The endothelial compartment as a disease modifier in bleeding disorders

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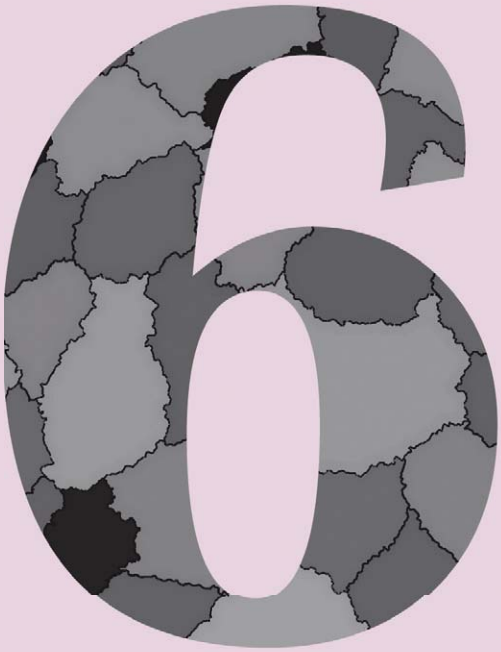
DDAVP response and its determinants in bleeding disorders: a systematic review and meta-analysis



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Blood 2025; 145 (16): 1814–1825.
doi: https://doi.org/10.1182/blood.2024026804
Accepted after revision

Abstract

Desmopressin (DDAVP) can be used to prevent or stop bleeding. However, large inter-individual variability is observed in DDAVP response and determinants are largely unknown. In this systematic review and meta-analysis we aim to identify the response to DDAVP, and the factors that determine DDAVP response in patients.

We included studies with patients with any bleeding disorder receiving DDAVP. First and second screening round and risk of bias assessment were performed by independent reviewers. The main outcome was proportion of patients with complete (factor level > 50 U/dL), or partial (30-50 U/dL) response to DDAVP. Determinants of response including disease type, age, sex, Von Willebrand factor (*VWF*) and factor VIII *(FVIII)* mutations, and baseline factor levels were investigated.

In total, 594 articles were found and 103 were included. Of these, 81 articles (1982 patients) were suitable for the study's definition of response. Meta-analysis showed a pooled response proportion of 0·74 [0·68;0·79] and a significant difference in response between disease subtypes. For hemophilia A, baseline FVIII:C was a significant determinant of response. In von Willebrand disease (VWD) type 1 patients, VWF:Ag, VWF:Act and FVIII:C were significant determinants. A large variation in response was observed for specific mutations in *VWF and F8*.

Response to DDAVP varied between disease subtypes, and was largely determined by the baseline levels of FVIII:C for hemophilia A and VWF:Ag for VWD. Our findings highlight the significant differences in response and emphasize the need for a standardized response definition and further research into response mechanisms.

Introduction

Patients with bleeding disorders experience frequent bleeding from mucocutaneous tissue of nose, uterus, and bleeding in joints and muscles, causing discomfort and pain. Von Willebrand disease (VWD) and hemophilia A (HA) are two of the most common bleeding disorders worldwide with a prevalence of 1:10000 individuals and 1:5000 males, respectively (1). VWD is characterized by quantitative or qualitative defects of von Willebrand factor (VWF), a large multimeric glycoprotein (2). VWF is produced by endothelial cells and megakaryocytes, can bind to collagen at sites of injury, and mediates the formation of a platelet plug. Furthermore, VWF protects coagulation factor VIII (FVIII) from degradation (3). FVIII is the protein that is (partly) deficient in patients with HA and a cofactor in the FIX mediated activation of FX which is crucial for thrombin generation (4).

The main goal of treatment in patients with bleeding disorders is to prevent or treat bleeding. Treatment options aim to increase plasma FVIII levels in HA or VWF and/or FVIII in VWD (2,5). The most common treatment options are replacement therapy that supplements the (partly) deficient coagulation factor and 1-deamino-8-D-arginine vasopressin (DDAVP), also known as desmopressin (6). DDAVP is a synthetic vasopressin analogue that increases endogenous VWF and FVIII levels by an average of three- to five-fold. The ability to increase plasma FVIII and VWF levels in response to DDAVP depends largely on the availability of stored FVIII/VWF, the efficacy of FVIII/VWF secretion and rate of clearance (7). DDAVP is therefore mostly prescribed in patients in which VWF and FVIII are not completely deficient, such as patients with VWD type 1, moderate and mild HA patients (8), and patients with platelet function disorders (PFD) (9).

DDAVP is one of the cheapest and readily available treatments for patients with bleeding disorders. Furthermore, the intranasal formulation of the drug, which can be administered by patients themselves, greatly improves convenience of use. Large inter-individual differences exist in the response to DDAVP, therefore, each individual patient receives a DDAVP test dose with multiple blood drawings to investigate how well they respond to the drug. When patients do not respond, they are fully dependent on the alternative treatments, which are more costly and may require hospital visits. Several studies have reported that DDAVP response is partly influenced by certain factors such as age, blood group type, disease severity or mutation type (7,10-23). However, most studies were conducted in smaller patient cohorts with a large heterogeneity in patient characteristics. Therefore, it is still largely unknown which factors determine a DDAVP response. For that reason, in this systematic review we aim to identify the response

rate in different diseases and to identify possible determinants that influence DDAVP response in order to gain a better understanding of the reason behind a non-response.

Methods

Search strategy and selection criteria

We performed a systematic review and meta-analysis to explore the factors that determine DDAVP response in patients with a bleeding disorder. Our PROSPERO study protocol is available at https://www.crd.york.ac.uk/prospero/ (CRD42021259033). We performed a comprehensive search in PubMed, Embase, Web of Science, COCHRANE Library, Emcare on October 16, 2020. The search was re-run once before the final analysis on September 1st, 2022 (Supplemental File 1). All studies were entered in Covidence (24), where duplicate records were removed. Title and abstract screening and full text screening was performed by at least two reviewers independently (SL, IvM, JdCA). Published studies were included that were performed in patients with any bleeding disorder treated with DDAVP in any dose or form of administration for the indication to improve hemostasis. Papers written in languages other than English, animal studies, reviews and studies on patients without a bleeding disorder were excluded. Any disagreements were resolved by consensus.

Data extraction

The primary outcome was the DDAVP response classified according to the following definition: complete response is defined as VWF Antigen (VWF:Ag) and/or FVIII activity (FVIII:C) above 50 U/dL, for VWD and hemophilia A respectively after 1 hour. Partial response is VWF:Ag and/or FVIII:C between 30 U/dL - 50 U/dL, and non-response is VWF:Ag and/or FVIII:C levels below 30 U/dL. This definition is a slight adjustment on the ASH ISTH NHF WFH 2021 guidelines (25). In these guidelines, a complete response is defined as VWF or FVIII level increasing at least two-fold over baseline, and levels reach >50 U/dL. We will refer to the adjusted definition as the "study definition". This response definition was used to compare complete responders with partial- and non-responders between studies. DDAVP response was also collected based on the response definitions applied in the respective papers, which usually comprised of the categories; complete-, partial- and non-response, and will be referred to as the "article definition". Data from articles where no definition was given were also collected, referred to as "undefined definition". Data were extracted by three reviewers (SL, IvM, JC) independently, using a template custom made within Microsoft Excel (Supplemental File 2 – Data extraction template). For all articles, summary data were collected and individual patient-level data were obtained if possible. Raw data was requested from

the authors of papers if summary data could not be extracted directly from the article. We collected potential determinants of a DDAVP response in patients with bleeding disorders. Expected determinants were diagnosis, blood group, mutations in *VWF* or *F8,* weight, age, sex, baseline factor levels of VWF or FVIII, multimer pattern of VWF, and dose and administration route of DDAVP. Note that VWF activity was measured with different platelet binding assays, the majority using VWF ristocetin cofactor activity. In this article all VWF activity levels will be indicated as VWF:Act.

Study grouping and data analysis

Analyses were performed separately per disease but also in one of five main disease types. Namely, VWD type 1, VWD type 2, VWD type 3, HA and if not fitting in one of these four disease types, "other". We categorized VWD subtypes as a result of their completely different pathophysiology. Most of the studies reported DDAVP as categorical outcome (e.g. non-, partial-, or complete response), other studies reported continuous variables (VWF:Ag, VWF:Act, FVIII:C). Meta-analysis per disease subtype was performed when data from at least three studies was available. As we were interested in the determinants of the DDAVP response with regard to the actual physiological mechanisms of secretion of factors from endothelial cells we based the "study definition" on the increase in VWF:Ag or FVIII:C. This definition, however, does not necessarily reflect an increase of functional VWF:Act as is usually considered in the context of clinical responsiveness and applicability of DDAVP in VWD. Response in VWF levels in the quantitative sense (on antigen level) or in a qualitative sense (on activity level) both offer different insights into the mechanisms of DDAVP response. Therefore, we also compared VWF:Act as a factor next to VWF:Ag over time in type 1 VWD compared to type 2 VWD patients, which are known to have qualitative defects of VWF. Meta-regression (Supplemental Methods) was performed when the association between a prognostic factor and DDAVP response was evaluated in at least three studies. Finally, the effect of *VWF/F8* mutations on response was analyzed per patient.

Results

Study selection and data extraction

The search strategy identified 570 studies and another 21 original articles were added after the re-run of the search. After 1st and 2nd round of screening, 103 studies (ranging from publication date 1980 to 2022) were included as shown in the PRISMA flow diagram (Figure 1) (7,10-23,26-113). The characteristics of all studies are presented in Supplemental Table 1. The majority of the included studies, are prospective case reports/series.

