REVIEW ARTICLE

Global estimation of the bleeding episodes treatable with desmopressin in von Willebrand disease and hemophilia A

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Abstract

Desmopressin increases plasma factor VIII and von Willebrand factor in non-severe hemophilia A (Hem A) and type 1 von Willebrand disease (VWD), following intravenous infusions, subcutaneous injections, or nasal spray. This medication, with almost 50 years of clinical experience and proven safety and efficacy, is often unavailable. Thus, there is a need to establish how many patients can benefit from it and how many bleeding episodes can be treated. We reviewed the literature to estimate the global prevalence of symptomatic patients with VWD type 1 and non-severe Hem A, the incidence of bleeds, and the rate of responsiveness to desmopressin. Real-world data indicate that 1.7 patients with VWD per 100,000 seek care in specialized centers. Of them, 1.15 per 100,000 have type 1 VWD and 80% are reported to respond to desmopressin. In type 1 VWD, the estimated frequency of bleeds treatable with desmopressin are 2.5 events per patient year. Non-severe cases are 45% of all Hem A cases, with a much lower incidence of bleeds than in severe disease (0.4 events / patient / year). Based on epidemiology, data on the rates of bleeding, and desmopressin responsiveness, we estimated that 84,000 people with VWD type 1 would benefit from desmopressin to treat 210,000 yearly bleeds, and that 81,000 people with non-severe Hem A can be treated yearly for 13,000 bleeds. Desmopressin is an essential therapeutic tool in non-severe Hem A and type 1 VWD that can treat more than 220,000 bleeding episodes successfully, safely, and economically, also in low-income settings with poor access to costly replacement therapies.

Introduction

von Willebrand disease (VWD) and hemophilia A (Hem A) are the most common inherited bleeding disorders.[1,2] Non-severe phenotypes (type 1) account for 70-80% of all VWD cases, while non-severe Hem A accounts for 40-50% of all Hem A cases. The administration of 1-deamino-8-D-arginine vasopressin, also known as desmopressin or DDAVP, increases plasma factor VIII in most patients with mild and in some with moderate Hem A, and also corrects von Willebrand factor (VWF) deficiency in patients with type 1 VWD.[3] Therefore, bleeding can be treated successfully, safely, and inexpensively in a large proportion of these patients. While desmopressin is administered intravenously, it can also be administered subcutaneously or intranasally. The latter formulations are particularly convenient for home treatment, and thus reduce in-hospital admissions and the inherent costs, and promote patient adherence and the prompt control of bleeding.[4] Nevertheless, this medication, with almost 50 years of clinical experience and proven safety and efficacy, is often neglected, underused or unavailable. With this background, there is a need to estimate how many patients could globally benefit from this treatment and how many bleeding events could be treated. Therefore, we carried out the present narrative review with the aim of filling these knowledge gaps.

Methods

We reviewed the literature on the global prevalence of symptomatic cases with mild and moderate Hem A and

VWD type 1, the average incidence in them of bleeding episodes, the rate of desmopressin-responsive cases, and the number of bleeds that can be treated.

We initially searched the MEDLINE electronic database with a non-systematic approach for full-text publications. We used MESH (Medical Subject Headings) terms for this search: "Hemophilia A/epidemiology" AND "Prevalence", and "von Willebrand diseases/epidemiology" AND "Prevalence", in order to estimate the global prevalence of these diseases. We also searched the literature to assess the average bleeding frequency in non-severe Hem A and VWD type 1 with the MESH terms: "Hemophilia A/complications", "Hemophilia A/drug therapy", "Hemarthrosis/prevention and control", "Hemorrhage/drug therapy" and "Hemorrhage/prevention and control", and with "von Willebrand disease/complications", "von Willebrand disease/drug therapy", "von Willebrand disease/prevention and control", "von Willebrand disease/therapy", "Hemorrhage/drug therapy" and "Hemorrhage/prevention and control". Moreover, in order to estimate the rate of responsiveness to desmopressin, we carried out a search with the MESH terms "Hemophilia A/therapy" and "Deamino arginine vasopressin/therapeutic use", and with "von Willebrand disease/therapy" and "deamino arginine vasopressin/therapeutic use". Data were also extracted from the World Federation of Hemophilia Report on the Annual Global Survey 2023[5] (WFH-AGS 2023) as well as from the national registries. The reference lists of the identified publications and the most relevant review articles for additional items not captured by the initial search were also screened and pragmatic searches were performed using Google, Google Scholar, the Cochrane Library, and the websites of scientific societies interested in congenital bleeding disorders. We used the 2023 population data from the United Nations[6] to calculate prevalences for each country that reported the number of VWD cases, national registries and/or epidemiological studies in the WFH AGS. When referring to income classes we used the World Bank classification, which divides economies into four classes using the per capita gross national income:[7] low (LIC), lower-middle (LMIC), upper-middle (UMIC), and high (HIC) income countries.

Results

Prevalence of von Willebrand disease

The estimation of the global population (both sexes combined) on 1 July 2023 was 8.1 billion.[6] The global prevalence of all type VWD is estimated to be 0.6 and 1.3%,[8] leading to an estimation of about 100 million affected people out of a population of 8 billion. Because not all cases are symptomatic and require treatment, a conservative estimate of the prevalence of those with symptomatic disease is 1 per 10,000 people.[9] The prevalence of patients with VWD actually diagnosed and registered is lower than that, and is highly variable among regions and countries, as shown by the WFH-AGS 2023 and by Stonebraker *et al.*:[10] prevalences varied from 1.1 per million people in low-income countries to 60.3 per million people in high-income countries, with an average of 25.6 per million people (Standard Deviation: 48.8), equivalent to about 207,000 cases globally.

