Received: 7 February 2022 | Revised: 16 July 2022 | Accepted: 23 July 2022

DOI: 10.1002/rth2.12784

rpth research & practice in thrombosis & haemostasis

ORIGINAL ARTICLE

# Desmopressin testing in von Willebrand disease: Lowering the burden

Jessica M. Heijdra MD[1] | Ferdows Atiq MD, PhD[2] | Wala Al Arashi MD[1] | Quincy Kieboom MD[1] | Esmee Wuijster MD[2] | Karina Meijer MD, PhD[3] | Marieke J. H. A. Kruip MD, PhD[2] | Frank W. G. Leebeek MD, PhD[2] | Marjon H. Cnossen MD, PhD[1] | in collaboration with the OPTI-CLOT Study Group

[1]Department of Pediatric Hematology, Erasmus MC – Sophia Children's Hospital, University Medical Center Rotterdam, Rotterdam, The Netherlands

[2]Department of Hematology, Erasmus MC, University Medical Center Rotterdam, Rotterdam, The Netherlands

[3]Department of Hematology, University of Groningen and University Medical Center Groningen, Groningen, The Netherlands

**Correspondence**
Marjon H. Cnossen, Department of Pediatric Hematology, Erasmus MC – Sophia Children's Hospital, SP-2435, P.O. Box 2060, 3000 CB Rotterdam, The Netherlands.
Email: m.cnossen@erasmusmc.nl

**Funding information**
Innovatiefonds Zorgverzekeraars, Grant/Award Number: Project number 3216

**Handling Editor:** Pantep Angchaisuksiri

## Abstract

**Background:** Individuals with von Willebrand disease (VWD) require desmopressin testing because of interindividual response differences. However, testing is burdensome, while not all patients may need extensive testing.

**Objectives:** To provide von Willebrand factor (VWF) cutoffs that predict desmopressin nonresponse and thereby identify individuals who do not need extensive testing in a retrospective cohort. We validated these cutoffs in a prospective cohort.

**Patients and Methods:** We included 376 patients (Type 1 VWD with VWF activity [VWF:Act] <0.30 IU/ml: $n = 112$; with VWF:Act 0.30–0.50 IU/ml: $n = 206$; Type 2 VWD: $n = 58$; ages, 5–76 years) from January 2000 to July 2020. We collected VWF:Act and factor VIII activity (FVIII:C) at baseline and several time points after desmopressin (T1–T6). We defined response as VWF:Act and FVIII:C 0.50 IU/ml or greater at T1 and T4. We compared VWF:Act and FVIII:C distribution (historically lowest level, baseline, and T1) between responders and nonresponders and determined cutoffs discriminating between these groups. Results were validated in a group of 30 individuals.

**Results:** All individuals with Type 1 VWD and Type 2 VWD, respectively, with baseline VWF:Act 0.34 IU/ml or greater or 0.28 IU/ml or greater were responders. In individuals with T1 VWF:Act ≥0.89 IU/ml (Type 1 VWD) or T1 VWF:Act 1.10 IU/ml or greater (Type 2 VWD), response remained at T4.

**Conclusion:** Desmopressin testing is not needed when lowest historical VWF:Act is 0.30 IU/ml or greater. In patients with Type 1 VWD who require testing, measurements after T1 are often not needed. In patients with Type 2 VWD who require testing, we advise performing T1 and T4 measurements.

KEYWORDS
desmopressin, factor VIII, humans, von Willebrand disease, von Willebrand factor

The OPTI-CLOT Study Group members are listed in Appendix A.

**Essentials**

- Desmopressin testing is time consuming and burdensome for patients and health care professionals.
- We analyzed the outcomes of patients with von Willebrand disease (VWD) after a desmopressin test dose.
- The majority of patients with Type 1 VWD respond well to desmopressin and do not need testing.
- Von Willebrand factor levels before testing predict which patients will respond to desmopressin.

## 1 | INTRODUCTION

Von Willebrand disease (VWD) is a bleeding disorder caused by a deficiency or qualitative defect of von Willebrand factor (VWF). VWF is essential for both primary and secondary hemostasis. It facilitates platelet plug formation at sites of vascular damage and functions as a chaperone protein for factor VIII (FVIII), which it protects from proteolytic degradation in the circulation. VWD is categorized into three types.[1] Type 1 is defined as a partial VWF deficiency (VWF less than 0.50 IU/ml) in individuals with a family history of VWD and/or abnormal bleeding, and Type 3 as a complete deficiency of VWF. Type 2 comprises several qualitative VWF defects, classified as Types 2A, 2B, 2M, and 2N.

Bleeding in individuals with VWD can be prevented or treated with either desmopressin (1-deamino-8D-arginine vasopressin) or VWF-containing concentrates. Desmopressin stimulates the release of VWF from vascular endothelial cells into the circulation, resulting in increased levels of FVIII.[2] After desmopressin administration, the maximum VWF and FVIII response and the duration of response differ significantly between patients, whereas the response in a single individual is reproducible and consistent over time.[3] It is therefore common practice for individuals who are potentially eligible for desmopressin treatment to first undergo desmopressin testing to determine their individual response. Individuals with Type 2B and Type 3, respectively, are not eligible for treatment with desmopressin because of the risk of thrombocytopenia and because of the severely impaired synthesis of VWF.[4]

In most situations, desmopressin testing involves administering an intravenous dose of 0.3 μg/kg of desmopressin diluted in 50 ml NaCl 0.9% over 30 min, and measuring VWF and FVIII at several time points (usually at baseline and 1 and 4 h after desmopressin administration).[5] Various experts and studies have proposed different definitions of clinical response. Most commonly, complete responders are defined by VWF ristocetin cofactor activity (VWF:RCo) and FVIII levels of 0.50 IU/ml or higher after desmopressin.[6–9] The most recent international guidelines on the management of VWD state that a patient is considered responsive to desmopressin if his or her VWF level increases at least two times over baseline level, and if both VWF and FVIII levels of >0.50 IU/ml are achieved after administration of desmopressin.[5] In these guidelines, it is recommended that VWF:Act levels should be increased to ≥0.50 IU/ml before performing a minor invasive procedure, and a desmopressin test should be performed before starting treatment with desmopressin in patients with a VWF baseline level less than 0.30 IU/ml. However, this level is mainly based on expert opinion.

In this study, we retrospectively collected desmopressin test data from a large group of individuals with different types of VWD and analyzed plasma VWF and FVIII levels at various time points after desmopressin administration. Our primary aim was to provide relevant cutoff levels for prediction of an individual's response to desmopressin and to identify individuals who do not require a complete desmopressin test or no desmopressin test at all. Our second aim was to validate these cutoff levels by applying them to a cohort of prospectively included patients who underwent desmopressin testing. We hypothesize that many patients, especially those with Type 1 VWD, will not need testing if certain cutoff levels are applied.