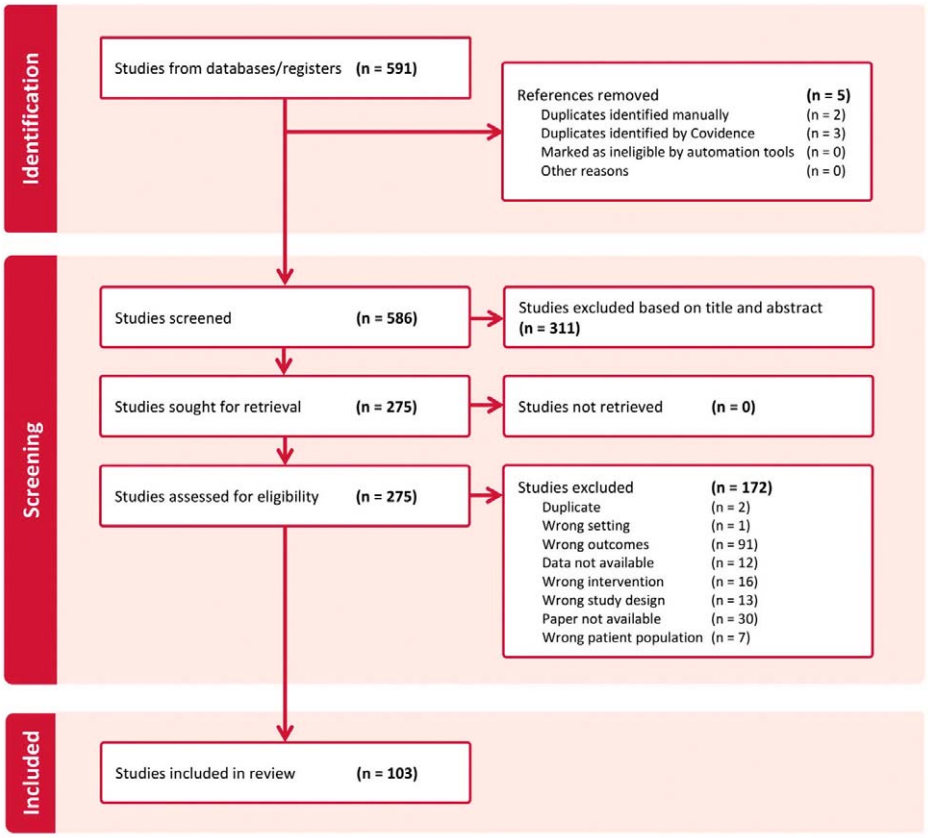


Figure 1. PRISMA flow diagram of inclusion and exclusion of articles.

Data on DDAVP response could be extracted and classified according to the "study definition" in 81 articles and according to the "article definition" in 36 articles (Supplemental Table 1). The definitions that were employed for the "article definitions" are listed in Supplemental Table 2. Data from studies with an "undefined definition" of DDAVP response were also extracted from 52 articles. Unfortunately, due to heterogeneity between article definitions and small patient numbers in the studies only reporting the "article definition" and "undefined definition", these could not be used for further meta-analysis and meta-regression. Risk of bias (RoB) was assessed, with most articles being low (40/103) or moderate RoB (52/103) with some high RoB studies (11/103). Almost all studies reported only intravenous (71/103) or intravenous or subcutaneous administration of DDAVP (13/103). A few reported subcutaneous administration (14/103), intranasal (1/103) or not reported administration (5/103). All

extracted data, e.g. the RoB score, study design, bleeding disorder and administration route, per study can be found in Supplemental File 3.

Meta-analysis on response to DDAVP per disease subtype

For the meta-analysis, 81 articles were used where the "study definition" of response could be applied. In Supplemental Table 1, patient number reflects the patients from which data could be extracted based on the "study definition" (total of 1982 patients). Of these patients, the average age was 34·2 ± 11·6 and 25·6% was female. A large part of the patients were male hemophilia A patients (396 patients). Patient numbers per disease subtype are shown in Figure 2A. Data from three or more articles were obtained for the following subtypes of disease: VWD type 1 (28 studies), VWD type 2A (eight studies), VWD type 2B (nine studies), VWD type 2M (five studies), VWD type 2N (four studies), VWD type 3 (three studies), VWD undefined (four studies), HA carriers (three studies), HA mild (nine studies), HA mild & moderate (11 studies), HA moderate (five studies), PFD (ten studies) and Other (seven studies). As seen in Figure 2A, most patients had either HA (n=923) or VWD type 1 (n=669).

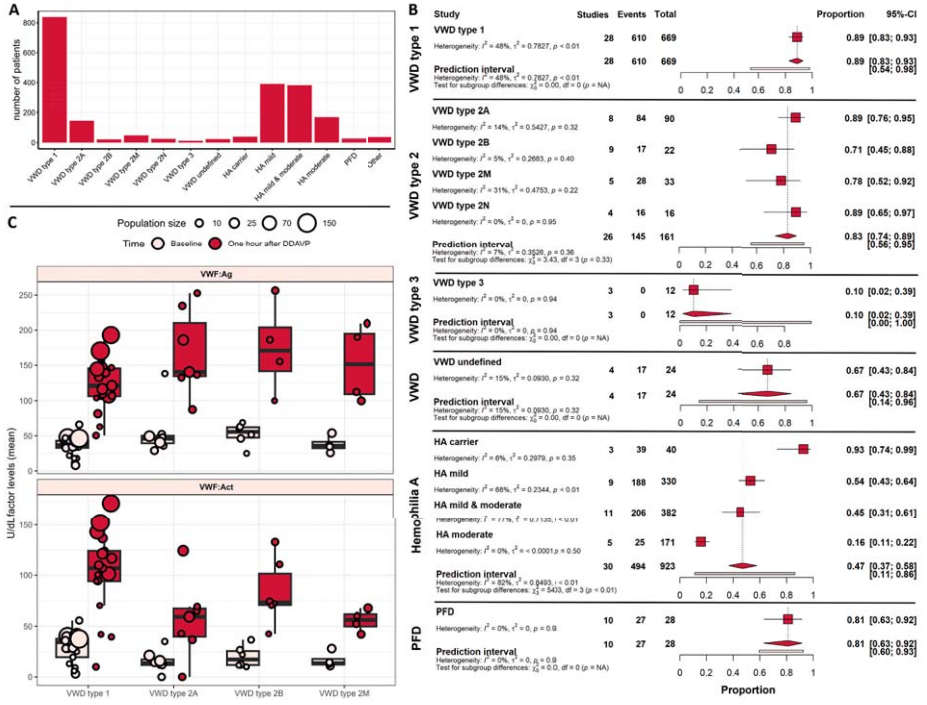


Figure 2. Complete response rate varies per disease subtype according to the study definition. A) Number of patients per disease type. Disease types with <3 articles are excluded from this analysis. "Other" is, everything that is not VWD type 1, 2 or 3, Hemophilia A or PFD. B)

Meta-analysis on response to DDAVP at one hour in patients with various bleeding disorders per subtype according to the study definition. Using a random effect model the proportion of complete response per disease type are shown. The proportion of response is not zero in zero-event studies due to the continuity correction that was performed to prevent mathematical errors. C) Response to DDAVP of patients with VWD type 1 and VWD types 2A, 2B, 2M. In the top panel, VWF:Ag (U/dL) before (light red) and after one hour of DDAVP (dark red) are shown. In the bottom panel, VWF:Act (U/dL) is shown. VWD type 2N is not displayed in this figure as only two studies had data on both VWF:Ag and VWF:Act. Abbreviations: HA = Hemophilia, PFD = Platelet function disorder, VWD = Von Willebrand disease.

The results of the meta-analyses for the complete response rate are given in Figure 2B. Forest plots presenting data points per study instead of subtype summaries are shown in Supplemental Figure 1. Meta-analysis showed a pooled response proportion of 0·74 [0·68;0·80] for all patients and a significant difference in DDAVP response between disease subtypes. The overall proportion of complete response was 0·89 (CI 0·83-0·93) in VWD type 1 patients, 0·83 (CI 0·75-0·89) in type 2 and 0·10 (CI 0·02-0·39) in type 3. The response in HA carriers was 0·93 (CI 0·74-0·99), mild HA 0·54 (CI 0·43-0·64), mild and moderate HA 0·45 (CI 0·31-0·61), and moderate HA only 0·16 (CI 0·11-0·22). We observed significant differences in proportions of complete response between disease subtypes in HA patients with a lower response in moderate patients. VWD type 1 and 2 also showed large differences in proportion of response between subtypes although most subtypes responded quite well to DDAVP according to the "study definition". Finally, the observed proportion of response in PFD patients was 0·81 (CI 0·63-0·92). It should be noted that levels of VWF and FVIII at baseline were above 50 U/dL in almost all PFD patients leading to complete response according to the "study definition".

We analyzed the increase from baseline in VWF:Ag in VWD patients and observed a large increase in VWF:Ag in all type 1 VWD patients as well as in patients affected by types 2A, 2B and 2M VWD (Figure 2C). Median VWF:Ag levels (U/dL) with standard deviation one hour after DDAVP administration is 121·20 ± 35·39 in type 1 VWD, in type 2A, 2B and 2M the levels are 140·28 ± 59·77, 170·79 ± 65·23 and 151·30 ± 54·82 respectively. All subtypes increase above 100 U/dL. However, levels of VWF:Act only increase strongly in VWD type 1 and VWD type 2B (106·93 ± 42·38 and 73·06 ± 32·41). Although limited data was available, the average platelet count in type 2B patients (12 patients in four articles (31,57,76,104)) was reported to be reduced after DDAVP ($90x10^9$/L) compared to before administration ($172x10^9$/L). In VWD type 2A and 2M median levels remain low (59·36 ± 37·84 and 56·20 ± 10·84). Both barely reaching levels above 50 U/dL. In VWD type 2B VWF:Act levels do increase, which makes sense, as type 2B mutations do not cause less activity of VWF, but rather, increased binding affinity to platelets. VWD type 2N was not included in this analysis as only two studies had data on both VWF:Ag and VWF:Act.