Estimated prevalence of symptomatic von Willebrand disease

Because data from the WFH-AGS 2023 might not reflect the country-specific estimates of symptomatic VWD patients, and particularly of those with VWD type 1, we looked for the prevalences reported by the available national registries (Table 1).[11-26] These data were then integrated with those of the WFH-AGS 2023 and reported by Du *et al.* in a systematic review[28] (Table 2). To estimate the prevalence of patients with VWD type 1 when specific data were not available, we considered 70% of all VWD types in high-income and upper middle-income countries, representing the median of ratios, and 20% in all the other countries, representing the median of ratios in lower-middle income and low-income countries.

It is well known that there is a higher proportion of women with all VWD types, and that this differs according to country income[10] (Table 3). The female-to-male ratios for VWD prevalence ranged from 1.53 to 1.85, the mean value for all countries being 1.67.[29] In the USA, 66% of people with VWD (all types) who attended a hemophilia treatment center (HTC) were females.[11] Moreover, in the "Willebrand in the Netherlands" (WiN) study, 64% of adult cases were females,[30] and in the US Centers for Disease Control (CDC) Registry of Bleeding Disorders, 68% of cases with VWD (all types) were females.[31] In 2023, the Data Report of the World Bleeding Disorders Registry[32] of the WFH collected data from 22 countries on 999 people with VWD and found that 560 were females (56%). The United Kingdom Haemophilia Centre Doctors' Organisation (UKHCDO) Annual Report 2023[16] identified 3,257 females with type 1 VWD, i.e., 64% of all people with this type of VWD. The largest collection of data is provided by the WFH-AGS 2023,[5] which reported that 62% of 87,425 VWD cases were females. It is plausible that this higher proportion of women is due to heavy menstrual bleeding (HMB) that triggers hemostasis investigation. This is confirmed by the age when diagnosis rates peak, i.e., between 10 and 20 years.[8] Finally, the systematic review of Du *et al.* in 2023[28] reported 55.3-83.3% female predominance in VWD type 1. All in all, we can assume that of 83,571 identified cases with VWD type 1, at least 50,143 (60%) are females and 33,428 males.

Prevalence of hemophilia A

According to Iorio *et al.*,[33] based on the global prevalence estimate of 17.1 per 100,000 males, the expected number of patients with Hem A is 747,191 cases in the global population of about 8.1 billion.[6] Of these, 6.0 cases per 100,000 males

Table 1. Reported country-based prevalence estimates of von Willebrand disease.

Country / year	Source	Prevalence estimate
North America		
US / 2021	ATHN, CDC and HTCN[11] Last CDC report (2024)[12]	Age-adjusted HTC-treated prevalence was 8.6 cases/100,000 (7.2/100,000 type 1, 1.2/100,000 type 2, and 1.7/million type 3). Between 2012 and 2023, more than 33,456 cases were seen at HTC for treatment of VWD.
Canada / 2020	AHCDC[13]	4,653 cases (3,099 type 1, 371 type 2A-2B, 103 type 3) were recorded in the Canadian Blood Disorders Registry and British Columbia. Equivalent to 11.8 cases/100,000 (7.9/100,000 type 1, 0.9/100,000 type 2A and 2B, and 2.6/million type 3).
Europe		
Italy / 2024	ISS-AICE Registro Coagulopatie Congenite[14]	2,832 cases (2,384 type 1, 385 type 2, 63 type 3), equivalent to 4.8 cases/100,000 (4.0/100,000 type 1, 0.6/100,000 type 2, and 1/million type 3).
France / 2021	FranceCoag Network[15]	2,963 cases, equivalent to 4.4 cases per 100,000.
UK / 2023	UKHCDO[16]	11,937 cases (5,074 type 1, 1,501 type 2, 187 type 3), equivalent to 17.4 cases/100,000 (7.4/100,000 type 1, 2.2/100,000 type 2 and 2.7/million type 3).
Czech Republic / 2023	CNHP registry[17]	688 cases (296 type 1, 202 type 2, 19 type 3), equivalent to 6.4 cases/100,000 (2.7/100,000 type 1, 2.2/100,000 type 2 and 2.7/million type 3).
Spain / 2011	Spanish VWD registry[18]	5,753 cases (3,203 type 1, 886 type 2, 235 type 3), equivalent to 12.2 cases/100,000 (6.8/100,000 type 1, 4.0/100,000 type 2, and 5.0/million type 3).
Nordic countries (Denmark, Iceland, Finland, Norway, and Sweden) and autonomous territories (Greenland, Faroe Islands, and Åland Islands) / 2011	Nordic Hemophilia Council[19]	1,658 cases (1,456 type 1,141 type 2, 61 type 3), equivalent to 6.4 cases/100,000 (5.6/100,000 type 1, 0.5/100,000 type 2, and 2.3/million type 3).
Turkey / 2011	Dept. of Pediatric Hematology, Ege University, Faculty of Medicine, Izmir, Turkey[20]	Extrapolated prevalence from the adolescent population of the Aegean region of Turkey: overall 1.13 cases/100,000.
Asia		
India / 2011	ICMR, KEM Hospital, Parel, Mumbai, India[21]	Data extrapolated from those of Western India. Overall, 81 cases out of a regional population of 12.5 million people, equivalent to 0.6 cases/100,000 (15 with type 1, equivalent to 0.12/100,000).
Iran / 2011	Iranian Ministry of Health[22]	900 cases (118 type 1, 142 type 2, 460 type 3), equivalent to 1.1 cases/100,000 (0.1/100,000 type 1, 0.6/100,000 type 2, and 5.9/million type 3).
China / 2014	Systematic review and meta-analysis[23]	Reported prevalence of VWD (all types): 0.09 cases/100,000.
Latin America		
Brazil / 2023	Dados Perfil Coagulopatias Hereditárias Brasil - 2023[25]	11,375 cases (equivalent to 1.1 cases/100,000). Type 1 prevalence is estimated on data from a subgroup of patients (52.3% of all types VWD).
Oceania		
Australia / 2021	Australian Bleeding Disorders Registry[26]	2,460 cases equivalent to 9.05 cases/100,000 (5.6/100,000 type 1, 2.2/100,000 type 2, and 2.0/million type 3).
New Zealand / 2011	Dept. of Haematology, Christchurch Hospital, New Zealand[27]	Extrapolated prevalence from the population of South Island (all types): 15.08/100,000 (7.7/100,000 type 1, 1.6/100,000 type 2, and 3.0/million type 3).