By limiting desmopressin testing in general and by decreasing the number of blood samples needed to be taken during testing, health care professionals will save time, and patient burden as well as health care costs will be reduced.

## 2 | PATIENTS AND METHODS

### 2.1 | Patient selection—initial cohort

The initial cohort was derived from a retrospective, single-center cohort study. We included all individuals with VWD (defined as having a positive family history of VWD and/or abnormal bleeding and historically lowest VWF antigen (VWF:Ag), VWF activity (VWF:Act), and/or VWF collagen binding (VWF:CB) less than 0.50 IU/ml or FVIII less than 0.40 IU/ml in the case of Type 2N VWD), in whom a desmopressin test was performed between January 1, 2000, and June 1, 2020, at the Erasmus University Medical Center Rotterdam, the Netherlands.

### 2.2 | Patient selection—validation cohort

To validate the results from the initial cohort, we analyzed data of patients who were prospectively included in the OPTI-CLOT: To WiN study (Netherlands Trial Register, trial registration number: NL7212; www.trialregister.nl) between June 2019 and July 2020 from the Erasmus University Medical Center Rotterdam and University Medical Center Groningen, using the same inclusion criteria as for the retrospective cohort. All individuals included in this cohort provided signed informed consent.

## 2.3 | Ethics review

The study protocol for the retrospective study (number: MEC-2020-0683), as well as the study protocol for the prospective OPTI-CLOT: To WiN study was reviewed and approved by the Medical Ethics Committee of the Erasmus University Medical Center Rotterdam.

## 2.4 | Desmopressin testing

In all patients, a single intravenous desmopressin test dose of 0.3 μg/kg was administered in 30 min. Venous blood samples were routinely obtained immediately before desmopressin administration (baseline) and at 1, 3 and 6 h after desmopressin administration (T1, T3, T6) in adults, and at baseline, T1, T2, T4, and T6 in children, according to local protocol.

## 2.5 | Laboratory measurements

VWF:Ag, VWF:Act, VWF:CB, and FVIII:C were measured for routine diagnostics in the hemostasis laboratory of the Erasmus University Medical Center. VWF:Act was measured using different assays over the years: a VWF:RCo assay from 2000 to 2005, a monoclonal antibody assay from 2005 to 2012, and a VWF glycoprotein 1b binding assay from 2012 onwards. These specific laboratory measurements have been described in detail in an earlier publication.[10]

## 2.6 | Clinical response definition

Primarily, we defined responders as individuals with both VWF:Act and FVIII:C ≥0.50 IU/ml at T1 and T4, as the most recent international guidelines recommend that levels of VWF:Act and FVIII:C before performing a minor invasive procedure should be 0.50 IU/ml or greater.[5] Nonresponders were defined as individuals with VWF:Act and/or FVIII:C <0.50 IU/ml at T1 and/or T4. Secondarily, we investigated the fold increase in VWF:Act over baseline as an additional measure of efficacy.

## 2.7 | Statistical analysis

Descriptive data are presented as numbers with percentages for categorical variables and as means with standard deviations or medians with interquartile ranges for continuous data, depending on the distribution of the data.

In case the VWF or FVIII level measured was below the lower limit of quantification (LLOQ), we calculated $\text{LLOQ} \div \sqrt{2}$ and imputed the outcome. As timing of measurements differed between children and adults, we calculated VWF:Act and FVIII:C at T4 for adults as follows:

$$\text{T4 level} = \text{T3 level} - \frac{1}{t_{1/2}} \times \text{T3 level}$$

We compared the distribution of VWF:Act and FVIII:C between responders and nonresponders to establish sensitivity and specificity of the test for Type 1 VWD and Type 2 VWD separately. In addition, we performed receiver operating characteristic (ROC) analysis to determine specific cutoffs that discriminated best between responders and nonresponders. We performed logistic regression analysis to assess the influence of sex and age on desmopressin response.

We performed statistical analysis with IBM SPSS statistics for Windows version 25.0 and GraphPad Prism version 8.4.3.

# 3 | RESULTS

## 3.1 | Patients

We included 376 individuals in the initial cohort: 112 with Type 1 VWD and historically lowest VWF levels less than 0.30 IU/ml, 206 with Type 1 VWD and historically lowest VWF levels between 0.30 and 0.50 IU/ml, and 58 with Type 2 VWD (2A: $n = 41$; 2M: $n = 14$ and 2N: $n = 3$). Sixty-nine percent were females. Mean age was 29 ± 15 years, mean body weight was 66 ± 20 kg, and 65% had blood group O. Median VWF:Act at baseline immediately before desmopressin administration was 0.31 IU/ml in Type 1 VWD with historically lowest VWF less than 0.30, 0.55 IU/ml in Type 1 VWD with historically lowest VWF less than 0.30–0.50 and 0.18 IU/ml in Type 2 VWD. Median FVIII:C at this time point was 0.62 IU/ml in Type 1 VWD (VWF <0.30 IU/ml), 0.80 IU/ml in Type 1 VWD (VWF 0.30–0.50 IU/ml) and 0.58 IU/ml in Type 2 VWD. Patient characteristics of the initial cohort are shown in Table 1.

We found 37 individuals eligible for inclusion in the prospective validation cohort. Four potential inclusions were missed; one patient was planned to have a short desmopressin test with only one measurement after administration of desmopressin; and two patients declined to participate. In total, we included and analyzed 30 individuals in the validation cohort: 11 with Type 1 VWD (VWF <0.30 IU/ml), 14 with Type 1 VWD (VWF 0.30–0.50 IU/ml), 4 with Type 2A VWD, and 1 with Type 2M VWD, all of whom completed the desmopressin test. Seventy-three percent were females and mean age was 23 ± 16 years. Mean body weight was 60 ± 23 kg, and 75% had blood group O. Median VWF:Act at baseline directly before desmopressin administration was 0.37 IU/ml in Type 1 VWD (VWF less than 0.30 IU/ml), 0.48 IU/ml in Type 1 VWD (VWF 0.30–0.50 IU/ml), and 0.13 IU/ml in Type 2 VWD. Median FVIII:C at this time point was 0.78 IU/ml in Type 1 VWD (VWF < 0.30), 0.80 IU/ml in Type 1 VWD (VWF 0.30–0.50 IU/ml), and 0.62 IU/ml in Type 2 VWD. Patient characteristics of the validation cohort are shown in Table 2.