Determinants of DDAVP response in patients with bleeding disorders

Based on the meta regression analyses, determinants of DDAVP response, according to the "study definition" differed per disease type (Figure 3). For HA patients higher baseline factor levels of FVIII:C (U/dL) and female sex showed a significant association with higher proportion of complete response (OR=1·054 per U/dL, 95%CI 1·014–1·095 and OR=1·024 per percentage point more women, 95%CI 1·007–1·040). As all females were carriers of HA they logically had higher baseline FVIII levels compared to men which explains the difference is response. Although increased baseline VWF:Ag levels per unit and higher age per year showed a positive association with complete response, these were not significant (OR=1·009 per U/dL, 95%CI 0·973–1·045 and OR=1·055 per year, 95%CI 0·965–1·153 respectively). In VWD type 1 patients, VWF:Ag (OR=1·055 per U/dL, 95%CI 1·016–1·096), VWF:Act (OR=1·048 per U/dL, 95%CI 1·008–1·090) and FVIII:C (OR=1·023 per U/dL, 95%CI 1·002–1·045) were associated with the proportion of complete response, age (OR=1·006 per U/dL, 95%CI 0·935–1·082) and VWF Collagen Binding (CB) did not (OR=1·058 per U/dL, 95%CI 0·896–1·246). No determinants showed a significant association with response in VWD type 2 patients. However, blood group non-O and weight did show some trend (OR=1·037, 95%CI 0·996–1·080 and OR=1·027 per kg, 95%CI 0·986–1·069), respectively. Route of administration is presented in Supplemental Figure 2. However, meta-regression was not performed on the route of administration as not enough data of different routes was available. Other determinants like bleeding time and sex in VWD, showed no positive nor negative effect in our study. All estimated odds ratios with 95% CI of the determinants per disease type are shown in Supplemental Table 3.

Assessing F8 and VWF mutations as determinants of DDAVP response

Genetic variants of *F8* and *VWF* may impact folding, storage, secretion and interaction with other proteins, thereby affecting DDAVP response. We collected patient mutation information from the articles when available (18 studies, eight reported *F8* mutations and ten *VWF* mutations). For HA, data of 389 patients with known *F8* genetic annotations were extracted. Of these patients, 215 were complete-, 113 partial- and 61 non-responders. In total, 165 distinct missense variants were recorded while the rest of the variants represented mutations at noncoding regions, repetitions and possible exon deletions. We plotted peak FVIII:C levels against amino acid positions affected by missense mutations to investigate whether missense mutations at specific protein locations associated with response (Figure 4A). This revealed that mutations were distributed over all *FVIII* domains, but scarcely along the B domain. Importantly, we observed that mutations in the same location were associated with different responses. For instance, in 26 subjects with the variant Arg2169His, nine had a complete response, 13 partial and four were non-responders.

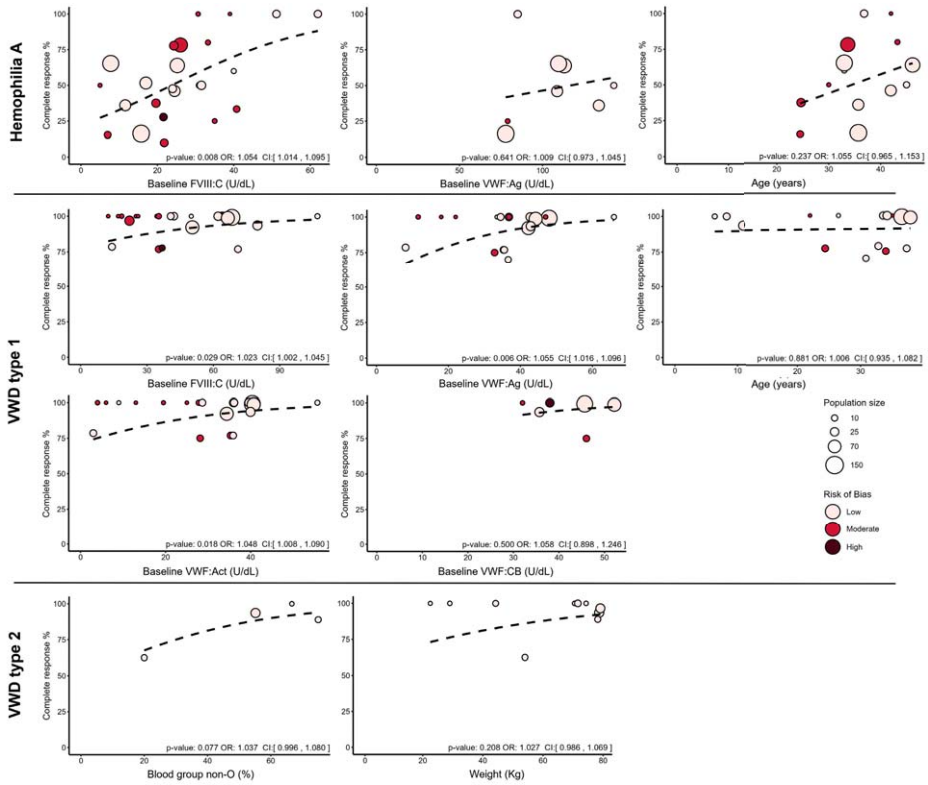


Figure 3. Baseline factor levels and other determinants affect DDAVP response. Complete response rate according to the study definition is plotted against possible determinants for DDAVP response per disease. Bubble size indicates the population size per study. Color indicates risk of bias of the study: low (light red), moderate (red) or high (dark red) risk of bias. The fitted values of the meta regression are indicated by the black dotted line. Odds ratio with Confidence interval and p-value) are shown in the lower right corner. Abbreviations: Odds ratio (OR), Confidence interval (CI).

For VWD data on 209 individuals with genetic information were collected; 136 VWD type 1 patients and 73 VWD type 2 patients. Of these patients, 189 had missense mutations, of which 172 were complete, 13 were partial and only four were non-responders. The majority of the response profiles originated from two studies (10,12). Altogether, 85 different *VWF* missense mutations were reported. To assess possible associations between protein structure and DDAVP response, peak VWF:Ag levels were plotted against amino acid position (Figure 4B).

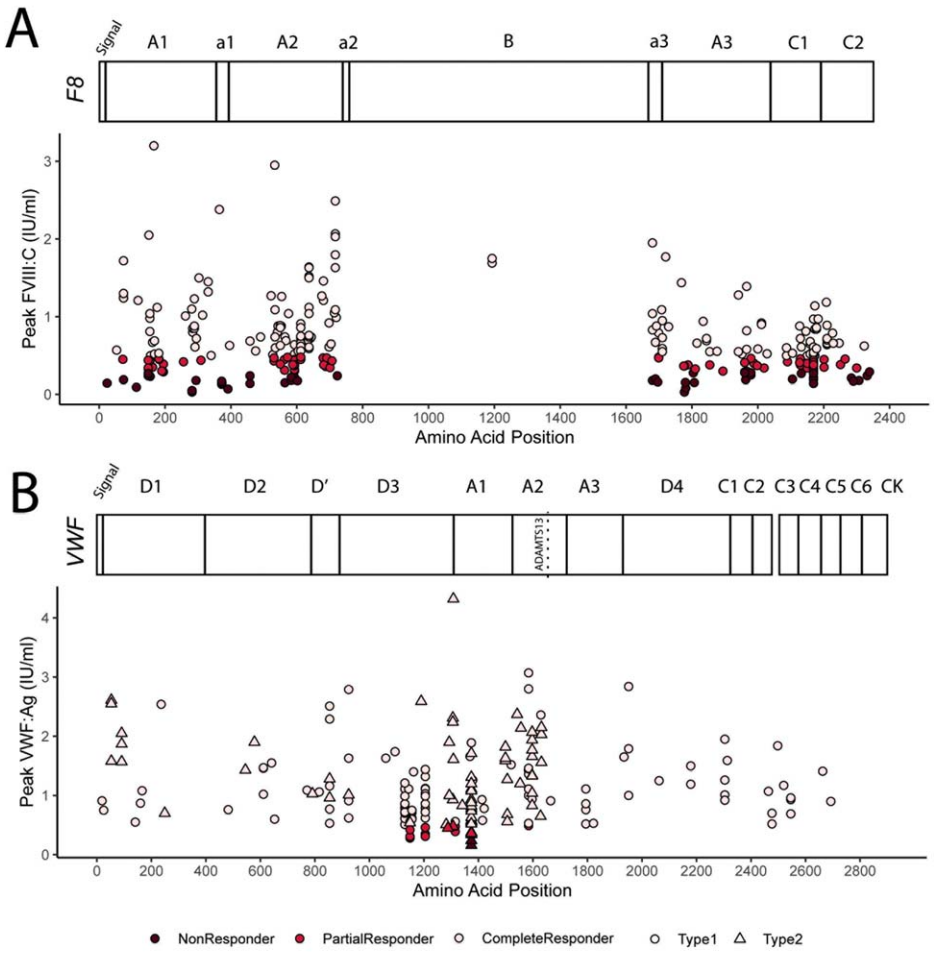


Figure 4: Mutation landscape of individual responses to DDAVP. Each dot represents a patient. Colors represent non (dark red), partial (red) and complete (light red) response. Missense mutation position relative to the protein sequence are plotted on the x-axis against response. A) Variants in HA; y-axis represents peak FVIII:C levels after DDAVP. B) Variants in VWD; y-axis represents peak VWF:Ag levels after DDAVP. Shape depicts VWD type 1 (circle) and type 2 (triangle). Protein domains and relevant annotations are plotted at the top of each graph. Abbreviations: Factor 8 (F8), von Willebrand factor (VWF).