AHCDC: Association of Hemophilia Clinic Directors of Canada; ATHN: Collaboration of American Thrombosis and Hemostasis Network; CDC: the Centers for Disease Control and Prevention; CNHP: Czech National Haemophilia Programme; Dept.: Department; HTC: hemophilia treatment center; HTCN: Hemophilia Treatment Center Network; ICMR: National Institute of Immunohaematology; ISS-AICE: Istituto Superiore di Sanità-Associazione Italiana Centri Emofilia; UKHCDO: United Kingdom Haemophilia Centre Doctors' Organization; VWD: von Willebrand disease.

have severe Hem A, and 11.1 per 100,000 males non-severe Hem A (262,172 moderate Hem A and 485,019 mild Hem A). The WFH-AGS 2023[5] reported much lower figures, likely due to an inadequate diagnostic rate: 179,703 observed/identified cases with Hem A from 119 countries in the context of an overall population of 5,842,599,408 (3.08 per 100,000). Similarly to VWD, the prevalence of patients with Hem A (all severities) actually diagnosed and registered at HTC

Table 2. Estimate of patients with von Willebrand disease seeking care and thus potentially suitable for desmopressin treatment.

Country or region	2023 population estimate x10³ inh.	Reported VWD patient prevalence x10⁵ inh.	N of reported VWD patients	Reported VWD type 1 patient prevalence x10⁵ inh.	N of reported VWD type 1 patients
North America					
US	343,477	9.7	33,456	8.05	27,641
Canada	39,299	11.8	4,637	7.9	3,104
Europe					
Nordic Countries	39,614	6.4	2,535	5.6	2,218
United Kingdom	68,683	10.5	7,212	7.4	5,083
Eastern Europe* (excl. Czechia and Russia)	129,797	4.97§	6,451	(3.48)	4,516
Czech Republic	10,810	6.4	692	2.7	292
Russian Federation	145,441	1.88	2,734	(1.32)	1,914
Rest of Europe (excl. Italy, France, Spain and the Netherlands)**	126,730	5.09§	6,451	(3.56)	4,515
Italy	59,499	4.8	2,856	4.0	2,380
France	66,439	4.4	2,923	(3.08)	2,046
Spain	47,912	12.2	5,845	6.8	3,258
The Netherlands	18,093	6.06	1,096	(4.24)	768
Asia					
Western Asia° (excl. Turkey)	177,304	1.63§	2,890	(1.14)	2,023
Turkey	87,271	1.13	986	(0.79)	690
Rest of Asia°° (excl. Western Asia, China, India, Iran, Japan)°	1,398,404	0.16§	2,237	(0.11)	1,566
India	1,438,070	0.6	8,628	0.12	1,726
Iran	90,609	1.10	997	0.1	91
Japan	124,371	2.3	2,861	(1.61)	2,002
China	1,422,585	0.09	1,280	(0.06)	896
Australia	26,451	9.05	2,394	5.6	1,676
New Zealand	5,173	15.08	780	7.7	398
Latin America					
Countries from Latin/Central/South America (excl. Brazil)@	324,869	3.56§	11,565	(2.49)	8,096
Brazil	211,141	5.39	11,375	2.82	5,952
Africa					
Northern Africa^	221,797	1.04	2,307	(0.21)	461
Sub-Saharian Africa (excl. South Africa) ^^	588,404	0.002	12	(0.00)	2
South Africa	63,212	1.06	670	0.40	256
Worldwide	**7,275,455**	**1.73**	**125,871**	**1.15**	**83,571**

When epidemiological data were not available, the estimated prevalence of von Willebrand disease type 1 patients (in brackets) is considered to be 70% of the overall prevalence in high- and upper middle-income countries and 20% in lower middle- and low-income countries. *Eastern Europe subregion includes data available from Belarus, Bulgaria, Czechia, Hungary, Poland, Romania, Slovakia, and Ukraine. **Rest of Europe includes United Nations (UN) subregions of Western and Southern Europe after the exclusion (excl.) of France, Italy, the Netherlands, and Spain. (Includes data available from Albania, Belgium, Bosnia and Herzegovina, Germany, Greece, Montenegro, North Macedonia, Portugal, Serbia, Slovenia, and Switzerland.) °Western Asia sub-region includes data available from Armenia, Azerbaijan, Bahrain, Cyprus, Georgia, Iraq, Israel, Jordan, Kuwait, Lebanon, Oman, Qatar, Saudi Arabia, Palestine, Syrian Arab Republic, and the United Arab Emirates. °°Rest of Asia includes UN subregions of Central Asia, Eastern Asia (after excluding Japan and China), Southern Asia, and South-Eastern Asia. @Includes the data available from Argentina, Bahamas, Bolivia, Colombia, Cuba, the Dominican Republic, El Salvador, Honduras, Mexico, Panama, Paraguay, Trinidad and Tobago, Uruguay, and Venezuela. ^Northern Africa includes data available from Algeria, Egypt, Libya, Morocco, Sudan, and Tunisia. ^^Sub-Saharan Africa includes data available from Botswana, Cameroon, Congo, Cote d'Ivoire, Gambia, Ghana, Guinea, Kenya, Lesotho, Madagascar, Mali, Mauritania, Mauritius, Nigeria, Rwanda, Senegal, Uganda, and Zambia. §Country population-weighted average. N: number; inh: inhabitants; VWD: von Willebrand disease.