## 3.2 | Desmopressin response rates in the initial cohort

Ninety percent of patients ($n = 338/376$) were responders (VWF:Act and FVIII:C ≥0.50 IU/ml at T1 and T4). We observed large differences

**TABLE 1** Patient characteristics of the initial cohort

| Patient characteristics | Total cohort | Type 1 VWD (VWF <0.30 IU/ml) | Type 2 VWD | | Type 1 VWD (VWF 0.30–0.50 IU/ml) |
|---|---|---|---|---|---|
| Number of patients (%) | 376 (100) | 112 (29.8) | 58 (15.4) | – | 206 (54.8) |
| Disease type (Type 2) | – | – | *Type 2A* | *41 (10.9)* | – |
| | – | – | *Type 2M* | *14 (3.7)* | – |
| | – | – | *Type 2N* | *3 (0.8)* | – |
| Age (years) | 29 ± 15 | 29 ± 16 | 32 ± 18 | | 29 ± 14 |
| Sex (female) | 259 (69) | 70 (63) | 31 (53) | | 158 (77) |
| Body weight (kg)[a] | 66 ± 20 | 67 ± 22 | 65 ± 22 | | 66 ± 19 |
| Blood group O[a] | 244 (65) | 73 (65) | 25 (43) | | 146 (71) |
| Historically lowest levels plasma levels (IU/ml) | | | | | |
| VWF:Ag | 0.42 (0.32–0.50) | 0.30 (0.25–0.36) | 0.34 (0.22–0.49) | | 0.48 (0.42–0.54) |
| VWF:Act | 0.36 (0.23–0.47) | 0.25 (0.19–0.29) | 0.14 (0.07–0.23) | | 0.46 (0.39–0.51) |
| FVIII:C | 0.62 (0.46–0.78) | 0.50 (0.39–0.65) | 0.42 (0.29–0.59) | | 0.69 (0.58–0.85) |
| Plasma levels immediately before desmopressin administration (T0) (IU/ml) | | | | | |
| VWF:Ag | 0.50 (0.37–0.61) | 0.36 (0.28–0.50) | 0.39 (0.24–0.60) | | 0.56 (0.47–0.64) |
| VWF:Act | 0.46 (0.29–0.59) | 0.31 (0.24–0.46) | 0.18 (0.08–0.28) | | 0.55 (0.47–0.63) |
| VWF:CB[a] | 0.51 (0.32–0.69) | 0.32 (0.23–0.50) | 0.20 (0.11–0.36) | | 0.63 (0.51–0.75) |
| FVIII:C | 0.73 (0.56–0.93) | 0.62 (0.47–0.88) | 0.56 (0.38–0.71) | | 0.80 (0.68–0.97) |
| Fold increase over baseline | | | | | |
| VWF:Ag | 3.29 (2.57–3.89) | 3.55 (2.64–4.47) | 3.35 (2.57–4.58) | | 3.17 (2.52–3.68) |
| VWF:Act | 3.69 (2.99–4.80) | 3.85 (3.05–5.41) | 4.29 (3.31–6.63) | | 3.54 (2.91–4.20) |
| VWF:CB[a] | 3.64 (2.83–4.84) | 4.25 (3.04–6.79) | 4.20 (3.14–6.47) | | 3.45 (2.73–4.35) |
| FVIII:C | 3.65 (3.06–4.45) | 3.73 (3.10–4.96) | 4.37 (3.36–5.87) | | 3.53 (3.00–4.11) |

*Note*: Data are presented as mean ± SD, *n* (%), or median (interquartile range). As VWF collagen binding was not routinely measured during the early 2000s, historically lowest VWF collagen binding levels are not stated. Italic entries to emphasize the different types of type 2 VWD.

Abbreviations: FVIII:C, factor VIII activity; VWD, von Willebrand disease; VWF:Act, von Willebrand factor activity; VWF:Ag, von Willebrand factor antigen; VWF:CB, von Willebrand factor collagen binding.

[a]Number of subjects (total cohort) with missing data: weight (19); blood group (46); VWF collagen binding at T0 (26).

between disease types: all patients with Type 1 VWD with historically lowest VWF levels between 0.30–0.50 IU/ml ($n$ = 206/206); 88% of patients with Type 1 VWD ($n$ = 99/112); and 57% of patients with Type 2 VWD ($n$ = 33/58) were responders (Table 3). All patients with a VWF:Act response also showed a FVIII:C response. In Figure 1, the individual VWF:Act levels measured in the different disease types at different time points during desmopressin testing are plotted and categorized into responders and nonresponders.

In patients with Type 1 VWD and historically lowest VWF less than 0.30 IU/ml, females were more likely to respond than males (odds ratio [OR], 4.5; 95% confidence interval [CI], 1.3–16.1; $p$ = 0.02). Mean historically lowest VWF:Act did not differ between females and males with Type 1 VWD and historically lowest VWF:Act <0.30 IU/ml (0.24 vs. 0.22 IU/ml, $p$ = 0.44); however, males were more than twice as likely to have historically lowest VWF:Act <0.10 IU/ml. We did not find a difference in response between children (less than 16 years) and adults (16 years or older). In Type 2, we did not find a significant difference in response between males and females, but children (less than 16 years) were less likely to respond than adults (16 years or older) (OR, 0.08; 95% CI, 0.02–0.42; $p$ = 0.003).

All individuals who showed an increase in VWF:Act also showed an increase in FVIII:C and vice versa. We did not observe very large or unexpected discrepancies between fold increase in VWF:Act and FVIII:C in any of the subjects. In 10 of the 376 patients (3%), VWF:Act increased less than twofold over baseline at T1 (range, 1.30–1.97-fold). Three of these patients were nonresponders: one patient with Type 1 VWD with historically lowest VWF <0.30 IU/ml, and two patients with Type 2A VWD. The seven responders with a less than twofold increase were patients with Type 1 VWD with VWF:Act 0.50 IU/ml or greater at baseline already, and included one individual with historically lowest VWF levels less than 0.30 IU/ml and six individuals with historically lowest VWF levels between 0.30 and 0.50 IU/ml.

### 3.3 | Desmopressin response rates in the prospective validation cohort

Twenty-six of the 30 patients were responders (87%). In Type 1 VWD (VWF less than 0.30 IU/ml), 91% ($n$ = 10/11) classified as responder