Risk of bias sensitivity analysis

The sensitivity analysis with removal of high RoB studies from the meta-analysis showed that high RoB studies did not substantially influence the results of the meta-analysis on proportion of response. The total proportion of response remained 0·74. The proportion per subtype stayed the same except for a small change in mild & moderate

HA (0·45 to 0·48), PFD (0·81 to 0·79) and VWD type 2B (0·71 to 0·66). The results of the meta regression on the influence of determinants also did not change significantly. An overview of the slightly changed results after removing high RoB articles can be seen in Supplemental Table 4.

Discussion

Patients with bleeding disorders experience frequent bleeding which is often treated by administration of DDAVP. However, despite that DDAVP has long been used, there is still an unexplained large inter-individual heterogeneity in DDAVP response. It is still largely unknown which factors determine a complete DDAVP response. In this systematic review we aimed to identify factors that determine DDAVP response in bleeding disorders from the collective data available in the literature. Our meta-analysis, which was based on 81 out of 103 included articles and contained 1982 patients, found that subtype of disease is a strong determinant of response. Furthermore, we show higher baseline levels of FVIII:C significantly increase response rate in HA and that higher FVIII:C, VWF:Ag and VWF:Act baseline levels increase response rate in VWD type 1. Furthermore, although not significant, a trend is shown that higher age (per year) and weight (per Kg) correlates with better response in HA and VWD. Finally, comparison of mutations with response profiles revealed heterogeneous responses to DDAVP for patients carrying the same mutation. Remarkably, for both *F8* and *VWF* we observed that the same amino acid substitution could be present in complete, partial and non-responders and that in VWD only mutations in the D3 and A1 domain led to non/partial responders.

Our results indicate that disease subtype is an important determinant, which aligns with previous reports (10,22). It is important to note that there is a large discrepancy in VWF:Ag and VWF:Act response for patients with VWD type 2. Especially VWD type 2A and 2M show a strong increase in antigen levels after DDAVP administration, while activity levels only rise slightly, indicating low hemostatic efficacy as the secreted protein is dysfunctional. However, in many patients the activity level did rise above 50 U/dL which may be sufficient for milder bleeding episodes. It is therefore important to test DDAVP effectivity in these patients as well. In addition, we show that patients with VWD type 2B respond quite well to DDAVP. However, due to the risk of thrombocytopenia, DDAVP is contraindicated.

Specific mutations, which are tied to disease type, have also been shown to influence DDAVP response based on activity levels of VWF (10,12) and FVIII:C (7,14,16,21), even

showing that similar mutations lead to similar responses to DDAVP (19). It may be explained by comparable baseline levels of FVIII that is present among patients with the same *F8* mutation (114). Our data showed that missense mutations were present along the whole *VWF* sequence. It also revealed that all partial and non-responders had mutations in the D3, A1 and A2 domain (position 1149-1584). This region is nestled between the intra- and interchain disulfide bridges in D3 and the cleavage site of ADAMTS13 in A2. Interestingly, this section influences VWF multimer stability and includes the binding site for the platelet glycoprotein GP1bα, which is important for platelet plug formation (115). Notably, in both HA and VWD, we observed that mutations on the same location were associated with different responses to treatment. Recently, Guillet *et al.* analyzed a link between desmopressin response and *F8* genotype in hemophilia A patients (116). The authors proposed that mutations could be categorized in four groups of response effectiveness. Our analysis contains 5 similar mutations. Although those classified as group 1 and group 2 mutations seem to respond similarly, group 3 and 4 mutations, labeled as moderately and frequently ineffective (116), also showed complete and partial responders in our dataset. For a complete analysis, adjustments for other determinants should be performed in a multivariate model, but this was not possible in our analysis due to insufficient sample size. Furthermore, as a result of combining diverse groups of patients with the same mutations, we captured a more heterogeneous sample of other determinants that may outweigh the influence of mutations on DDAVP response. Taken together, our analyses suggests that *F8* and *VWF* mutations are not the main determinants of response, which precludes prediction of DDAVP response based on mutations alone.

Other determinants have been described in literature extensively. For instance, higher baseline factor levels have been associated with better response (11,14,17-19) which is confirmed by our meta-regression analysis in the case of FVIII:C in HA and FVIII:C, VWF:Ag and VWF:Act in VWD type 1. This observation may be explained by lower clearance of VWF, higher production rate or storage of VWF. Age was not found to be a significant determinant in our analysis. However, this has been shown previously in children (17-19), and adults (14). This finding was recently confirmed by Atiq *et al.* in low VWF and type 1 VWD patients (117) (not in systematic review). Our study shows no significant effect of blood group on response. Literature has shown a correlation between blood group and response in VWD type 1C Vicenza (13), while no effect was seen in patients with platelet normal VWD (23) and children with VWD type 1 (18). This could be explained by the inherent higher VWF baseline levels of patients with blood group non-O (118). Previously, route of administration has been tested, but no differences in response were observed (15,20). It has also been reported that onset of effect after DDAVP does not differ significantly between administration routes

(199,120). Unfortunately, in our study, administration route could not be analyzed due to insufficient data, although intravenous and subcutaneous administration seem to yield similar responses in HA. For the remaining determinant, weight, no effect was observed in our data and no effect has been described in the literature.

Our meta-analysis has some limitations. First, variation in the setting and route of administration of the DDAVP test might influence the response rate. Most studies reported DDAVP response measurements in steady state, but 21 studies reported measurements perioperatively or in the context of bleeding episodes. Second, none of the included articles excluded patients based on their DDAVP response. However, this does not exclude selection bias as some studies excluded patients with VWD type 3 or type 2B as these patients were expected to have a weak response or where DDAVP is considered contra-indicated. Third, the included studies ranged from 1980 to 2022. As such, the definitions of response as stated by the articles laboratory tests used are exceptionally heterogeneous. Definitions of response varied with respect to time to peak, if fold change was calculated, cut-off for complete response and whether activity or antigen was measured. Due to this heterogeneity, we could not pool the extracted data for our analysis. We therefore strongly recommend standardized definitions of response should be maintained and data should be made available for other definitions of response to be calculated. Fourth, we calculated response based on the rise of VWF:Ag and FVIII above 50 U/dL. Therefore, the "study definition" was not applicable on patients with baseline levels above 50 U/dL. This was the case in PFD, VWD type 2 and HA carriers which could have resulted in an overestimation of response rate. For VWD type 2 we therefore performed an additional analysis on VWF:Act response. Whereas for PFD and HA carriers an alternative definition of response should be used. Fifth, the potential misdiagnosis between severity types in HA and VWD due to variation in assays could influence the response rate calculated in this study. Finally, as we used aggregated data, we can only study the effect of determinants on the response rates between studies, but not assess the effect on individuals within a study. For future research we suggest performing studies using individual patient data.

Our study also has several strengths. First, to the best of our knowledge, this is the first meta-analysis to show the response rate of DDAVP in various bleeding disorders and identify determinants influence this response rate. Second, the high number of studies and disease types included, allowed us to analyze many different aspects of DDAVP response. Furthermore, the large patient numbers with VWD type 1 and HA allowed for accurate analysis in these subtypes. We were able to extract mutation data of 389 patients with HA and 209 patients with VWD. Finally, after sensitivity analysis we

determined that removal of high RoB articles did not significantly change the analysis outcome.

This study offers a comprehensive overview of DDAVP response proportions in various bleeding disorders and which determinants might play a role in DDAVP response. Especially coagulation factor base levels have been found as an important determinant for the response to DDAVP. These factors should be kept in mind when performing DDAVP tests. Our analysis, which indicates that the vast majority of patients with VWD type 1 (baseline VWF:Ag >30 U/dL) have a complete DDAVP response, lends support to the current guidelines regarding DDAVP testing in patients with VWD type 1 (121). Furthermore, the relative low proportion of response in mild and mild/moderate hemophilia A indicates that DDAVP response should be tested in those patients to ensure a sufficient response. This information can be used as a guide by clinicians treating patients with bleeding disorders. However, despite the strong relationship between DDAVP response with baseline factor levels and disease subtype, individual DDAVP tests may still be required in these heterogeneous bleeding disorders. Furthermore, heterogeneity in article definition precluded meta-analysis and therefore we strongly recommend the use of a clear and uniform definition of response in future studies. Finally, our detailed analysis on mutations and DDAVP response can be used in future studies into the biological mechanisms of DDAVP response.

Acknowledgements

The SYMPHONY consortium, which aims to orchestrate personalized treatment in patients with bleeding disorders, is a unique collaboration between patients, health care professionals, and translational and fundamental researchers specializing in inherited bleeding disorders, as well as experts from multiple disciplines (122). It aims to identify the best treatment choice for each individual based on bleeding phenotype. To achieve this goal, work packages (WP) have been organized according to three themes (e.g. Diagnostics [WPs three and four], Treatment [WPs 5-9], and Fundamental Research [WPs 10-12]). Principal investigator: M.H. Cnossen; project manager: S.H. Reitsma.

Beneficiaries of the SYMPHONY consortium: Erasmus University Medical Center-Sophia Children's Hospital, project leadership and coordination; Sanquin Diagnostics; Sanquin Research; Amsterdam University Medical Centers; University Medical Center Groningen; University Medical Center Utrecht; Leiden University Medical Center; Radboud University Medical Center; Netherlands Society of Hemophilia Patients

(NVHP); Netherlands Society for Thrombosis and Hemostasis (NVTH); Bayer B.V., CSL Behring B.V., Swedish Orphan Biovitrum (Belgium) BVBA/SPRL.

We would like to thank J. Schoones from the Walaeus library for his assistance in the set-up of the search strategy.

All collected data is made available as a supplementary file.

Authorship Contributions

SNJL, JdCA and IvM performed article selection, screening and data extraction. SNJL, JdCA and IvM analyzed data; SNJL, JdCA and IvM wrote the manuscript; all authors participated in the design of the research, revised the manuscript and approved the final manuscript.

