TITLE

Long-term outcome after joint bleeds in Von Willebrand disease compared to haemophilia A: a post-hoc analysis

SHORT RUNNING TITLE: Outcome after joint bleeds in VWD compared to haemophilia A

AUTHORS AND AFFILIATIONS

Karin PM van Galen*, Merel Timmer*, Piet de Kleijn*°, Frank WG Leebeek§, Wouter Foppen†, Roger EG Schutgens*, Jeroen Eikenboom‡, Karina Meijer¥, Karin Fijnvandraat¶, Britta A.P. Laros-van Gorkom#, Jos W Twisk^, Evelien P Mauser-Bunschoten*, Kathelijn Fischer**, on behalf of the WiN studygroup

*Van Creveldkliniek, University Medical Center Utrecht, University Utrecht, Utrecht, The Netherlands

°Department of Rehabilitation, Physical Therapy Science and Sports, University Medical Centre Utrecht, University Utrecht, The Netherlands

§Department of Hematology, Erasmus University Medical Center, Rotterdam, The Netherlands

†Department of Radiology, University Medical Center Utrecht, Utrecht, The Netherlands

‡Department of Thrombosis and Hemostasis and Einthoven Laboratory for Vascular and Regenerative Medicine, Leiden University Medical Center, Leiden, The Netherlands

¥Department of Hematology, University of Groningen, University Medical Center Groningen, The Netherlands

¶Department of Pediatric Hematology, Academisch Medisch Centrum, Emma children's hospital, Amsterdam, The Netherlands

#Department of Hematology, Radboud university medical center, Nijmegen, The Netherlands

^Department of Clinical Epidemiology and Biostatistics, VU University Medical Center, Amsterdam, The Netherlands

**Van Creveldkliniek and Julius Center Department of Epidemiology, University Medical Center Utrecht, University Utrecht, Utrecht, The Netherlands

CORRESPONDING AUTHOR:

Karin van Galen, M.D., MSc., PhD

University Medical Center Utrecht, Van Creveldkliniek

Heidelberglaan 100, Room C01.425

PO box 85500, 3508 GA Utrecht

The Netherlands

Telephone: +31 8 875 584 50

Fax: +31 88 75 554 38

E-mail: k.p.m.vangalen@umcutrecht.nl

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Authorship

Karin PM van Galen: performing research, writing the paper, analyzed data

Merel Timmer, Piet de Kleijn: performing research, writing the paper

Frank WG Leebeek: supervising analysing the data and writing the paper

W Foppen: performing research

Roger EG Schutgens, Jeroen Eikenboom, Karina Meijer, Karin Fijnvandraat and Britta A.P. Laros-van Gorkom: made substantial contributions to the data analyses and writing of the paper

Jos W Twisk: designing data analysis plan and supervising writing the paper sections on statistical analysis and results

Evelien P Mauser-Bunschoten and Kathelijn Fischer: designing the research, supervising data analysis and writing the paper

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ABSTRACT

Long-term outcome after joint bleeds in VWD (VWF activity≤30IU/dL) could differ from moderate or severe haemophilia A (FVIII 1-5IU/dL or FVIII<1IU/dL). We performed a post-hoc analysis on Haemophilia Joint Health Scores (HJHS, 0-124), X-ray Pettersson scores (PS, 0-13/joint) and the Haemophilia Activities List (HAL, 0-100), using multivariable regression to adjust for age (rate-ratio or odds-ratio [95% confidence interval]). We included 48 VWD (median age 47yrs, type 3 VWD n=19), 39 moderate HA (median 39yrs) and 59 severe HA patients (median 25yrs) with documented joint bleeds. VWD-patients suffered repeated bleeding (lifetime>5/joint) less often than moderate and severe HA patients (52% vs. 77% vs. 98%). HJHS and PS in VWD were similar to moderate HA (median HJHS 5 vs. 6, RR 0.9[0.5-1.4] and PS>3 of ≥1 joint OR 0.3[0.1-1.4]), but better than in severe HA patients (median HJHS 5 vs. 9, RR 1.8[1.1-2.9]; PS>3 in any joint OR 0.1[0.0-0.3]). Self-reported limitations in activities were comparable across VWD, moderate HA (HAL score<95: 67% vs. 49%; OR 1.4[0.5-3.6]) and young adults with severe HA (67% vs. 48%; OR 1.7[0.7-4.4]). Despite fewer joint bleeds, joint outcome after joint bleeds was similar in VWD and moderate HA patients. Type 3 VWD patients had worst joint outcome, comparable to younger intensively treated severe HA patients. Limitations in activities occurred as often in VWD as in both moderate and severe HA.