**TABLE 2** Patient characteristics of the validation cohort

| Patient characteristics | Total cohort | Type 1 VWD (VWF <0.30 IU/ml) | Type 2 VWD | | Type 1 VWD (VWF 0.30–0.50 IU/ml) |
|---|---|---|---|---|---|
| Number of patients | 30 (100) | 11 (36.7) | 5 (16.6) | | 14 (46.7) |
| Disease type (Type 2) | – | – | *Type 2A* | *4 (13.3)* | – |
| | | | *Type 2M* | *1 (3.3)* | – |
| | | | *Type 2N* | – | – |
| Age (years) | 23 ± 16 | 31 ± 21 | 11 ± 5 | | 20 ± 11 |
| Sex (female) | 22 (73) | 8 (73) | 3 (60) | | 11 (79) |
| Body weight (kg) | 60 ± 23 | 65 ± 23 | 38 ± 12 | | 64 ± 22 |
| Blood group O[a] | 15 (75) | 7 (78) | 0 (0) | | 8 (100) |
| Historically lowest plasma levels (IU/ml) | | | | | |
| VWF:Ag | 0.39 (0.28–0.50) | 0.28 (0.21–0.39) | 0.35 (0.17–0.62) | | 0.47 (0.38–0.52) |
| VWF:Act | 0.37 (0.22–0.45) | 0.26 (0.22–0.31) | 0.20 (0.08–0.32) | | 0.44 (0.41–0.50) |
| FVIII:C | 0.65 (0.48–0.80) | 0.53 (0.38–0.54) | 0.48 (0.19–0.86) | | 0.79 (0.67–0.87) |
| Plasma levels immediately before desmopressin administration (baseline) (IU/ml) | | | | | |
| VWF:Ag | 0.50 (0.32–0.56) | 0.35 (0.24–0.59) | 0.33 (0.16–0.47) | | 0.52 (0.50–0.56) |
| VWF:Act | 0.40 (0.31–0.54) | 0.37 (0.30–0.58) | 0.13 (0.12–0.25) | | 0.48 (0.38–0.55) |
| VWF:CB[a] | 0.47 (0.25–0.55) | 0.41 (0.24–0.52) | 0.07 (0.04–0.25) | | 0.53 (0.48–0.67) |
| FVIII:C | 0.76 (0.62–0.97) | 0.78 (0.47–1.09) | 0.62 (0.36–0.62) | | 0.80 (0.67–0.89) |
| Fold increase over baseline | | | | | |
| VWF:Ag | 3.57 (3.01–4.14) | 3.14 (2.62–3.98) | 4.55 (3.31–5.46) | | 3.60 (3.19–3.96) |
| VWF:Act | 3.94 (3.32–4.79) | 3.36 (2.93–4.34) | 4.46 (3.35–6.02) | | 4.06 (3.71–4.91) |
| VWF:CB[a] | 3.45 (2.77–4.79) | 3.88 (2.59–4.77) | 5.43 (3.38–6.83) | | 3.23 (2.85–3.58) |
| FVIII:C | 4.01 (3.17–4.81) | 3.21 (2.59–4.93) | 4.69 (4.28–6.95) | | 4.01 (3.25–4.61) |

*Note*: Data are presented as mean ± SD, *n* (%) or median (interquartile range). Italic entries to emphasize the different types of type 2 VWD.

Abbreviations: FVIII:C, factor VIII activity; VWD, von Willebrand disease; VWF:Act, von Willebrand factor activity; VWF:Ag, von Willebrand factor antigen; VWF:CB, von Willebrand factor collagen binding.

[a]Number of subjects (total cohort) with missing data: blood group ($n = 10$), VWF:CB at baseline and fold increase over baseline ($n = 5$).

**TABLE 3** Response to desmopressin in the initial cohort and the validation cohort, according to disease type

| | Total cohort | Type 1 VWD (VWF <0.30 IU/ml) | Type 2 VWD | Type 2A VWD | Type 2M VWD | Type 2N VWD | Type 1 VWD (VWF 0.30–0.50 IU/ml) |
|---|---|---|---|---|---|---|---|
| Initial cohort | | | | | | | |
| Number of patients | 376 | 112 | 58 | 41 | 14 | 3 | 206 |
| Responder | 338 (90%) | 99 (88%) | 33 (57%) | 22 (54%) | 8 (57%) | 3 (100%) | 206 (100%) |
| Non-responder | 38 (10%) | 13 (12%) | 25 (43%) | 19 (46%) | 6 (43%) | – | – |
| Validation cohort | | | | | | | |
| Number of patients | 30 | 11 | 5 | 4 | 1 | – | 14 |
| Responder | 26 (87) | 10 (91) | 2 (40) | 1 (25) | 1 (100) | – | 14 (100) |
| Nonresponder | 4 (13) | 1 (9) | 3 (60) | 3 (75) | – | – | – |

Abbreviation: VWF, von Willebrand factor.

and all patients with historically lowest VWF levels between 0.30 and 0.50 IU/ml (100%) were responders. Forty percent of the patients with Type 2 VWD ($n = 2/5$) were responders (Table 3). All VWF:Act responders were also FVIII:C responders. None of the patients had a VWF:Act or FVIII:C increase less than twofold over baseline.

### 3.4 | Receiver operating characteristic analysis

We used ROC curves to analyze the potential of VWF:Act and FVIII:C at different time points (baseline, T1, and historically lowest level) to predict desmopressin nonresponse. As only three patients