varies between regions and countries.[5,34] The calculated global prevalence per 100,000 males is 5.70, assuming a male : female ratio of 1.08 in the general population. Of them, about 45% have non-severe Hem A, with no relevant differences among high-income (44%), upper middle-income (47%), and lower-middle income (44%) countries. The weighted average according to income is 24% and 21% of cases with mild Hem A and moderate Hem A, respectively. These figures are consistent with those of an earlier global survey[35] that involved 147 HTC and supplied data for 16,115 patients with Hem A, 47% of them with mild or moderate disease. Another survey conducted in the Netherlands[36] reported that 906 respondents (out of 1,567 patients with hemophilia, all types) had Hem A, 46% with mild FVIII deficiency and 17% with moderate deficiency. Hem A female carriers should be added to these figures, but data on the prevalence of those with FVIII below 40 IU/dL are limited: only the UKHCDO Annual Report 2023[16] registered 832 women with these characteristics. Thus, by extrapolation from the UK population, the prevalence of carriers with low FVIII (68,683,000) is estimated to be 1.21 cases per 100,000 persons.

To sum up, it is assumed that 80,866 males have non-severe Hem A, 43,128 (53%) of them with mild and 37,737 (47%) with moderate disease. Female carriers should be added to these cases, but their prevalence is uncertain.

Bleeding events in type 1 von Willebrand disease and hemophilia A

Type 1 VWD

Data on the frequency of bleeds are scanty, because of a low number of prospective studies with an adequate size (Table 4). Moreover, the heterogeneity of type 1 VWD[37] further hampers the accurate evaluation of the bleeding phenotype.

In the context of a retrospective study[38] designed to evaluate the efficacy and safety of two VWF/FVIII concentrates in a large cohort of patients with VWD followed up for 60 months, 52 bleeds were treated in 22 cases with VWD type 1, with an incidence of 0.47 events per patient year. An Italian prospective study[39] with 71 months of follow-up evaluated bleeding events in 60 heterozygous cases with VWD Vicenza and 23 with the C1130F mutation, both characterized by an increased VWF plasma clearance. The rates of bleeding events differed significantly: 7.5/100 patients-year in cases with the C1130F mutation and 1.9/100 patients-year in those with VWD Vicenza (R1205H).

The Italian National Registry of von Willebrand Disease (RENAWI[40]) was started in 2002 with the aim of evaluating the natural history of VWD in 1,234 patients, 779 of them with VWD type 1. Over a time-frame of four years, 2,036 bleeding episodes were recorded in type 1 cases (0.65 episodes per patient-year).

Table3. Prevalence of female cases in type 1 von Willebrand disease.

Source	Country	Cohort size, N	Females, %
Stonebraker *et al.*, 2023[10]	121 countries	85,562 (all types)	63.2
Soucie *et al.*, 2021[11]	USA	19,845 type 1	66.6
De Wee *et al.*, 2012[30]	The Netherlands	664 (all types)	64
CDC Community Counts[31]	USA	7,173 (all types)	68
WFH World Bleeding Disorders Registry[32]	22 countries	999 (all types)	56
UKHCDO Annual Report, 2023[16]	UK	5,089 type 1	64
WFH-AGS 202[35]	All countries	87,425 (all types)	62
Du *et al.*, 2022[28]	7 countries	type 1 (N=NA)	55.3-83.3

CDC: the US Center for Disease Control; N: number; NA: not available; UKHCDO: The United Kingdom Haemophilia Centre Doctors Organisation; WFH-AGS: World Federation of Hemophilia Annual Global Survey.

Table 4. Bleeding frequency in type 1 von Willenbrand disease and non-severe hemophilia A.

Source	Study type	Cohort size, N	Follow-up in months, N	Annual bleeding frequency (events/patient/year)
von Willebrand disease type 1				
Federici *et al.*, 2010[38]	Retrospective	22	60	0.47
Castaman *et al.*, 2011[39]	Prospective	83	71	0.075
Federici *et al.*, 2010[40]	Registry	779	48	0.65
Non-severe hemophilia A				
Kloosterman *et al.*, 2022[41]	Literature review	NA	NA	Moderate Hem A: min-max 1-11
				Mild Hem A: min-max 0-4.5
Kloosterman *et al.*, 2022[41]	Retrospective	70 mod. Hem A&B	11 years	Moderate A&B : 0.6 (min-max: 0-11)
		234 mild Hem A&B		Mild A&B: 0.2 (min-max: 0-4)

Hem: hemophilia; mod.: moderate; N: number; NA: not available.

As mentioned above, HMB is the most common symptom in women with VWD (Table 5). It occurs in 93% of adult women, as demonstrated in a cohort of 38 women with type 1 VWD referred for diagnosis and care to a single HTC in the USA.[42] In addition, a survey conducted in the USA[43] in 99 VWD type 1 women reported that 78 of them (79%) perceived their periods as being heavy and 55/78 (71%) sought medical attention. Another survey of 75 women with VWD registered at HTC in the USA found that menorrhagia was the most commonly reported symptom (84%).[44] The forementioned RENAWI[38] reported that 374 of 468 women (80%) with type 1 VWD have HMB. This rate is likely to further increase when only women of reproductive age are considered (*data not available*). Similarly, in a cohort of VWD cases in Taiwan,[45] 36 of 45 women with menses had menorrhagia (80%). In a survey of women with inherited bleeding disorders in HTC in the USA, 76.0% of the 217 menstruating women reported that in the heaviest menses day they needed changes of protection pads at least every 2 hours.[46] In 2016, a survey of USA HTC collected data from 1,321 women with VWD type 1 between 18 and 45 years of age: 816 of them (61.8%) had menorrhagia.[47]

Non-severe hemophilia A

The bleeding rate (Table 4) has been evaluated in a relatively small number of studies that were summarized by Kloosterman *et al.*[41] They reported varied annualized bleeding rates (ABR) ranging from 0[36] to 100[48] events, with median ABR of 1.0-11.0 and 0-4.5 for moderate and mild Hem A, respectively.[48,49] An international multicenter retrospective cohort study (DYNAMO) conducted in 15 HTC in Europe and Canada[41] included data from 304 non-severe Hem A and B cases, aged 12 to 55 years and with FVIII/IX levels ranging from 2 to 35 IU/dL (55 cases had moderate Hem A and 193 had mild Hem A). The median ABR was 0.6 (min-max 0-11) in moderate Hem A and 0.2 (min-max 0-3) in mild Hem A. Among patients with moderate and mild Hem A, only 10% and 26%, respectively, had zero bleeding events.