Conflict of interest disclosures

SNJL, JdCA, IvM, RB and JE, KF received research funding from SYMPHONY: NWO-NWA.1160.18.038. Funding had no role in the writing or decision making of this manuscript.

References

1. Sadler JE, Mannucci PM, Berntorp E, et al. Impact, diagnosis and treatment of von Willebrand disease. *Thromb Haemost*. 2000;84(2):160-174.
2. Leebeek FWG, Eikenboom JCJ. Von Willebrand's Disease. *New England Journal of Medicine*. 2016;375(21):2067-2080.
3. Nogami K, Shima M, Nishiya K, et al. A novel mechanism of factor VIII protection by von Willebrand factor from activated protein C–catalyzed inactivation. *Blood*. 2002;99(11):3993-3998.
4. Lenting PJ, van Mourik JA, Mertens K. The life cycle of coagulation factor VIII in view of its structure and function. *Blood*. 1998;92(11):3983-3996.
5. van Galen KPM, Mauser-Bunschoten EP, Leebeek FWG. Hemophilic arthropathy in patients with von Willebrand disease. *Blood Reviews*. 2012;26(6):261-266.
6. Mannucci. Desmopressin (DDAVP) in the treatment of bleeding disorders: the first twenty years. *Haemophilia*. 2000;6(s1):60-67.
7. Castaman G, Mancuso ME, Giacomelli SH, et al. Molecular and phenotypic determinants of the response to desmopressin in adult patients with mild hemophilia A. *J Thromb Haemost*. 2009;7(11):1824-1831.
8. BOREL-DERLON A, FEDERICI AB, ROUSSEL-ROBERT V, et al. Treatment of severe von Willebrand disease with a high-purity von Willebrand factor concentrate (Wilfactin®): a prospective study of 50 patients. *Journal of Thrombosis and Haemostasis*. 2007;5(6):1115-1124.
9. Leissinger C, Carcao M, Gill JC, Journeycake J, Singleton T, Valentino L. Desmopressin (DDAVP) in the management of patients with congenital bleeding disorders. *Haemophilia*. 2014;20(2):158-167.
10. 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.
11. Biguzzi E, Siboni SM, Peyvandi F. Acquired Von Willebrand syndrome and response to desmopressin. *Haemophilia*. 2018;24(1):e25-e28.
12. 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.
13. Castaman G, Tosetto A, Eikenboom JC, Rodeghiero F. Blood group significantly influences von Willebrand factor increase and half-life after desmopressin in von Willebrand disease Vicenza. *J Thromb Haemost*. 2010;8(9):2078-2080.
14. Di Perna C, Riccardi F, Franchini M, Rivolta GF, Pattacini C, Tagliaferri A. Clinical efficacy and determinants of response to treatment with desmopressin in mild hemophilia a. *Semin Thromb Hemost*. 2013;39(7):732-739.
15. Lethagen S, Egervall K, Berntorp E, Bengtsson B. The administration of desmopressin by nasal spray: a dose-determination study in patients with mild haemophilia A or von Willebrand's disease. *Haemophilia*. 1995;1(2):97-102.
16. Nance D, Fletcher SN, Bolgiano DC, Thompson AR, Josephson NC, Konkle BA. Factor VIII mutation and desmopressin-responsiveness in 62 patients with mild haemophilia A. *Haemophilia*. 2013;19(5):720-726.

17. Revel-Vilk S, Blanchette VS, Sparling C, Stain AM, Carcao MD. DDAVP challenge tests in boys with mild/moderate haemophilia A. *Br J Haematol*. 2002;117(4):947-951.
18. Revel-Vilk S, Schmugge M, Carcao MD, Blanchette P, Rand ML, Blanchette VS. Desmopressin (DDAVP) responsiveness in children with von Willebrand disease. *J Pediatr Hematol Oncol*. 2003;25(11):874-879.
19. Seary ME, Feldman D, Carcao MD. DDAVP responsiveness in children with mild or moderate haemophilia A correlates with age, endogenous FVIII:C level and with haemophilic genotype. *Haemophilia*. 2012;18(1):50-55.
20. Sharthkumar A, Greist A, Di Paola J, et al. Biologic response to subcutaneous and intranasal therapy with desmopressin in a large Amish kindred with Type 2M von Willebrand disease. *Haemophilia*. 2008;14(3):539-548.
21. Stoof SC, Sanders YV, Petrij F, et al. Response to desmopressin is strongly dependent on F8 gene mutation type in mild and moderate haemophilia A. *Thromb Haemost*. 2013;109(3):440-449.
22. Loomans JI, Kruip M, Carcao M, et al. Desmopressin in moderate hemophilia A patients: a treatment worth considering. *Haematologica*. 2018;103(3):550-557.
23. Castaman G, Rodeghiero F. No influence of blood group on the responsiveness to desmopressin in type I "platelet normal" von Willebrand's disease. *Thromb Haemost*. 1995;73(3):551-552.
24. Covidence. Veritas Health Innovation; 2023.
25. 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.
26. Dewald DL, Briggs B, Smith RE. Intranasal administration of desmopressin acetate (DDAVP) to hemophiliacs. *Thromb Res*. 1980;18(5):617-622.
27. Ockelford PA, Menon NC, Berry EW. Clinical experience with arginine vasopressin (DDAVP) in von Willebrand's disease and mild haemophilia. *N Z Med J*. 1980;92(672):375-378.
28. Korninger C, Niessner H, Lechner K. Impaired fibrinolytic response to DDAVP and venous occlusion in a sub-group of patients with von Willebrand's disease. *Thromb Res*. 1981;23(4-5):365-374.
29. Sweeney JD, Crosby P, McCann SR, Temperley IJ. Clinical experience with deamino-8-D-AGR-Vasopressin (DDAVP) in patients with Factor VIII deficiency. *Ir J Med Sci*. 1981;150(8):236-239.
30. Takahashi H. Studies on the pathophysiology and treatment of von Willebrand's disease. V. Properties of factor VIII after DDAVP infusion in variant von Willebrand's disease. *Thromb Res*. 1981;21(4-5):357-365.
31. Holmberg L, Nilsson IM, Borge L, Gunnarsson M, Sjörin E. Platelet aggregation induced by 1-desamino-8-D-arginine vasopressin (DDAVP) in Type IIB von Willebrand's disease. *N Engl J Med*. 1983;309(14):816-821.
32. Kobrinsky NL, Watson CM, Cheang MS, Bishop AJ. Improved hemophilia A carrier detection by DDAVP stimulation of factor VIII. *J Pediatr*. 1984;104(5):718-724.
33. Mariana G, Ciavarella N, Mazzucconi MG, et al. Evaluation of the effectiveness of DDAVP in surgery and in bleeding episodes in haemophilia and von Willebrand's disease. A study on 43 patients. *Clin Lab Haematol*. 1984;6(3):229-238.
34. Sakariassen KS, Cattaneo M, vd Berg A, Ruggeri ZM, Mannucci PM, Sixma JJ. DDAVP enhances platelet adherence and platelet aggregate growth on human artery subendothelium. *Blood*. 1984;64(1):229-236.

35. de la Fuente B, Kasper CK, Rickles FR, Hoyer LW. Response of patients with mild and moderate hemophilia A and von Willebrand's disease to treatment with desmopressin. *Ann Intern Med*. 1985;103(1):6-14.
36. Vincente V, Alberca I, Gonzalez R, Lopez Borrasca A. DDAVP in a non-haemophiliac patient with an acquired factor VIII inhibitor. *Br J Haematol*. 1985;60(3):585-586.
37. Gralnick HR, Williams SB, McKeown LP, et al. DDAVP in type IIa von Willebrand's disease. *Blood*. 1986;67(2):465-468.
38. Greer IA, McLaren M, Belch JJ, Lowe GD, Forbes CD. Endothelial stimulation by DDAVP in von Willebrand's disease and haemophilia. *Haemostasis*. 1986;16(1):15-19.
39. Marti GE, Rick ME, Sidbury J, Gralnick HR. DDAVP infusion in five patients with type Ia glycogen storage disease and associated correction of prolonged bleeding times. *Blood*. 1986;68(1):180-184.
40. Kentro TB, Lottenberg R, Kitchens CS. Clinical efficacy of desmopressin acetate for hemostatic control in patients with primary platelet disorders undergoing surgery. *Am J Hematol*. 1987;24(2):215-219.
41. Prince S. An alternative to blood product therapy for dental extractions in the mild to moderate haemophiliac patient. *Br Dent J*. 1987;162(7):256-257.
42. Cuthbert RJ, Watson HH, Handa SI, Abbott I, Ludlam CA. DDAVP shortens the bleeding time in Bernard-Soulier syndrome. *Thromb Res*. 1988;49(6):649-650.
43. Ghirardini A, Chistolini A, Tirindelli MC, et al. Clinical evaluation of subcutaneously administered DDAVP. *Thromb Res*. 1988;49(3):363-372.
44. Kim HC, Salva K, Fallot PL, et al. Patients with prolonged bleeding time of undefined etiology, and their response to desmopressin. *Thromb Haemost*. 1988;59(2):221-224.
45. Mannucci PM, Lombardi R, Castaman G, et al. von Willebrand disease "Vicenza" with larger-than-normal (supranormal) von Willebrand factor multimers. *Blood*. 1988;71(1):65-70.
46. Rodeghiero F, Castaman G, Di Bona E, Ruggeri M, Lombardi R, Mannucci PM. Hyper-responsiveness to DDAVP for patients with type I von Willebrand's disease and normal intra-platelet von Willebrand factor. *Eur J Haematol*. 1988;40(2):163-167.
47. Royer JE, Bates WS. Management of von Willebrand's disease with desmopressin. *J Oral Maxillofac Surg*. 1988;46(4):313-314.
48. Williamson R, Eggleston DJ. DDAVP and EACA used for minor oral surgery in von Willebrand disease. *Aust Dent J*. 1988;33(1):32-36.
49. Castaman G, Rodeghiero F, Di Bona E, Ruggeri M. Clinical effectiveness of desmopressin in a case of acquired von Willebrand's syndrome associated with benign monoclonal gammopathy. *Blut*. 1989;58(4):211-213.
50. Fowler WE, Berkowitz LR, Roberts HR. DDAVP for type IIB von Willebrand disease. *Blood*. 1989;74(5):1859-1860.
51. Köhler M, Hellstern P, Tarrach H, Bambauer R, Wenzel E, Jutzler GA. Subcutaneous injection of desmopressin (DDAVP): evaluation of a new, more concentrated preparation. *Haemostasis*. 1989;19(1):38-44.
52. 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.
53. Thomas N, O'Callaghan U, Lowe GD, et al. Response to desmopressin in type IID von Willebrand's disease. *Clin Lab Haematol*. 1989;11(3):189-197.