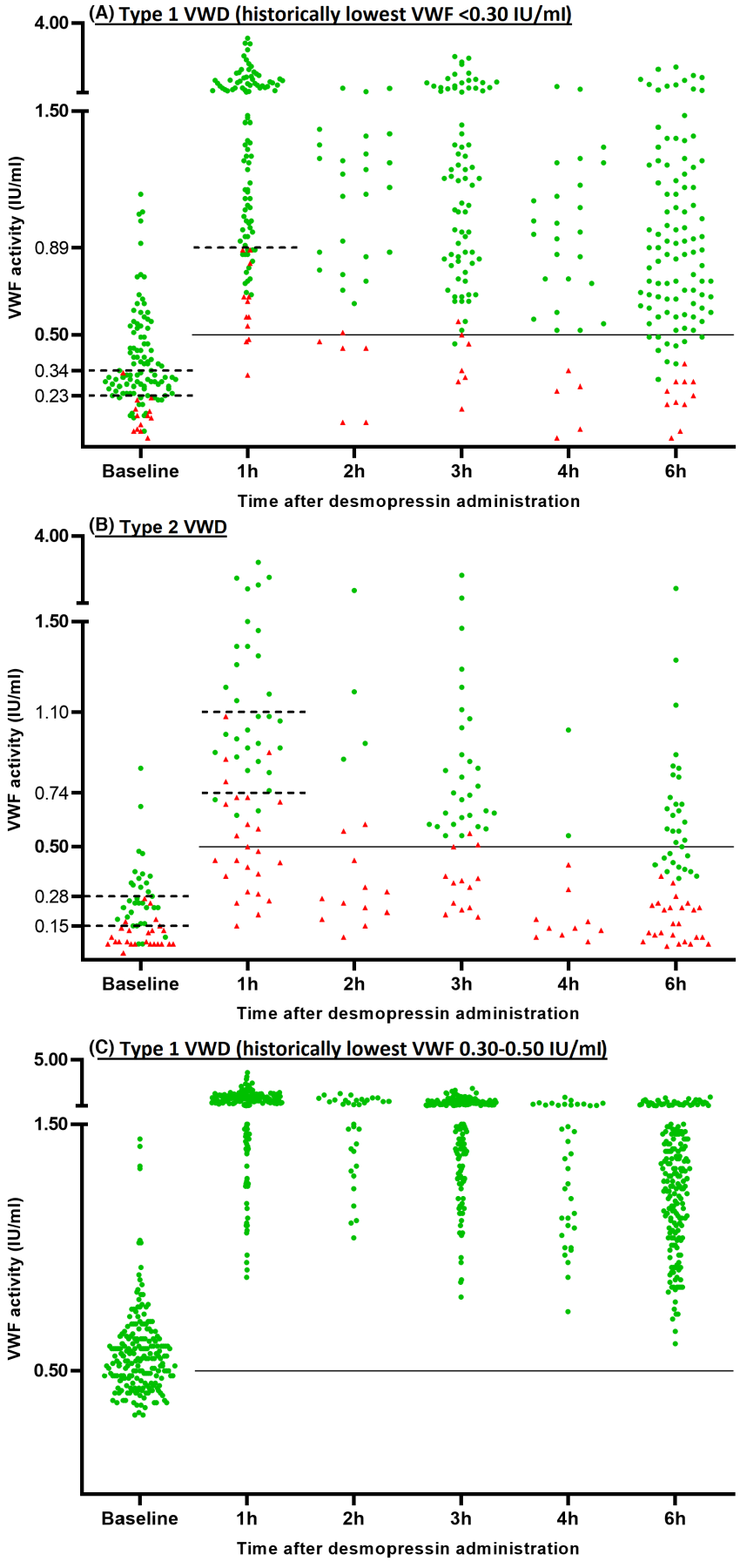


**FIGURE 1** VWF activity (IU/ml) in responders and nonresponders during desmopressin testing in patients with Type 1 VWD (VWF <0.30 IU/ml) (upper panel), Type 2 VWD (middle panel), and Type 1 VWD (VWF 0.30–0.50 IU/ml) (lower panel). Every green dot depicts a single VWF:Act measurement in one of the responders; every red triangle depicts a single VWF:Act measurement in one of the nonresponders. Dashed lines in upper panel depict optimal threshold at baseline (0.23 IU/ml), threshold with sensitivity 100% at baseline (0.34 IU/ml), and both optimal threshold and threshold with sensitivity 100% at T1 (0.89 IU/ml) in Type 1 VWD (VWF <0.30 IU/ml). Dashed lines in middle panel depict optimal threshold at baseline (0.15 IU/ml), threshold with sensitivity 100% at baseline (0.28 IU/ml), optimal threshold at T1 (0.74 IU/ml), and threshold with sensitivity 100% at T1 (1.10 IU/ml) in Type 2 VWD. The uninterrupted line at 0.50 IU/ml in all panels depicts the threshold for response at T1 and T4. Abbreviations: VWD, von Willebrand disease; VWF, von Willebrand factor; VWF:Act, von Willebrand factor activity

with Type 2N were present in our cohort, we excluded these patients from the analysis. Comparison of the areas under the curve (AUCs) shows that VWF:Act measured at T1 has the highest accuracy to distinguish responders from nonresponders with an AUC of 0.98 in Type 1 VWD (VWF less than 0.30 IU/ml) and an AUC of 0.94 in Type 2 VWD, followed by VWF:Act at baselinewith an AUC of 0.93 in Type 1 VWD (VWF <0.30 IU/ml) and an AUC of 0.88 in Type 2 VWD. Historically lowest VWF:Act was least predictive of desmopressin response.

The optimal predictive baseline cutoff—the VWF:Act level with the highest sensitivity and specificity—is 0.23 IU/ml in Type 1 VWD (VWF <0.30 IU/ml) and 0.15 IU/ml in Type 2 VWD. The most sensitive predictive baseline cut-off—the level with 100% sensitivity, at which no nonresponders will be missed—is 0.34 IU/ml in Type 1 VWD (VWF less than 0.30 IU/ml) and 0.28 in Type 2 VWD. In Figure 1, the different cutoffs at baseline, T1, and historically lowest level are visualized. The predictive potential of VWF:Act is shown in Figure 2 and Table 4.

### 3.5 | Validation of cutoffs in the prospective cohort

In the only patient with nonresponding Type 1 VWD (VWF less than 0.30 IU/ml), VWF:Act was 0.14 IU/ml at baseline and 0.47 IU/ml at T1. Historical lowest VWF:Act was 0.07 IU/ml. The three Type 2A VWD nonresponders had baseline VWF:Act of 0.10–0.13 IU/ml, T1 VWF:Act of 0.30–0.58 IU/ml, and historically lowest VWF:Act of 0.05–0.22 IU/ml. All of these values are below the most sensitive predictive cutoff. In one patient with Type 2A VWD, the historically lowest level was above the optimal predictive cutoff of 0.15 IU/ml.

## 4 | DISCUSSION

The results of this study show that desmopressin testing is not needed in individuals with Type 1 VWD with historically lowest VWF levels between 0.30 and 0.50 IU/ml as well as in a substantial number of individuals with Type 1 VWD with historically lowest VWF levels less than 0.30 IU/ml, and those with Type 2A and Type 2M VWD.

In individuals with Type 1 (VWF < 0.30 IU/ml), Type 2A, and Type 2M VWD, we suggest using the most recently measured VWF:Act during a regular outpatient clinic visit as a surrogate for the baseline measurement during a desmopressin test, as this is in essence a random time point. In our study, all patients with Type 1 VWD with historically lowest VWF levels less than 0.30 IU/ml with baseline VWF:Act 0.23 IU/ml or greater were responders except for one patient who had a baseline VWF:Act of 0.33 IU/ml. All patients with Type 2 VWD with baseline VWF:Act 0.28 IU/ml or greater also were responders. For practical reasons, we therefore propose to test only those patients with Type 1 (VWF less than 0.30 IU/ml), Type 2A and Type 2M VWD in whom the most recent VWF:Act measured is below 0.30 IU/ml. This is in accordance with the 2021 guidelines on the management of VWD, which suggest performing a desmopressin test over not performing a test before starting treatment with desmopressin in patients with a VWF baseline level less than 0.30 IU/ml.[5] Our data therefore confirm this guideline, which was mainly based on expert opinion.