To sum up, we estimated that the number of annual bleeding episodes in males and females with VWD type 1 is 41,786 (0.5 yearly events in 83,571 people) but that the number of HMB in menstruating women should be added to this figure. Taking into account the proportion of women of reproductive age (15-49 years) reported by the UN Population Division[6] (49%), the number of annual bleeding events in VWD type 1 women is estimated to be 221,129 (24,570 menstruating cases x 75% HMB incidence x 12 menses). Moreover, we estimated that the number of bleeding events in non-severe Hem A is 31,268 (0.6 annual events in 37,737 moderate Hem A cases, and 0.2 annual events in 43,128 mild Hem A cases). It should be recognized that the varied prevalence estimates reported here may be related to differences in the definition of HMB.

Desmopressin response rate in type 1 von Willebrand disease and non-severe hemophilia A

Whilst desmopressin increases endogenous FVIII and VWF in type 1 VWD as well as in non-severe Hem A, the degree of factor increase is highly variable, being dependent on the baseline level and on gene variants.[50,51] Owing to this variability, a desmopressin challenge test is recommended before this medication is used in the clinic.[52,53] However, the challenge test may be waived in members of families that include persons who have been reported to respond to this drug. On the other hand, the pattern of responsiveness observed after a desmopressin test is consistent over time in the context of non-contiguous administrations, thus it can be reliably used to help determine clinical bleeding management choices.[54]

Type 1 von Willebrand disease

A limited number of reports have evaluated responsiveness to desmopressin in VWD type 1,[55] with varied criteria for response definition and a huge variation in response rates, ranging from 27%[56] to 100%,[57] which is likely due to the relatively small size of the cohorts and selection bias. Therefore, we chose to consider only larger studies of at least 75 patients with VWD type 1 (Table 6). In an open-label multicenter trial,[58] 332 bleeding events were treated with only desmopressin in 172 patients with type 1 VWD. Clinical response was deemed excellent when bleeding stopped after a single administration (in 68% of cases), and good when two or three doses were required to stop bleeding (in an additional 27% cases). The Molecular and Clinical Markers for the Diagnosis and Management of Type 1 von Willebrand Disease (MCMDM-1VWD) study[59] showed that 64 of 77 cases (83%) had a post-infusion increase of VWF:RCo and FVIII:C higher than 50 IU/dL (defined a complete response); an additional 10 cases had levels lower than 50 IU/dL but these were at least 3-fold higher than baseline (defined a partial response).

A retrospective chart review of 89 patients with VWD type 1 who underwent a desmopressin challenge test was conducted in the USA.[60] In all, 97% responded; responders were defined as those in whom factor VIII, VWF:Ag, or VWF:RCo

Table 5. Prevalence of heavy menstrual bleeding in women with type 1 von Willenbrand disease.

Source	Study type	Cohort size, N	Women with HMB, N (%)
Ragni *et al.*, 1999[42]	Retrospective	38	35 (93)
Kouides *et al.*, 2000[43]	Survey	99	78 (79)
Kirtava *et al.*, 2004[44]	Survey	75	63 (84)
Federici *et al.*, 2010[38]	Registry	468	374 (80)
Chen *et al.*, 2011[45]	Retrospective	45	36 (80)
Byams *et al.*, 2011[46]	Survey	217	165 (76)
Ragni *et al.*, 2016[47]	Survey	1,321	816 (62)

HMB: heavy menstrual bleeding; N: number.

plasma levels increased more than 2-fold their baseline levels at any of the post-infusion time points. Of 89 cases, 69 (80%) showed a response for all the forementioned measurements.

The WiN study[57] compared desmopressin response in 180 type 1 VWD cases with and without a VWF gene variant. All those with reduced synthesis/secretion of VWF but normal clearance (FVIII:C/VWF:Ag ≥1.9 and VWFpp/VWF:Ag <2.2), and all those with an undetermined mechanism underlying low VWF levels (FVIII:C/VWF:Ag <1.9 and VWFpp/VWF:Ag <2.2), had a complete response to desmopressin. In contrast, cases with an enhanced clearance of VWF (i.e., VWFpp/VWF:Ag ratio >7) had an incomplete response. Another retrospective study in the Netherlands[55] showed that the 206 patients with type 1 VWD and historically lowest VWF levels between 30-50 IU/dL (N=206/206), and 88% of those with type 1 VWD and historically VWF levels lower than 30 IU/dL (N=99/112), were responders. A prospective cohort confirmed these findings, 91% of type 1 cases with baseline VWF lower than 30 IU/dL and all those with baseline VWF between 30 and 50 IU/dL (100%) being classified as responders (N=10/11). A potential limitation of these responsiveness rates is the inclusion or not of women with HMB.

The rate of desmopressin responsiveness depends greatly on how response is defined. A Canadian single-center retrospective review[61] assessed 94 patients with VWD using six different definitions for responsiveness, that ranged from 53.2% to 91.5%, according to the most widely-used definition (VWF activity and FVIII ≥50 IU/dL at 1-hour post-infusion); 84 of 94 (89.4%) cases were responders.