54. Wijermans PW, van Dorp DB. Hermansky-Pudlak syndrome: correction of bleeding time by 1-desamino-8D-arginine vasopressin. *Am J Hematol.* 1989;30(3):154-157.
55. Baldree LA, Ault BH, Chesney CM, Stapleton FB. Intravenous desmopressin acetate in children with sickle trait and persistent macroscopic hematuria. *Pediatrics*. 1990;86(2):238-243.
56. Casonato A, Fabris F, Girolami A. Platelet aggregation and pseudothrombocytopenia induced by 1-desamino-8-D-arginine vasopressin (DDAVP) in type IIB von Willebrand's disease patient. *Eur J Haematol*. 1990;45(1):36-42.
57. Casonato A, Sartori MT, de Marco L, Girolami A. 1-Desamino-8-D-arginine vasopressin (DDAVP) infusion in type IIB von Willebrand's disease: shortening of bleeding time and induction of a variable pseudothrombocytopenia. *Thromb Haemost*. 1990;64(1):117-120.
58. Quitt M, Froom P, Veisler A, Falber V, Sova J, Aghai E. The effect of desmopressin on massive gastrointestinal bleeding in hereditary telangiectasia unresponsive to treatment with cryoprecipitate. *Arch Intern Med.* 1990;150(8):1744-1746.
59. Van Dorp DB, Wijermans PW, Meire F, Vrensen G. The Hermansky-Pudlak syndrome. Variable reaction to 1-desamino-8D-arginine vasopressin for correction of the bleeding time. *Ophthalmic Paediatr Genet*. 1990;11(3):237-244.
60. Casonato A, Sartori MT, Pontara E, Bertomoro A, Dannhäuser D, Girolami. Discrepant increase in factor VIII: C and von Willebrand factor after DDAVP infusion in a patient with variant von Willebrand's disease. *Blood Coagul Fibrinolysis*. 1991;2(4):567-573.
61. Lopez-Fernandez MF, Gonzalez-Boullosa R, Blanco-Lopez MJ, Perez M, Batlle J. Abnormal proteolytic degradation of von Willebrand factor after desmopressin infusion in a new subtype of von Willebrand disease (ID). *Am J Hematol.* 1991;36(3):163-170.
62. Waldenström E, Holmberg L, Axelsson U, Winqvist I, Nilsson IM. Bernard-Soulier syndrome in two Swedish families: effect of DDAVP on bleeding time. *Eur J Haematol.* 1991;46(3):182-187.
63. Castaman G, Rodeghiero F. Failure of DDAVP to shorten the prolonged bleeding time of two patients with congenital afibrinogenemia. *Thromb Res*. 1992;68(3):309-315.
64. Lethagen S, Nilsson IM. DDAVP-induced enhancement of platelet retention: its dependence on platelet-von Willebrand factor and the platelet receptor GP IIb/IIIa. *Eur J Haematol*. 1992;49(1):7-13.
65. Mannucci PM, Bettega D, Cattaneo M. Patterns of development of tachyphylaxis in patients with haemophilia and von Willebrand disease after repeated doses of desmopressin (DDAVP). *Br J Haematol.* 1992;82(1):87-93.
66. Patrassi GM, Sartori MT, Casonato A, et al. Urokinase-type plasminogen activator release after DDAVP in von Willebrand disease: different behaviour of plasminogen activators according to the synthesis of von Willebrand factor. *Thromb Res*. 1992;66(5):517-526.
67. Sultan Y, Loyer F, Venot A. Impaired fibrinolytic response to DDAVP in patients with von Willebrand's disease. *Nouv Rev Fr Hematol.* 1992;34(1):55-60.
68. Castaman G, Rodeghiero F. Consistency of responses to separate desmopressin infusions in patients with storage pool disease and isolated prolonged bleeding time. *Thromb Res*. 1993;69(4):407-412.
69. Castaman G, Rodeghiero F, Lattuada A, Mannucci PM. Desmopressin-induced thrombocytopenia in type I platelet discordant von Willebrand disease. *Am J Hematol*. 1993;43(1):5-9.

70. Greinacher A, Pötzsch B, Kiefel V, White JG, Müller-Berghaus G, Mueller-Eckhardt C. Evidence that DDAVP transiently improves hemostasis in Bernard-Soulier syndrome independent of von Willebrand-factor. *Ann Hematol.* 1993;67(3):149-150.
71. Kemahli S, Canatan D, Uysal Z, Akar N, Cin S, Arcasoy A. DDAVP shortens bleeding time in Bernard-Soulier syndrome. *Thromb Haemost*. 1994;71(5):675.
72. Mazurier C, Gaucher C, Jorieux S, Goudemand M. Biological effect of desmopressin in eight patients with type 2N ('Normandy') von Willebrand disease. Collaborative Group. *Br J Haematol.* 1994;88(4):849-854.
73. Castaman G, Eikenboom JC, Rodeghiero F, Briët E, Reitsma PH. A novel candidate mutation (Arg611-->His) in type I 'platelet discordant' von Willebrand's disease with desmopressin-induced thrombocytopenia. *Br J Haematol.* 1995;89(3):656-658.
74. Castaman G, Lattuada A, Mannucci PM, Rodeghiero F. Factor VIII:C increases after desmopressin in a subgroup of patients with autosomal recessive severe von Willebrand disease. *Br J Haematol.* 1995;89(1):147-151.
75. Castaman G, Ruggeri M, Rodeghiero F. Clinical usefulness of desmopressin for prevention of surgical bleeding in patients with symptomatic heterozygous factor XI deficiency. *Br J Haematol.* 1996;94(1):168-170.
76. McKeown LP, Connaghan G, Wilson O, Hansmann K, Merryman P, Gralnick HR. 1-Desamino-8-arginine-vasopressin corrects the hemostatic defects in type 2B von Willebrand's disease. *Am J Hematol.* 1996;51(2):158-163.
77. Lozano M, Escolar G, Bellucci S, et al. 1-Deamino (8-D-arginine) vasopressin infusion partially corrects platelet deposition on subendothelium in Bernard-Soulier syndrome: the role of factor VIII. *Platelets*. 1999;10(2-3):141-145.
78. Mauz-Körholz C, Budde U, Körholz D, Göbel U. DDAVP treatment in a child with von Willebrand disease type 2M. *Eur J Pediatr.* 1999;158 Suppl 3:S174-176.
79. Franchini M, de Gironcoli M, Lippi G, Manzato F, Aprili G, Gandini G. Prophylactic use of desmopressin in surgery of six patients with symptomatic heterozygous factor XI deficiency. *Haematologica.* 2000;85(1):106-107.
80. Kavakli K, Aydinok Y, Karapinar D, Balkan C. DDAVP treatment in children with haemophilia B. *Br J Haematol.* 2001;114(3):733-734.
81. Kavakli K, Hüseyinov A, Coker I, Aydinok Y, Nisli G. Intraleucocyte platelet-activating factor levels in desmopressin-treated patients with haemophilia A and von Willebrand disease. *Haemophilia.* 2001;7(5):482-489.
82. Franchini M, Gandini G, Manzato F, Lippi G. Evaluation of the PFA-100 system for monitoring desmopressin therapy in patients with type 1 von Willebrand's disease. *Haematologica*. 2002;87(6):670.
83. Jimenez-Yuste V, Prim MP, De Diego JI, et al. Otolaryngologic surgery in children with von Willebrand disease. *Archives of otolaryngology: head and neck surgery.* 2002;128(12):1365-1368.
84. Michiels JJ, van de Velde A, van Vliet HH, van der Planken M, Schroyens W, Berneman Z. Response of von Willebrand factor parameters to desmopressin in patients with type 1 and type 2 congenital von Willebrand disease: diagnostic and therapeutic implications. *Semin Thromb Hemost*. 2002;28(2):111-132.
85. Brown SA, Eldridge A, Collins PW, Bowen DJ. Increased clearance of von Willebrand factor antigen post-DDAVP in Type 1 von Willebrand disease: is it a potential pathogenic process? *J Thromb Haemost*. 2003;1(8):1714-1717.