If a desmopressin test is required, VWF:Act should be measured before and at least at 1 and 4 h after desmopressin administration to quantify the peak as well as the duration of the response. If it is logistically possible to acquire VWF:Act results from the laboratory rapidly after T1 blood withdrawal, the test may be terminated

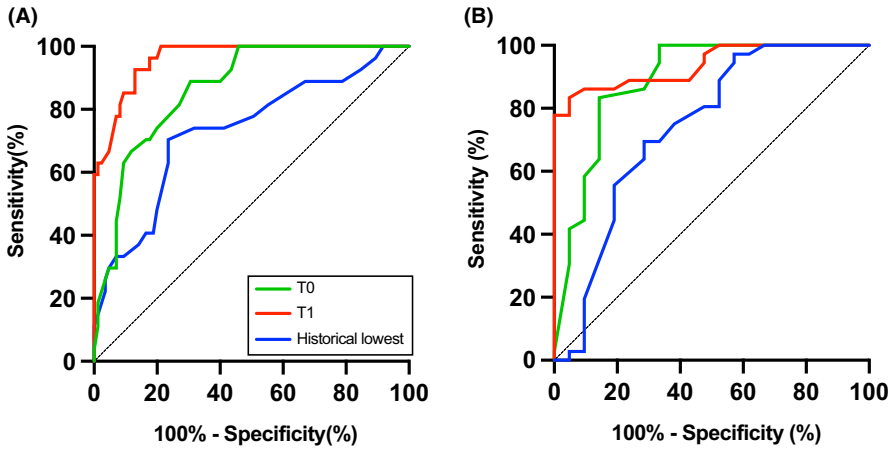


**FIGURE 2** ROC curves comparing the potential of VWF:Act at different time points to discriminate between responders and nonresponders. (A) VWF:Act in patients with Type 1 VWD (VWF <0.30 IU/ml); (B) VWF:Act in patients with Type 2 VWD (excluding patients with Type 2N). Figures show that VWF:Act at T1 predicts response to desmopressin best (AUC of 0.98 in Type 1 VWD (VWF <0.30 IU/ml) and 0.94 in Type 2 VWD), followed by measurements at baseline (AUC of 0.93 in Type 1 VWD (VWF <0.30 IU/ml), 0.88 in Type 2 VWD). Historical lowest VWF:Act is the least predictive of desmopressin response (AUC of 0.79 in Type 1 VWD (VWF <0.30 IU/ml), and 0.79 in Type 2 VWD). All individuals who show a VWF:Act response also show a FVIII response. AUC, area under the curve; ROC, receiver operating characteristic; VWD, von Willebrand disease; VWF, von Willebrand factor; VWF:Act, von Willebrand factor activity

**TABLE 4** ROC analysis of VWF:Act and FVIII at baseline (directly before desmopressin administration), 1 h after desmopressin administration (T1) and at historically lowest level

| | Type 1 VWD (VWF <0.30 IU/ml) | Type 2 VWD[a] |
|---|---|---|
| VWF:Act at baseline | | |
| Area under the ROC curve (95% CI) | 0.93 (0.85–1.00) | 0.88 (0.79–0.98) |
| Optimal cut-off (IU/ml) | 0.23 | 0.15 |
| Sensitivity, % (95% CI) | 92 (67–100) | 80 (61–91) |
| Specificity, % (95% CI) | 87 (79–92) | 90 (74–97) |
| Cutoff with sensitivity 100% | 0.34 | 0.28 |
| Sensitivity, % (95% CI) | 100 (77–100) | 100 (87–100) |
| Specificity, % (95% CI) | 48 (39–58) | 40 (25–58) |
| VWF:Act at T1 | | |
| Area under the ROC curve (95% CI) | 0.98 (0.95–1.00) | 0.94 (0.87–1.00) |
| Optimal cutoff | 0.89 | 0.74 |
| Sensitivity, % (95% CI) | 100 (77–100) | 84 (65–94) |
| Specificity, % (95% CI) | 86 (78–91) | 90 (74–97) |
| Cutoff with sensitivity 100% | – | 1.10 |
| Sensitivity, % (95% CI) | – | 100 (87–100) |
| Specificity, % (95% CI) | – | 37 (22–54) |
| Historically lowest VWF:Act level | | |
| Area under the ROC curve (95% CI) | 0.79 (0.62–0.95) | 0.79 (0.64–0.93) |
| Optimal cutoff (IU/ml) | 0.22 | 0.15 |
| Sensitivity, % (95% CI) | 85 (58–97) | 92 (75–99) |
| Specificity, % (95% CI) | 72 (62–80) | 67 (45–83) |
| Cutoff with sensitivity 100% | 0.33 | 0.29 |
| Sensitivity, % (95% CI) | 100 (77–100) | 100 (87–100) |
| Specificity, % (95% CI) | 7 (4–14) | 19 (8–40) |

*Note*: *p* values for all areas under the ROC curve are <0.001.

Abbreviations: CI, confidence interval; FVIII:C, factor VIII activity; ROC, receiver operating characteristic; VWD, von Willebrand disease; VWF:Act, von Willebrand factor activity.

[a]Patients with Type 2N ($n = 3$) were excluded from this analysis.

in patients with Type 1 VWD (VWF less than 0.30 IU/ml) if T1 VWF:Act is less than 0.50 or 0.89 IU/ml or greater, as the patient will surely be a nonresponder or a responder, respectively. In patients with Type 2A and Type 2M VWD who qualify for desmopressin testing (baseline VWF:Act less than 0.30 IU/ml), we strongly advise to always perform measurements at T1 as well as T4 (Figure 3).

Our results show that the use of historically lowest VWF:Act levels is not recommended when deciding if desmopressin testing should be performed, as these levels are least predictive of desmopressin response. This is in accordance with the most recent guidelines, which recommend to perform a desmopressin test shortly after diagnosis.[11] Our results do not apply to patients with Type 2N, as the number of patients with Type 2N in our study was too small and was therefore excluded from the analysis.

If the approach as described above is adopted in clinical practice, the number of desmopressin tests performed can be reduced by 55% in patients with Type 1 VWD (VWF less than 0.30 IU/ml) and by 20% in patients with Type 2A and Type 2M VWD. Of the individuals with Type 1 VWD (VWF <0.30 IU/ml) who *will* need a desmopressin test, 64% will require blood sampling only at T1. Our data also demonstrate that FVIII does not necessarily have to be measured in patients with Type 1, Type 2A, and Type 2M VWD during a desmopressin test, as in all individuals who showed a VWF:Act response, a FVIII response was observed as well.

In the 2021 guidelines on the management of VWD, responsiveness to desmopressin is defined as an increase of the baseline VWF level of at least twofold, combined with the achievement of both VWF and FVIII levels of greater than 0.50 IU/ml.[5] However, when evaluating the criterion of a twofold VWF:Act increase over baseline, we found that this does not add any value when VWF:Act and FVIII:C of 0.50 IU/ml or above at T1 and T4 are regarded as responsiveness, as the few patients who showed a less than twofold increase over baseline already had baseline levels ≥0.50 IU/ml.