Non-severe hemophilia A

In non-severe Hem A patients, responsiveness to desmopressin correlates with FVIII levels, age, and F8 gene mutation. A relatively large number of studies investigated the rates of responsiveness to a challenge test using a huge variety of definitions (Table 7). In an open-label multicenter trial,[58] 399 bleeding events were treated with desmopressin alone in 124 cases with mild Hem A. Clinical response was deemed excellent when bleeding stopped after a single administration (67% of cases), and good when two or three administrations were required to stop bleeding (in an additional 27% of cases). A single-center retrospective chart review[62] in the USA showed that 32 of 62 cases (52%) with mild Hem A had a complete response, defined as a FVIII:C peak at 5 IU/dL or more, plus 15 additional cases (24%) with a partial response, defined as a FVIII:C peak ≥30 IU/dL (but <50 IU/dL) and increased at least 2-fold. In an Italian retrospective study,[63] 75 patients underwent a desmopressin test, and of these, 76% had a complete response (≥ 50 UI/dL: 49%, N=37) or partial response (< 50 IU/dL, but at least a 2-fold increase: 27%, N=20). Moreover, during a 12-year follow-up, 82 bleeding events occurred in 27 responders treated with 246 desmopressin infusions with complete or partial efficacy in 92% (75/82). In complete responders, full efficacy (one administration stopped bleeding) was observed in 53% of the episodes (N=34/64), and partial efficacy (2-4 administrations required) in 42% of episodes (N=27/64). An international cohort study evaluated desmopressin responses in 169 moderate Hem A patients[64] and found an excellent response (with peak FVIII levels ≥50 UI/dL) following different administration routes (intravenous, subcutaneous, and intranasal) in 15% of cases (N=25), a complete response (with FVIII peaks 30-49 UI/dL) in 25% of cases (N=43), and a partial response (FVIII peaks 20-29 UI/dL) in 18% (N=31).

A Canadian retrospective study[65] of 52 cases with mild and

Table 6. Desmopressin response in type 1 von Willebrand disease.

Source	Desmopressin challenge	Cohort	Response rate, % (N of responders)
Leissinger *et al.*, 2001[58]	Intranasal, bleeding treatment	332 bleeding events in 172 patients	Clinical response: Excellent (one administration): 68 (266/332) Good (2-3 administrations): 27 (49/332)
Castaman *et al.*, 2008[59]	i.v.	77 patients	Complete (≥ 50 UI/dL): 83 (64) Partial (< 50 IU/dL, ≥3-fold increase): 13 (10)
Guddati *et al.*, 2019[60]	i.v.	89 patients	Positive response: >2-fold increase of FVIII, VWF:Ag, or VWF:RCo: 97 (86); >2-fold increase of all measurements: 80 (69)
Atiq *et al.*, 2022[57]	i.v.	180 patients	Complete response (2 times increase in VWF:Act and VWF:Act and FVIII 50 IU/dL until 4 hr after): 100 in patients without VWF variants (72/72) and 64.3 in patients with a variant (69/108)
Heijdra *et al.*, 2022[55]	i.v., retrospective	206 (VWF 30-50 IU/dL)	Complete (≥ 50 UI/dL): 100 (206)
		112 (VWF <30 IU/dL)	Complete (≥50 UI/dL): 88 (99)
	i.v., prospective	14 (VWF 30-50 IU/dL)	Complete (≥50 UI/dL): 100 (14)
		11 (VWF <30 IU/dL)	Complete (≥50 UI/dL): 91 (10)
Chandrakumaran *et al.*, 2023[61]	i.v.	94 patients	Complete (≥50 UI/dL at 1 hr): 89 (84).

FVIII: factor VIII; hr: hour(s); i.v.: intravenous; N: number; VWF: von Willebrand factor.

Table 7. Desmopressin response in non-severe hemophilia A.

Source	Desmopressin challenge / bleeding treatment	Cohort	Response rate, % (N of responders)
Leissinger *et al.*, 2001[58]	Intranasal	399 bleeding events in 124 mild patients	Excellent (one administration): 67 (269/399 bleeding events) Good (2-3 administrations): 27 (109/399 bleeding events)
Nance *et al.*, 2013[62]	i.v.	62 mild patients	Complete (≥ 50 IU/dL): 52 (32) Partial (< 50 IU/dL, 2 times increase): 24 (15)
Di Perna *et al.*, 2013[63]	i.v.	75 mild patients	Complete (≥ 50 UI/dL): 49 (37) Partial (< 50 IU/dL, 2 times increase): 27 (20)
	i.v.	82 bleeding events	In complete responders, complete efficacy (one administration): 53 (34/64), partial efficacy (2-4 administrations): 42 (27/64).
			In partial responders, complete efficacy (one administration): 33 (6/18), partial efficacy (2-4 administrations): 44 (8/18).
Loomans *et al.*, 2018[64]	i.v., s.q. or intranasal	169 moderate patients	Excellent (≥ 50 UI/dL): 15 (25) Complete (30-49 UI/dL): 25 (43) Partial (20-29 UI/dL): 18 (31)
Hews-Girard *et al.*, 2018[65]	s.q.	44 mild patients	Complete (≥ 50 UI/dL): 70 (31) Partial (20-49%): 20 (9)
		8 moderate patients	Partial (20-49 UI/dL): 38 (3)
	s.q.	13 bleeding events 30 surgical procedures	Good: 96 (22/23 patients treated only with desmopressin: 15 complete response, 5 partial response, and 2 non-responders)
Zwagemaker *et al.*, 2022[66]	i.v.	141 mild patients	Complete (≥ 50 UI/dL): 72 (101) Partial (30-49 UI/dL): 32 (32)
		31 moderate patients	Complete (≥ 50 UI/dL): 16 (5) Partial (30-49 UI/dL): 39 (12)
	i.v.	118 bleeding events	Complete: 71 (84) Partial: 27 (32)

i.v.: intravenous; N: number; s.q.: subcutaneous.