86. Fuse I, Higuchi W, Mito M, Aizawa Y. DDAVP normalized the bleeding time in patients with congenital platelet TxA2 receptor abnormality. *Transfusion*. 2003;43(5):563-567.
87. Reiter RA, Knöbl P, Varadi K, Turecek PL. Changes in von Willebrand factor-cleaving protease (ADAMTS13) activity after infusion of desmopressin. *Blood*. 2003;101(3):946-948.
88. 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.
89. Cordova A, Barrios NJ, Ortiz I, Rivera E, Cadilla C, Santiago-Borrero PJ. Poor response to desmopressin acetate (DDAVP) in children with Hermansky-Pudlak syndrome. *Pediatr Blood Cancer*. 2005;44(1):51-54.
90. Lombardo VT, Sottilotta G. Recombinant activated factor VII combined with desmopressin in preventing bleeding from dental extraction in a patient with Glanzmann's thrombasthenia. *Clin Appl Thromb Hemost*. 2006;12(1):115-116.
91. 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(12):1647-1654.
92. Guglielmone H, Minoldo S, Jarchum G. Response to the DDAVP test in a patient with combined deficiency of factor V and factor VIII. *Haemophilia*. 2009;15(3):838-839.
93. Shortt J, Opat SS, Gorniak MB, Aumann HA, Collecutt MF, Street AM. A retrospective study of the utility of desmopressin (1-deamino-8-D-arginine vasopressin) trials in the management of patients with von Willebrand disorder. *Int J Lab Hematol*. 2010;32(1 Pt 1):e181-183.
94. Knöfler R, Koscielny J, Tauer JT, et al. Desmopressin testing in haemophilia A patients and carriers: results of a multi centre survey. *Hamostaseologie*. 2012;32(4):271-275.
95. Santoro C, Hsu F, Dimichele DM. Haemostasis prophylaxis using single dose desmopressin acetate and extended use epsilon aminocaproic acid for adenotonsillectomy in patients with type 1 von Willebrand disease. *Haemophilia*. 2012;18(2):200-204.
96. Akin M. Response to low-dose desmopressin by a subcutaneous route in children with type 1 von Willebrand disease. *Hematology*. 2013;18(2):115-118.
97. Siew DA, Mangel J, Laudenbach L, Schembri S, Minuk L. Desmopressin responsiveness at a capped dose of 15 µg in type 1 von Willebrand disease and mild hemophilia A. *Blood Coagul Fibrinolysis*. 2014;25(8):820-823.
98. Stoof SC, Sanders YV, Cnossen MH, de Maat MP, Leebeek FW, Kruip MJ. Desmopressin response in hemophilia A patients with FVIII:C < 0.10 IU mL(-1.). *J Thromb Haemost*. 2014;12(1):110-112.
99. Archer NM, Samnaliev M, Grace R, Brugnara C. The utility of the DDAVP challenge test in children with low von Willebrand factor. *Br J Haematol*. 2015;170(6):884-886.
100. Arshad F, Stoof SC, Leebeek FW, et al. Infusion of DDAVP does not improve primary hemostasis in patients with cirrhosis. *Liver Int*. 2015;35(7):1809-1815.
101. Mansouritorghabeh H, Shirdel A. Desmopressin acetate as a haemostatic elevator in individuals with combined deficiency of factors V and VIII: a clinical trial. *J Thromb Haemost*. 2016;14(2):336-339.
102. Mason JA, Robertson JD, McCosker J, Williams BA, Brown SA. Assessment and validation of a defined fluid restriction protocol in the use of subcutaneous desmopressin for children with inherited bleeding disorders. *Haemophilia*. 2016;22(5):700-705.

103. Takeyama M, Nogami K, Onaka M, Yada K, Shida Y, Shima M. The utility of VWF multimer analysis in response to the desmopressin administration for the diagnosis of severe type 1 von Willebrand disease. *Haemophilia*. 2016;22(2):e106-e108.
104. Sánchez-Luceros A, Woods AI, Bermejo E, et al. PT-VWD posing diagnostic and therapeutic challenges - small case series. *Platelets*. 2017;28(5):484-490.
105. Stoof SCM, Schütte LM, Leebeek FWG, Cnossen MH, Kruip M. Desmopressin in haemophilia: The need for a standardised clinical response and individualised test regimen. *Haemophilia*. 2017;23(6):861-867.
106. Candy V, Whitworth H, Grabell J, et al. A decreased and less sustained desmopressin response in hemophilia A carriers contributes to bleeding. *Blood Adv*. 2018;2(20):2629-2636.
107. Hews-Girard J, Rydz N, Lee A, Goodyear MD, Poon MC. Desmopressin in non-severe haemophilia A: Test-response and clinical outcomes in a single Canadian centre review. *Haemophilia*. 2018;24(5):720-725.
108. Okoye HC, Nielsen BI, Lee K, Abajas YL, Key NS, Rollins-Raval MA. DDAVP trial in discrepant non-severe haemophilia A patients. *Haemophilia*. 2018;24(3):e152-e154.
109. Polzella P, Coutts K, Bignell P, Curry N. Unexpectedly high response to DDAVP in two patients with moderate haemophilia A. *Haemophilia*. 2018;24(4):e292-e294.
110. Schütte LM, van Hest RM, Stoof SCM, et al. Pharmacokinetic Modelling to Predict FVIII:C Response to Desmopressin and Its Reproducibility in Nonsevere Haemophilia A Patients. *Thromb Haemost*. 2018;118(4):621-629.
111. Atiq F, Schütte LM, Looijen AEM, et al. von Willebrand factor and factor VIII levels after desmopressin are associated with bleeding phenotype in type 1 VWD. *Blood Adv*. 2019;3(24):4147-4154.
112. Guddati AK, Rosovsky RP, Van Cott EM, Kuter DJ. Quantitative analysis of desmopressin (DDAVP) response in adult patients with type 1 von Willebrand disease. *Int J Lab Hematol*. 2019;41(3):325-330.
113. 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.
114. Loomans JI, van Velzen AS, Eckhardt CL, et al. Variation in baseline factor VIII concentration in a retrospective cohort of mild/moderate hemophilia A patients carrying identical F8 mutations. *J Thromb Haemost*. 2017;15(2):246-254.
115. Bonazza K, Iacob RE, Hudson NE, et al. Von Willebrand factor A1 domain stability and affinity for GPIbα are differentially regulated by its O-glycosylated N- and C-linker. *Elife*. 2022;11.
116. Guillet B, Pawlowski M, Boisseau P, et al. Genotype-Dependent Response to Desmopressin in Hemophilia A and Proposal of a Predictive Response Score. *Thromb Haemost*. 2024.
117. Atiq F, Blok R, van Kwawegen CB, et al. Type 1 VWD classification revisited: novel insights from combined analysis of the LoVIC and WiN studies. *Blood*. 2024;143(14):1414-1424.
118. Gill JC, Endres-Brooks J, Bauer PJ, Marks WJ, Jr., Montgomery RR. The effect of ABO blood group on the diagnosis of von Willebrand disease. *Blood*. 1987;69(6):1691-1695.
119. De Sio L, Mariani G, Muzzucconi MG, Chistolini A, Tirindelli MC, Mandelli F. Comparison between subcutaneous and intravenous DDAVP in mild and moderate hemophilia A. *Thromb Haemost*. 1985;54(2):387-389.
120. Mannucci PM, Vicente V, Alberca I, et al. Intravenous and subcutaneous administration of desmopressin (DDAVP) to hemophiliacs: pharmacokinetics and factor VIII responses. *Thromb Haemost*. 1987;58(4):1037-1039.

121. Connell NT, Flood VH, Brignardello-Petersen R, et al. ASH ISTH NHF WFH 2021 guidelines on the management of von Willebrand disease. *Blood Advances*. 2021;5(1):301-325.
122. Cnossen MH, van Moort I, Reitsma SH, et al. SYMPHONY consortium: Orchestrating personalized treatment for patients with bleeding disorders. *J Thromb Haemost*. 2022;20(9):2001-2011.

Supplementary Methods

Risk of Bias

Risk of bias was assessed using an adjusted Quality in Prognostic Studies (QUIPS) (1) checklist (see Supplemental File 2 for the edited QUIPS checklist). Each article was evaluated by two reviewers and disagreements were resolved by consensus. In short, questions per domain were weighted based on relevance. A cut-off to decide whether a domain is low, moderate or high risk of bias is reported in the adjusted quips checklist. A DDAVP test is completed a few hours after administration and most studies gathered the data retrospectively. Therefore, the study attrition domain was removed from the checklist as these questions were not applicable for this review. Furthermore, sub question b and c were removed from domain Statistical analysis and reporting. These were removed as data from each study were collected and not values as calculated by statistical analysis. A study was considered as low overall risk of bias when all domain scores were rated as low or if one domain was scored moderate. We scored a study as having high overall risk of bias if two or more of the domains were judged as high. A study was scored as moderate if the criteria for 'low' or 'high' were not met.

Statistical analysis

Logistic random-effects models were applied to pool proportions of complete responders to DDAVP both pooled and separately by disease type according to the "study definition". Heterogeneity between studies was assessed by calculating I^2 and Tau^2 and by calculating a prediction interval for new studies. Forest plots were generated to show the variation between studies. Studies that could not be combined due to lack of sufficient data were assessed qualitatively. Median response in VWF levels over time in the quantitative sense (on antigen level) or in a qualitative sense (on activity level) were reported. The association between the different determinants and the response rate was assessed by performing meta-regressions; bubble plots were generated to visualize the association. As sensitivity analysis, the analyses were repeated using only low or moderate risk of bias studies. All analyses were performed using R (version 4·2·3) (2) with the packages meta (version 7·0-0), to pool the proportions and metareg to perform meta regression. The package forestplot (version 4·2·3) was used to make forest plots and ggplot2 (version 3·4·4) to make bubble plots. P-values < 0·05 were considered statistically significant.

1. Evaluation of the Quality of Prognosis Studies in Systematic Reviews. Annals of Internal Medicine. 2006;144(6):427-437.
2. R development Core Team. R: A language and environment for statistical computing: R foundation for statistical computing; 2024.

Supplemental Table 3: Odds ratio of response per determinant from meta-regression.