Key words: Von Willebrand disease, joint bleed, arthropathy, haemophilia A, HJHS, Pettersson, HAL

INTRODUCTION

Von Willebrand disease (VWD) is the most common inherited bleeding disorder with a prevalence of 1/100 – 1/10.000, followed by haemophilia A (HA), with a prevalence of 1/5000 males.(1;2) Deficient or dysfunctional Von Willebrand Factor (VWF) causes predominantly mucocutaneous bleeding symptoms in VWD.(3) In HA, bleeding is due to a deficiency of clotting factor VIII (FVIII). Greatly reduced FVIII levels also occur in more severe VWD, since VWF is a carrier protein for FVIII in the circulation. In the Willebrand in the Netherlands (WiN) study, a nationwide cohort study on more than 800 VWD patients (VWF activity ≤30 IU/dL), 6% of the participants had very low FVIII levels <10 IU/dL at diagnosis.(3;4) In HA, low FVIII leads to recurrent joint bleeds that cause damage to the cartilage and synovium, resulting in arthropathy.(5) Haemophilic arthropathy is characterized by pain, physical restrictions and limitations in both activities and participation.(6) Current haemophilia treatment aims to prevent this complication by regular prophylactic FVIII infusions starting at young age.(7) Preventing joint bleeds by VWF/FVIII prophylaxis is not a clearly defined treatment goal in VWD.(8)

Joint bleeds occur in approximately half of the patients with type 3 VWD, characterized by the absence of VWF and strongly reduced FVIII levels, but also in 5-10% of type 1 and type 2 VWD patients.(4) Especially in VWD patients with FVIII levels <10 IU/dL, recurrent joint bleeds can result in arthropathy.(9-13) Therefore, it is important to assess clinical outcome after joint bleeds, in order to identify arthropathy early and provide optimal treatment to prevent further limitations in activities, preserve social participation and quality of life.(14) The 'Haemophilia Joint Health Score' (HJHS) is a widely used physical examination score, developed and proven valid to measure joint health in haemophilia.(15-17) The HJHS was recently validated in VWD.(18) In addition, joint X-rays can be used to detect arthropathy in both HA and VWD.(10;11;15;18-20) The 'Haemophilia Activity List' (HAL) patient questionnaire is used to assess self-perceived limitations in activities and aspect of participation and validated in VWD.(21;22)

In contrast to haemophilia, a limited number of studies addressed arthropathy in VWD.(4;9) A comparison of joint outcome between patients with VWD and haemophilia can help to obtain more insight into the long-term consequences of joint bleeds in VWD. The aim of this cross-sectional study is to compare differences in joint outcome after joint bleeds between adult patients with VWD and HA. We hypothesized that joint outcome after joint bleeds in patients with VWD would be comparable to moderate HA, but better than in severe HA, because of the higher incidence of recurrent joint bleeds in the latter patient category.

METHODS

The original studies were approved by the Medical Research Ethics Committee of the University Medical Center Utrecht in the Netherlands. Informed consent included permission for subsequent analyses of joint outcome data.