moderate Hem A (FVIII 1-40 IU/dL; 34 males and 18 female carriers) showed a complete response to a desmopressin test in 31 of 52 cases (60%), defined as peak FVIII levels ≥50 IU/dL, and partial response with peak FVIII levels from >20 to <50 IU/dL in 12 additional cases (23%). All the complete responders and the majority of the partial responders had a good clinical outcome after desmopressin for a variety of bleeding episodes and procedures, with the exception of one partial responder who required additional factor concentrate. Among 172 patients with a median age of 22 years (interquartile range 13-36 years) included in the DYNAMO study,[66] an adequate response to a desmopressin test was documented in 25% and 73% of the cases with moderate and mild Hem A, respectively. Of note, pediatric patients (aged <4 years) are less likely to respond than adults, but they can be rescued at an older age.[67]

Estimated number of bleeding events treatable with desmopressin in type 1 von Willebrand disease and non-severe hemophilia A

Notwithstanding the limitations imposed by the varied available data and the related assumptions, we estimate that, globally, 83,571 cases with VWD type 1 and 80,866 with non-severe Hem A have an annual number of 294,183 bleeding events (262,914 events in VWD type 1 and 31,268 in non-severe Hem A patients). Assuming an 80% desmopressin responsiveness rate in VWD type 1, 210,331 annual bleeding events can be treated with this medication. Because of the huge differences in the rate of desmopressin responsiveness in non-severe Hem A, which ranges from 50% to 90%, we assumed that the response rate (complete and partial) for patients with moderate Hem A is 25%, but as high as 80% for mild Hem A. According to this assumption, 12,561 annual bleeds are treatable with desmopressin in non-severe Hem A (5,661 in moderate and 6,901 in mild Hem A patients). To sum up, 222,893 spontaneous and post-traumatic bleeds in VWD type 1 and non-severe Hem A can be treated annually with desmopressin (Table 8).

Discussion

After the original report in 1977,[3] desmopressin has been used worldwide thanks to its ability to raise FVIII and VWF plasma levels in patients with non-severe Hem A or type 1 VWD who need treatment for spontaneous or provoked bleeding or in preparation for surgery and trauma. This medicine is characterized by its low-cost efficacy, convenient administration routes (subcutaneous and intranasal), the likelihood of avoiding having to use blood products

Table 8. Computation of estimates of number of patients, number of annual bleeding events, and successfully treated annual bleeding events according to responsiveness to desmopressin.

	WORLD
Overall reference population*	7,275,455,000
Prevalence of registered/identified pts. with VWD	1.68E-05
Identified pts. with VWD	121,954
Prevalence of registered/identified pts. with VWD type 1	1.15E-05
Identified pts. with VWD type 1	83,571
Proportion of males with VWD type I	0.40
Estimation of males with VWD type I	33,428
Proportion of females with VWD type I	0.60
Estimation of females with VWD type I	50,143
Proportion of women of fertile age (15-49 years)	0.49
Estimation of women of fertile age (15-49 years) with VWD type 1	24,570
Prevalence of registered/identified pts. with Hem A	3.08E-05
Identified pts. with Hem A	179,703
Prevalence of registered/identified pts. with non-severe Hem A	0.45
Identified pts. with non-severe Hem A	80,866
Prevalence of registered/identified pts. with moderate Hem A	0.47
Identified pts. with moderate Hem A	37,738
Prevalence of registered/identified pts. with mild Hem A	0.53
Identified pts. with mild Hem A	43,129
Prevalence of annual bleeding events per male with VWD type 1 and non-menstruating females	0.5
Potential ABE in males with VWD type 1 and non-menstruating females	41,786
Prevalence of ABE per female of fertile age (15-49 years) with VWD type 1	9
Potential ABE in female of fertile age (15-49 years) with VWD type 1	221,129
Prevalence of ABE per female not of fertile age (≤14 and ≥50) with VWD type 1	0.5
Potential ABE in females not of fertile age (≤14 and ≥50) with VWD type 1	12,786
Overall potential ABE in pts. with VWD type 1	262,914
Prevalence of ABE in pts. with moderate Hem A	0.6
Potential ABE in pts. with moderate Hem A	22,643
Prevalence of ABE in pts. with mild Hem A	0.2
Potential ABE in pts. with mild Hem A	8,626
Response rate to desmopressin of pts. with VWD type 1	0.80
Response rate to desmopressin of pts. with moderate Hem A	0.25
Response rate to desmopressin of pts. with mild Hem A	0.80
Potential ABE successfully treated in pts. with VWD type 1	210,331
Potential ABE successfully treated in pts. with mod. Hem A	5,661
Potential ABE successfully treated in pts. with mild Hem A	6,901
Potential annual bleeding events successfully treated	222,893

*Overall population of countries with published or reported information on number of people with von Willebrand disease (VWD) and hemophilia A. ABE: annual bleeding events; Hem: hemophilia; pts.: patients.

or recombinant factors, as well as a good safety record.[68] Moreover, its administration does not induce inhibitors in non-severe Hem A patients, who have a 3-13% lifetime inhibitor risk following FVIII replacement therapy. Desmopressin can also be used to treat bleeding episodes in non-severe Hem A patients who have developed inhibitors owing to the absence of any anamnestic rise of the inhibitor.[69] These characteristics prompted the World Health Organization (WHO) in 2015 to include desmopressin in its list of essential medicines.[70] The WHO Expert Committee acknowledged that "desmopressin is an important medicine in the hemostatic armamentarium for patients with bleeding disorders, particularly in view of the ease of its administration (notably the intranasal formulation)." All this notwithstanding, the medication is becoming unavailable or experiencing a dramatic shortage, particularly in the

intranasal and subcutaneous formulations.

With this background, we chose to estimate how many patients with VWD type 1 and non-severe Hem A can be treated with desmopressin worldwide and how many bleeding events could be treated annually. To achieve these objectives, we assessed the literature in the frame of a narrative review and also employed the data reported by the WFH-AGS 2023[5] and scientific societies involved in congenital bleeding disorders. We chose a non-systematic review, with all its limitations, in order to include a wide variety of studies. This choice was also based on the paucity of studies pertaining to type 1 VWD and non-severe Hem A, and bleeding frequency and response to desmopressin in these patients, as well as the great variability of study designs (e.g., no randomized clinical trials, few prospective studies, type of cohorts) and definitions of desmopressin response.