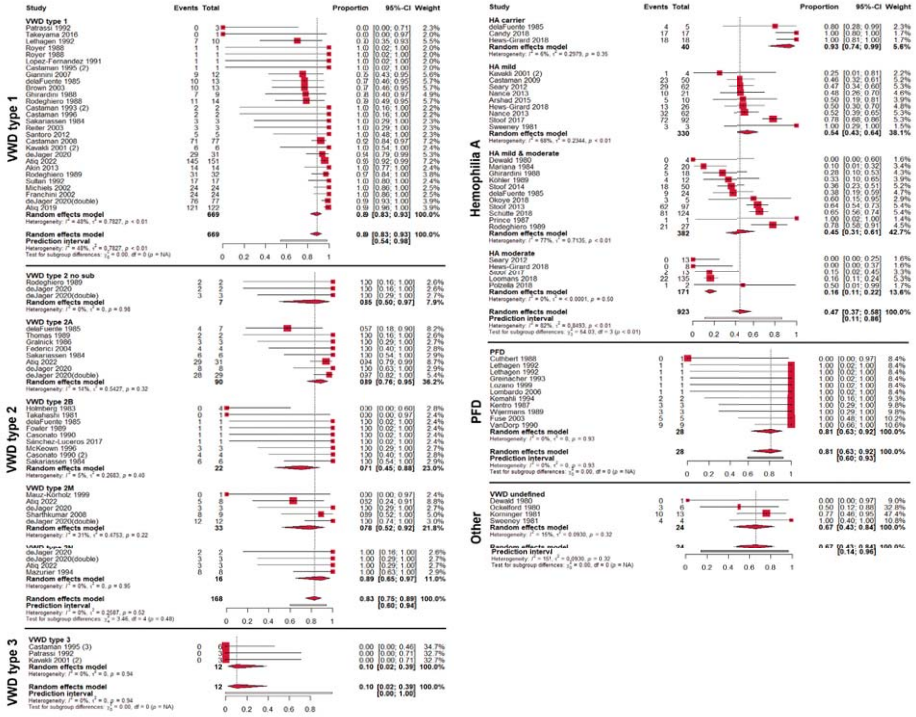
	VWD type 1			VWD type 2			Hemophilia A			PFD		
Determinant	**OR**	**95%CI**		**OR**	**95% CI**		**OR**	**95%CI**		**OR**	**95%CI**	
Age (years)	1,006	0,935	1,082	1,006	0,951	1,064	1,055	0,965	1,153	0,953	0,834	1,089
Blood group non-O vs O	0,997	0,941	1,057	1,037	0,996	1,080	0,972	0,920	1,028	x	x	x
Female (%)	1,003	0,976	1,030	x	x	x	1,024	1,007	1,040	0,996	0,963	1,030
Before DDAVP APTT (s)	0,995	0,938	1,056	x	x	x	1,010	0,706	1,446	1,025	0,801	1,312
Bleeding time (min)	0,917	0,759	1,109	0,946	0,822	1,090	x	x	x	0,987	0,785	1,242
FVIII:Ag (U/dL)	x	x	x	x	x	x	x	x	x	x	x	x
FVIII:C (U/dL)	1,023	1,002	1,045	x	x	x	1,054	1,014	1,095	0,996	0,944	1,050
Platelet count	0,998	0,946	1,052	1,001	0,982	1,020	x	x	x	1,000	0,998	1,001
VWF:Ag (U/dL)	1,055	1,016	1,075	x	x	x	1,009	0,973	1,045	0,996	0,956	1,038
VWF:CB (U/dL)	1,058	0,898	1,246	0,999	0,976	1,021	0,986	0,940	1,035	x	x	x
VWF:pp (U/dL)	x	x	x	x	x	x	x	x	x	x	x	x
VWF:Act (U/dL)	1,048	1,008	1,090	x	x	x	0,991	0,951	1,032	1,009	0,973	1,046
Bodyweight (kg)	1,044	0,974	1,119	1,033	0,982	1,086	1,120	0,983	1,276	x	x	x

X indicates determinants for which the meta-regression could not be performed. Abbreviations: VWD, von Willebrand disease; OR, Odds ratio; CI, Confidence interval; DDAVP, 1-deamino-8-D-arginine vasopressin; APTT, Activated partial thromboplastin time; Ag, Antigen; CB, Collagen binding; pp, Propeptide; Act, Activity.

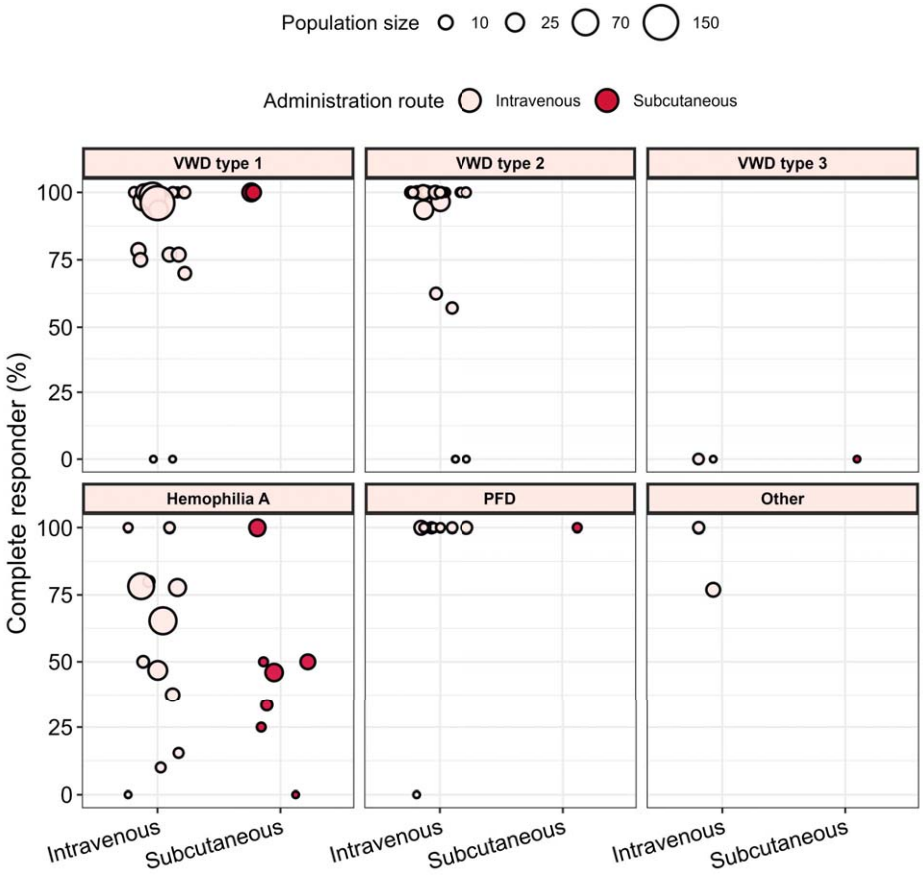
Supplemental Table 4. Sensitivity analysis on Odds ratio of response per determinant

	VWD type 1			VWD type 2			Hemophilia A			PFD		
Determinant	**OR**	**95%CI**		**OR**	**95% CI**		**OR**	**95%CI**		**OR**	**95%CI**	
Age (years)	1,006	0,935	1,082	1,006	0,951	1,064	1,055	0,965	1,153	0,929	0,787	1,096
Blood group non-O vs O	0,997	0,941	1,057	1,037	0,996	1,080	0,972	0,920	1,028	x	x	x
Female (%)	1,003	0,976	1,030	x	x	x	1,024	1,007	1,040	0,996	0,962	1,031
Before DDAVP APTT (s)	0,995	0,938	1,056	x	x	x	1,010	0,706	1,446	1,000	0,774	1,292
Bleeding time (min)	0,917	0,759	1,109	0,927	0,777	1,106	x	x	x	1,125	0,592	2,141
FVIII:Ag (U/dL)	x	x	x	x	x	x	x	x	x	x	x	x
FVIII:C (U/dL)	1,021	1,000	1,043	x	x	x	1,053	1,013	1,095	0,997	0,945	1,051
Platelet count	0,998	0,946	1,052	1,004	0,983	1,024	x	x	x	1,000	0,998	1,001
VWF:Ag (U/dL)	1,054	1,014	1,095	x	x	x	1,009	0,973	1,045	0,992	0,942	1,045
VWF:CB (U/dL)	1,077	0,904	1,283	0,999	0,976	1,021	0,986	0,940	1,035	x	x	x
VWF:pp (U/dL)	x	x	x	x	x	x	x	x	x	x	x	x
VWF:Act (U/dL)	1,047	1,007	1,088	x	x	x	0,991	0,951	1,032	1,009	0,973	1,046
Bodyweight (kg)	1,044	0,974	1,119	1,033	0,982	1,086	1,120	0,983	1,276	x	x	x

X indicates determinants for which the meta-regression could not be performed. Numbers in red have changed when compared to Supplemental Table 3. Abbreviations: VWD, von Willebrand disease; OR, Odds ratio; CI, Confidence interval; DDAVP, 1-deamino-8-D-arginine vasopressin; APTT, Activated partial thromboplastin time; Ag, Antigen; CB, Collagen binding; pp, Propeptide; act, Activity.



Supplemental Figure 1. Complete response rate varies per disease subtype according to the study definition. Meta-analysis on response to DDAVP at one hour in patients with various bleeding disorders per subtype. Using a random effect model the proportion of complete response per study, divided by subtype, are shown. Random effects are calculated per subtype of disease but also by main type of disease. The proportion of response is not zero in zero-event studies due to the continuity correction that was performed to prevent mathematical errors. Other is, everything that is not VWD type 1, 2 or 3, Hemophilia A or PFD. Abbreviations: HA = Hemophilia, PFD = Platelet function disorder, VWD = Von Willebrand disease.



Supplemental Figure 2. Response to DDAVP per disease per administration route. Response to DDAVP of patients with VWD type 1, 2 and 3, Hemophilia A, PFD or Other are shown per administration route of DDAVP. Intravenous is shown in light red and Subcutaneous is shown in dark red. Studies that did not clarify which route was used are excluded from this figure. Intranasal administration is not displayed in this figure as only two studies had this data. Other is everything that is not VWD type 1, 2 or 3, Hemophilia A or PFD. Abbreviations: VWD = Von Willebrand disease, PFD = Platelet function disorder.