We found that in Type 1 VWD, females are more likely to respond than males, and that the number of responders in Type 2 VWD seems to increase with age. These results correlate with earlier findings that clearance of VWF is lower in females, and that bioavailability of VWF increases with age.[10] The difference between females and males in Type 1 can possibly be explained because females are more often diagnosed with VWD Type 1 than males because of the hemostatic challenges they undergo, such as menstruation and childbirth. Overall, women diagnosed with Type 1 VWD therefore tend to have milder laboratory abnormalities.[12] As it is well known that coagulation factor levels do not always correlate with bleeding tendency, it is important that clinicians do not only establish desmopressin responsiveness based on coagulation factor levels when deciding which treatment modality to choose, but also take the bleeding tendency and type of VWD of the individual patient into account.

In the initial cohort, 3 of the 112 patients with Type 1 VWD had a VWF:Act elimination half-life less than 2 h. These patients had a VWF propeptide (VWFpp)/VWF:Ag ratio greater than 7 and a gene variant (R1205H or S2179R) associated with rapid clearance of VWF. In the validation cohort, none of the patients with Type 1 VWD had a VWF:Act half-life less than 2 h. Data regarding genetic variants and their association with desmopressin response in patients with Type 1 VWD with historically lowest VWF levels less than 0.30 IU/ml and in patients with Type 2 have been described in an another article by our group.[13] In patients with Type 1 VWD with a known VWFpp/VWF:Ag ratio greater than 7 and/or a gene variant associated with rapid clearance, desmopressin testing is therefore unnecessary.

Our study has several strengths. First, we included a large number of patients, likely representative for the VWD populations in hemophilia treatment centers worldwide, as a wide range of disease

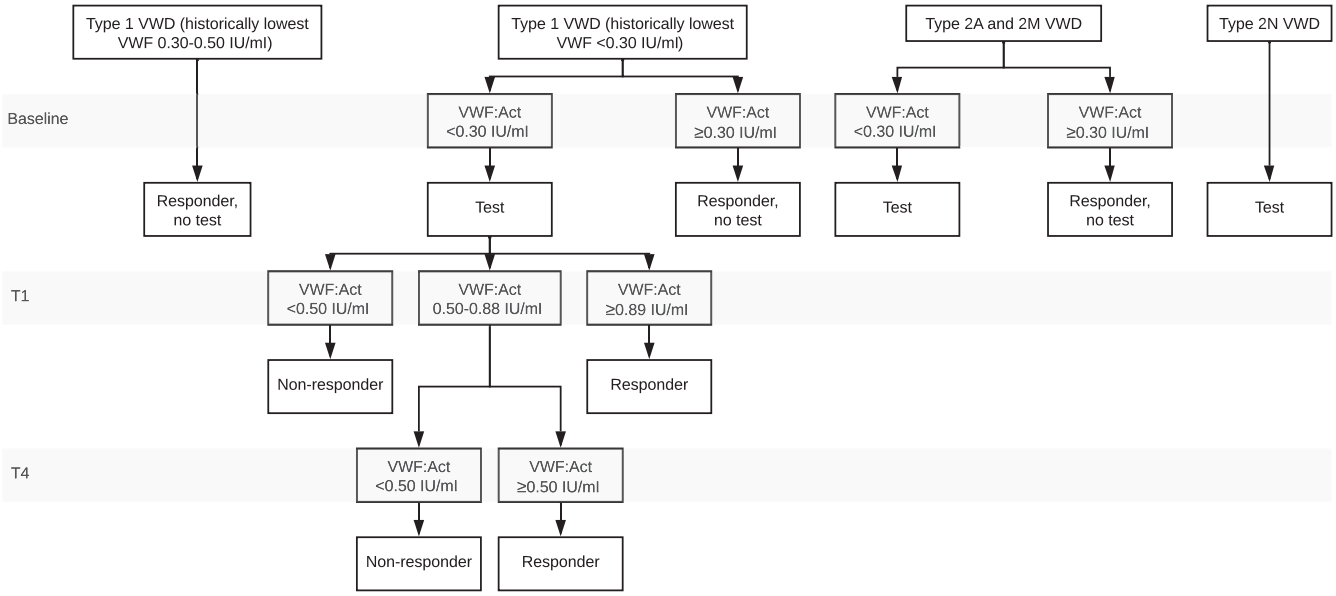


**FIGURE 3** Flowchart for desmopressin testing. VWD, von Willebrand disease; VWF, von Willebrand factor; VWF:Act, von Willebrand factor activity

types and ages are included. We consider inclusion bias to be low, as it is standard protocol at our center to perform a desmopressin test shortly after VWD diagnosis. Second, our study was conducted in a single center, using the same desmopressin test protocol over the studied time period. Third, we were able to validate our results in a prospective cohort of patients with VWD.

A limitation of this study is that in many centers, immediate laboratory measurement of VWF:Act is not possible. In those centers, a complete desmopressin test with measurements 1 h as well as 4 h after desmopressin will have to be conducted, when desmopressin testing is required. This may take away some of the benefits of implementing our advised testing protocol. Another limitation of our study is that ethnicity and socioeconomic status of the participants was not registered. However, the Erasmus University Medical Center is situated in the city of Rotterdam, where more than half of the population is of non-Western descent. Furthermore, it is a tertiary referral hospital for the larger area, including suburban and rural areas. We are therefore convinced that the studied population is racially, culturally, and socioeconomically diverse.

In conclusion, our results show that individuals with Type 1 VWD with historically lowest VWF levels between 0.30 and 0.50 IU/ml do not require desmopressin testing, as well as 55% of patients with Type 1 with historically lowest VWF levels less than 0.30 IU/ml, 20% of patients with Type 2A, and 21% of patients with Type 2M VWD. Current guidelines are in accordance with our finding that patients with Type 1 VWD with VWF levels less than 0.30 IU/ml need testing.[5] The results of the Type 2 VWD cohort would, however, benefit from replication in a larger cohort, with especially larger numbers of patients with Type 2M and 2N VWD. Furthermore, in patients with Type 1, 2A, and 2M VWD, it is not strictly necessary to measure FVIII, as all VWF:Act responders in our study were also FVIII responders. Application of this testing protocol in clinical practice will reduce both patient burden and time investments by health care professionals, as well as health care costs.

## AUTHOR CONTRIBUTIONS

JH designed the study, performed analyses, and wrote the manuscript. JH, FA, QK, and EW collected retrospective data. JH, WA, and KM included patients in the prospective study, and FA provided guidance on statistical analysis. JH, FA, KM, MK, MC, and FL interpreted and discussed the data. MC supervised the study. All authors contributed substantially to the critical revision of the manuscript and approved the final draft.

## FUNDING INFORMATION

This investigator-initiated research project was supported by the Innovation Fund of Health Care Insurance Companies (Innovatiefonds Zorgverzekeraars) in the Netherlands (project number 3216). The funder is not involved in the design or performance of the study and does not get any benefits from the study.