To sum up, we estimated that about 83,500 patients with VWD type 1, of whom about 60% were females, sought care and/or were identified out of an overall population of 7.3 billion people from countries with available information on registered patients (see Table 8 for more precise computations).[5] Accordingly, our calculated prevalence was 1.15 per 100,000 people. Based on the 180,000 patients with Hem A identified and registered by the WFH-AGS 2023, of whom about 81,000 had non-severe Hem A, we assumed that 43,000 cases (53%) had mild Hem A and 38,000 (47%) moderate Hem A.

We then calculated how many bleeding events might occur yearly in these patients. Based on our literature analysis, it was assumed that, globally, 59,000 male patients and non-menstruating females with VWD type 1 would suffer from 0.5 events yearly, and that 24,500 women of reproductive age (15-49 years) may have an average of about 7 yearly episodes of HMB (12 events in 60% of women). This leads to a total of 260,000 annual bleeds in VWD type 1, equal to 0.34 event / patient / year. We also estimated that a total of 81,000 patients with non-severe Hem A have about 0.6 bleeds in moderate Hem A (about 38,000 people) and 0.2 bleeds in mild Hem A patients (about 43,000 people), with a total of approximately 31,000 events (an average 0.4 annual bleeds per person with non-severe Hem A).

Responsiveness to desmopressin is similar in VWD type 1 and mild Hem A (80%), but it is definitely lower in moderate Hem A (25%). Based on these assumptions on the response rate, the number of bleeding events that can be treated yearly with desmopressin are approximately 210,000 in VWD type 1 and 12,500 in non-severe Hem A. There are limitations related to these estimates, considering that patient aging may be associated with fewer bleeds. On the other hand, our estimation, based on the treatment of actual bleeds, may underestimate desmopressin usage, such as, for example, for bleeding prophylaxis and conditions other than mild Hem A and type 1 VWD (e.g., type 2 N VWD and platelet function defects, which were excluded from the present review). Underestimation of its use is also related to the fact that our estimates have not included the use of desmopressin for diagnosis, surgery,[52,53,71] or childbirth,[72] nor its pre-emptive use for trauma or bleeding prophylaxis,[73] because it is impossible to have reliable data. We have also not included hemophilia carriers with FVIII levels below 40 IU/dL, who presumably account for at least 5% of the cases with severe Hem A,[16] nor patients with other VWD types,[57] such as 2M, who may be responsive to desmopressin.

This narrative review is also limited by the huge variability of bleeding incidence and desmopressin response rates in the published cohorts, owing to differences regarding choice of cases, methods of data collection (mainly retrospective), varied definitions of desmopressin responsiveness, as well as the role of individual genetic variants. Because this large variability compromises the accuracy of any estimation, we have adopted a very conservative approach (Table 8). The number of bleeding events that can be treated yearly was based on the global number of patients with VWD type 1 and non-severe Hem A. The number of cases with VWD type 1 included in our estimation is lower than that reported by the WFH-AGS 2023, because we chose to limit the analysis to the cases more likely to seek care, with the goal of avoiding overestimating the number of cases, and, thus, the number of bleeding episodes. In fact, by applying the same assumptions to a larger population (207,000 cases reported to be affected by VWD in the WFH-AGS 2023), the overall number of bleeding episodes treatable each year with desmopressin would increase to 350,000. Due to increasing diagnostic accuracy, we also expect that the number of diagnosed and treated patients will increase in the near future. However, despite the several advantages of desmopressin, available data on the real-world use of this medicine in the treatment of bleeding is still scarce. There is some evidence of a suboptimal use, so that patients with potential or confirmed adequate response are actually treated with the more costly factor concentrates.[64,66,74] This paradox is probably growing because of the increasing shortage or unavailability of the drug due to the fact that production has been discontinued, particularly for the more practical intranasal and subcutaneous formulations.[75,76] Poor access to desmopressin is particularly cogent in low-income countries that are characterized by poor access also to other forms of replacement therapy owing to their much higher cost.[77] Shortage and unavailability are principally due to a recall in August 2020 by the manufacturers and distributors of the subcutaneous formulation, but also of the intranasal formulation that is widely used particularly in pediatric cases and for HMB. The only formulation still available is the intravenous formulation used in the management of diabetes insipidus, that is much less concentrated than those formulations used subcutaneously or intranasally for bleeding disorders. The shortage and lack of availability of the intranasal and subcutaneous formulations prompted patient advocacy organizations to ask the US Food and Drug Administration (FDA) to add desmopressin to the National

Drug Shortage List. The FDA has reacted to this plea by asking STAQ Pharma to produce a new intranasal product, which is available in the USA but not in Europe or other countries outside the USA.[78,79]

In conclusion, desmopressin is an essential therapeutic tool in VWD type 1 and non-severe Hem A, because more than 220,000 bleeding episodes can be annually treated safely and economically. This number could almost double if all patients registered are considered, or even increase 6-fold if we allow for one symptomatic patient out of 10,000 people seeking tertiary care referral for VWD.[80-82] Finally, there is a need to improve VWD and hemophilia diagnosis globally, because it is reasonable to imply that 1 out of 1,000 individuals may suffer from bleeding symptoms,[79] but will not have been diagnosed or received appropriate treatment.

Disclosures

PMM reports honoraria for lectures at educational symposia from Roche and Octapharma. FP has sat on the Advisory Committee of CSL Behring, Biomarin, Roche, Sanofi, Sobi, and Pfizer, and has taken part in Educational Meetings / Simposia for Takeda and Sanofi. All of the other authors have no conflicts of interest to disclose.

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All the authors designed and wrote the review article, and approved the final version for publication.

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