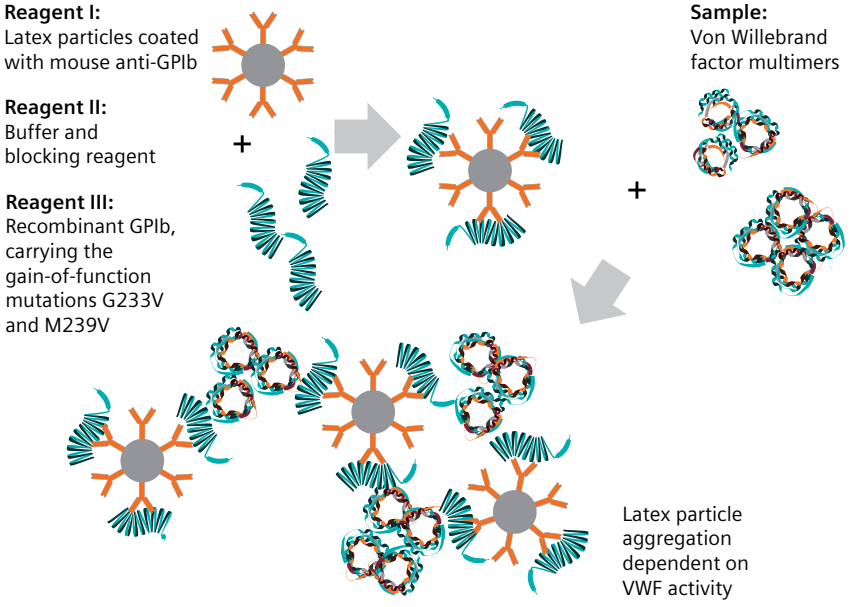
4–600% of norm
Measuring range

16 hours
Onboard stability on CS-2500 and CS-5100 Systems

12 days
Onboard stability on Atellica® COAG 360 System†

1.6%
Within-device CV of Control Plasma N on the Atellica COAG 360 System†

INNOVANCE VWF Ac assay principle



INNOVANCE VWF Ac assay employs an advanced new technology, allowing the assay to mimic the way in which VWF binds to glycoprotein Ib (GPIb), the major VWF receptor protein on platelets. Latex particles are coated with an antibody against GPIb, to which recombinant GPIb is added. The addition of patient plasma induces a VWF-dependent agglutination, which is detected turbidimetrically. Because the recombinant receptor protein includes two gain-of-function mutations, the assay does not require ristocetin.

*Except for CA-620 Systems.
†Not available for sale in the U.S. Product availability may vary from country to country and is subject to varying regulatory requirements.

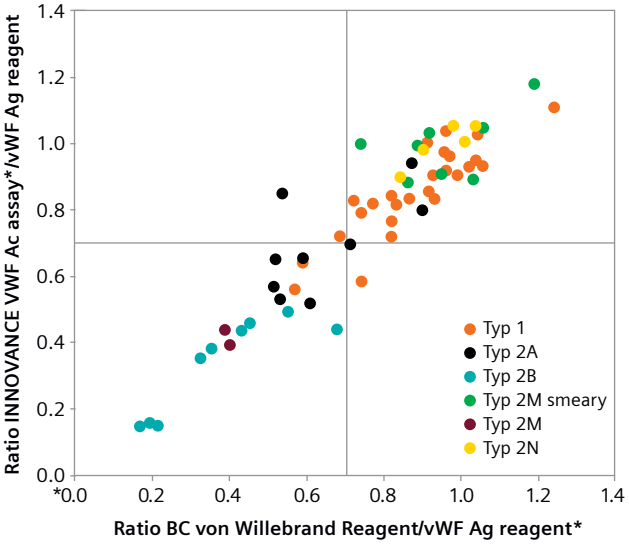
INNOVANCE VWF Ac assay and vWF Ag assay: a powerful combination

vWF Ag assay

For the evaluation for von Willebrand disease, the INNOVANCE VWF Ac assay can be combined with vWF Ag assay to detect and distinguish between quantitative and qualitative VWF deficiencies. vWF Ag assay is an immunoturbidimetric assay that can be used on Siemens Healthineers and Sysmex automated coagulation instruments.

- Wide measuring range of up to 600%
- Sensitive to type 1 and 3 of vWF
- Liquid reagents for streamlined handling

Clinical validation study



Assay performance

15 µL
Required sample volume

2–600% of norm
Measuring range

72 hours
Onboard stability on CS-2500 and CS-5100 Systems

14 days
Onboard stability on Atellica COAG 360 System†

vWF Ag assay principle

Small polystyrene particles to which specific antibodies have been attached by covalent binding are aggregated when mixing with samples containing von Willebrand antigen. This aggregation is detected turbidimetrically.

Siemens Healthineers offers a comprehensive portfolio of systems and assays for the diagnosis of bleeding disorders and therapy monitoring:

Platelet diseases
- INNOVANCE PFA-200 System†
- ADVIA® Hematology Systems
- Integrated light transmission aggregation‡ on Atellica COAG 360† and CS-2500/5100 Systems

Von Willebrand disease
- INNOVANCE PFA-200 System†
- BC von Willebrand Reagent
- INNOVANCE VWF Ac assay
- vWF Ag assay

FVIII, IX deficiency, hemophilia A+B
- Coagulation Factor VIII Deficient Plasma, Coagulation Factor IX Deficient Plasma (one-stage assay)
- Factor VIII Chromogenic Assay
- Biophen chromogenic FIX

FV, VII deficiency
- Coagulation Factor V Deficient Plasma
- Coagulation Factor VII Deficient Plasma

FXIII deficiency
- Berichrom® FXIII assay

Contact your Siemens Healthineers representative today for more information on our bleeding portfolio or explore more on siemens-healthineers.com/hemostasis.

‡Product availability may vary from country to country and is subject to varying regulatory requirements. Please contact your local Siemens Healthineers organization for further details. In the U.S., platelet aggregation testing is for research use only, not for use in diagnostic procedures.
Assay performance can vary from country to country as well as corresponding to the system application of the respective assay. The values listed above are provided as examples only.

At Siemens Healthineers, we pioneer breakthroughs in healthcare. For everyone. Everywhere. By constantly bringing breakthrough innovations to market, we enable healthcare professionals to deliver high-quality care, leading to the best possible outcome for patients.

Our portfolio, spanning from in-vitro and in-vivo diagnostics to image-guided therapy and innovative cancer care, is crucial for clinical decision-making and treatment pathways. With our strengths in patient twinning, precision therapy, as well as digital, data, and artificial intelligence (AI), we are well positioned to take on the biggest challenges in healthcare. We will continue to build on these strengths to help fight the world's most threatening diseases, improving the quality of outcomes, and enabling access to care.

We are a team of 66,000 highly dedicated employees across more than 70 countries passionately pushing the boundaries of what's possible in healthcare to help improve people's lives around the world.

Product availability may vary from country to country and is subject to varying regulatory requirements. Please contact your local representative for availability.

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