## RELATIONSHIP DISCLOSURE

JH received the CSL Behring-professor Heimburger Award 2018. FA received the CSL-Behring-professor Heimburger Award 2018 and a travel grant from Sobi. KM received research grants from Bayer, Pfizer, and Sanquin; speaker fees from Aspen, Bayer, BMS, Boehringer Ingelheidm, and Sanquin; and consulting fees from Uniqure. MK received grants from governmental research institutes, such as the Dutch Research Institute (ZonMW/NWO), Dutch Thrombosis Foundation, and Innovation fund; unrestricted grants from Bayer, Pfizer, Daiichi Sankyo, Sobi, and Boehringer Ingelheim and speaker's fee from Bayer. FL received research support from CSL Behring and Shire/Takeda for performing the Willebrand in the Netherlands (WiN) study, and from uniQure and Sobi for other

studies. He is a consultant for uniQure, Novo Nordisk, and Shire/Takeda, of which the fees go to the institution, and has received a travel grant from Sobi. He is also a DSMB member for a study by Roche. MC has received grants from governmental research institutes, such as the Dutch Research institute (NWO), ZonMW, Innovation fund, an NWO-NWA grant, and unrestricted investigator-initiated research grants as well as educational and travel funding from various companies over the years (Pfizer, Baxter/Baxalta/Shire, Bayer Schering Pharma, CSL Behring, Sobi Biogen, Novo Nordisk, Novartis, and Nordic Pharma), and has served as a member on steering boards of Roche, Bayer, and Octapharma. All grants, awards, and fees go to the institution. The other authors declare no potential conflicts of interest.

## ORCID

*Jessica M. Heijdra* https://orcid.org/0000-0003-1069-8097
*Ferdows Atiq* https://orcid.org/0000-0002-3769-9148
*Karina Meijer* https://orcid.org/0000-0001-9447-0465
*Marieke J. H. A. Kruip* https://orcid.org/0000-0002-0265-4871
*Frank W. G. Leebeek* https://orcid.org/0000-0001-5677-1371
*Marjon H. Cnossen* https://orcid.org/0000-0003-1557-2995

## TWITTER

*Frank W. G. Leebeek* @FLeebeek
*Marjon H. Cnossen* @CnossenMarjon
*OPTI-CLOT Study Group* @clotterdam

## REFERENCES

1. Leebeek FW, Eikenboom JC. Von Willebrand's disease. *N Engl J Med*. 2016;375(21):2067-2080.
2. Kaufmann JE, Vischer UM. Cellular mechanisms of the hemostatic effects of desmopressin (DDAVP). *J Thromb Haemost*. 2003;1(4):682-689.
3. Rodeghiero F, Castaman G, Di Bona E, Ruggeri M. Consistency of responses to repeated DDAVP infusions in patients with von Willebrand's disease and hemophilia a. *Blood*. 1989;74(6):1997-2000.
4. Federici AB, Mazurier C, Berntorp E, et al. Biologic response to desmopressin in patients with severe type 1 and type 2 von Willebrand disease: results of a multicenter European study. *Blood*. 2004;103(6):2032-2038.
5. Connell NT, Flood VH, Brignardello-Petersen R, et al. ASH ISTH NHF WFH 2021 guidelines on the management of von Willebrand disease. *Blood Adv*. 2021;5(1):301-325.
6. Castaman G, Lethagen S, Federici AB, et al. Response to desmopressin is influenced by the genotype and phenotype in type 1 von Willebrand disease (VWD): results from the European study MCMDM-1VWD. *Blood*. 2008;111(7):3531-3539.
7. Sánchez-Luceros A, Meschengieser SS, Woods AI, et al. Biological and clinical response to desmopressin (DDAVP) in a retrospective cohort study of children with low von Willebrand factor levels and bleeding history. *Thromb Haemost*. 2010;104(5):984-989.
8. Neff AT, Sidonio RF Jr. Management of VWD. *Hematology Am Soc Hematol Educ Program*. 2014;2014(1):536-541.
9. Rodeghiero F, Castaman G, Tosetto A. How I treat von Willebrand disease. *Blood*. 2009;114(6):1158-1165.
10. de Jager NCB, Heijdra JM, Kieboom Q, et al. Population pharmacokinetic modeling of von Willebrand factor activity in von Willebrand disease patients after desmopressin administration. *Thromb Haemost*. 2020;120(10):1407-1416.
11. James PD, Connell NT, Ameer B, et al. ASH ISTH NHF WFH 2021 guidelines on the diagnosis of von Willebrand disease. *Blood Adv*. 2021;5(1):280-300.
12. Atiq F, Saes JL, Punt MC, et al. Major differences in clinical presentation, diagnosis and management of men and women with autosomal inherited bleeding disorders. *EClinicalMedicine*. 2021;32:100726.
13. Atiq F, Heijdra JM, Snijders F, et al. Desmopressin response depends on the presence and type of genetic variants in patients with type 1 and type 2 von Willebrand disease. *Blood Adv*. 2022. doi:10.1182/bloodadvances.2021006757

**How to cite this article:** Heijdra JM, Atiq F, Al Arashi W, et al. Desmopressin testing in von Willebrand disease: Lowering the burden. *Res Pract Thromb Haemost*. 2022;6:e12784. doi: 10.1002/rth2.12784

## APPENDIX A

### The OPTI-CLOT Study Group

Steering Committee, the Netherlands: M.H. Cnossen (principal investigator and chair OPTI-CLOT), F.W.G. Leebeek, Rotterdam; K. Fijnvandraat, R.A.A. Mathôt (co-investigator), Amsterdam; K. Meijer, Groningen. Local principal investigators, other local collaborators the Netherlands: M.J.H.A. Kruip, S. Polinder, Rotterdam; M. Coppens, Amsterdam; R.Y.J. Tamminga, K. Meijer, Groningen; B.A.P. Laros-van Gorkom, P. Brons, S.E.M. Schols, Nijmegen; F.J.M. van der Meer, H.C.J. Eikenboom, Leiden; R.E.G. Schutgens, K. Fischer, Utrecht; F. Heubel-Moenen, Maastricht; L. Nieuwenhuizen, Veldhoven; P. Ypma, The Hague; M.H.E. Driessens, Nijkerk. Trial bureau: C.M. Zwaan, I. van Vliet, Rotterdam. Principal investigators and local collaborators in the United Kingdom: P. W. Collins, Cardiff; R. Liesner, P. Chowdary, London; D. Keeling, Oxford. OPTI-CLOT PhDs: J. Lock, H.C.A.M. Hazendonk, I. van Moort, T. Preijers, J.M. Heijdra, N.C.B. de Jager, M.C.H.J. Goedhart, L.H. Bukkems, W. Al Arashi, M.E. Cloesmeijer, A. Janssen.