Study design

We conducted a post hoc analysis on joint outcome data from three cross-sectional studies, one on VWD and two on moderate and severe HA.(13;17;23) The data on VWD patients were obtained from the WiN study.(24) Self-reported joint bleeds in the WiN study questionnaire were verified by obtaining the treatment history from medical files.(4) Subsequently these patients were contacted and joint assessment took place within the nationwide Willebrand Arthropathy Study between August 2013 and July 2015.(13) Data on moderate and severe HA were obtained from two cohort studies, previously conducted at the 'Van Creveldkliniek', a haemophilia treatment center in the University Medical Center Utrecht, The Netherlands, between June 2006-July 2009 and January 2006-July 2009, respectively.(13;17;23)

Patients

The selection procedure is shown in Figure 1. Adults ≥18 years with VWD (VWF activity ≤30 IU/dL) and moderate HA (FVIII 1-5 IU/dL) or severe HA (FVIII <1 IU/dL) and verified joint bleeds were

selected from the three original studies.(13;17;23) Within these studies there were no restrictions in year of birth at inclusion regarding the VWD and moderate HA patients. However the inclusion of severe HA patients was restricted to those born between January 1, 1970, and January 1, 1994 because the original study assessed outcome after the availability of clotting factor concentrates. We verified a history of joint bleeds by recording medical file documentation on treatment of joint bleeds with desmopressin or clotting factor concentrate. HA patients with comorbid VWD were excluded (n=1). Joint assessment, including X-rays, took place during one study visit in the Willebrand Arthropathy Study, of which the results have been published recently.(13) Within the two single center haemophilia studies, joint assessment was conducted during routine visits to the 'Van Creveldkliniek' University Medical Center Utrecht, the Netherlands.(17;23) Because in severe HA joint X-rays were performed routinely every five years and in moderate HA if indicated, independently from the HJHS, only Pettersson scores obtained 2.5 years before or after HJHS assessment were included in the analyses. This cut off was chosen based on previous publications showing a median change in Pettersson score of 0.4 points/yr in severe haemophilia patients and an inter-observer agreement of the Pettersson score of 1 point.(25;26)Patients with clinically relevant FVIII factor inhibitors had been excluded from these studies and did not occur within the VWD cohort, VWF inhibitors had not been excluded.(13)

We retrieved data on the number of joint bleeds and history of orthopedic surgery from the medical files of the HA and VWD patients. We recorded the lifetime number of joint bleeds in ankles, elbows and knees as 0, 1-5 or >5 joint bleeds at joint level, from birth until the age the HJHS had been performed. The reason to do so was twofold: first, because more than five joint bleeds are predictive of arthropathy and second, because of the limited reliability of medical file data to determine the number of joint bleeds per joint in patients with frequently recurrent joint bleeds.(4;13;27) Study definitions are provided in the Supplemental material.

Outcome parameters

The outcome parameters cover all three domains of the International Classification of Functioning, Disability and Health (ICF) standard as widely used by the WHO: the body structure and function level (HJHS and joint X-rays), as well as activity level and participation level (HAL).(28)

The primary outcome parameter was joint health as measured by the HJHS, a physical examination assessment scale of 11-items. One physiotherapist (PK) performed all HJHS assessments within the three included studies. The assessment includes several items of assessment of elbows, knees and ankles: range of motion (ROM), crepitus on motion, (duration of) swelling, muscle atrophy, pain, strength and a global gait score. This leads to a total score ranging from 0-124 points; a higher score indicates worse joint health.(16) There has been limited validation of the HJHS in adults with haemophilia and in women. (15) We have previously validated the HJHS within a large cohort of adult VWD patients, including 40% females.(22)

Secondary outcome parameters were osteochondral changes of elbows, ankles and knees on joint X-rays, assessed by the Pettersson score (PS, performed by radiologists, range 0-13 per joint), and self-reported limitations in activities, assessed by the HAL questionnaire.(21;29)

Based on the Limits of Agreement of the PS joint in hemophilia patients, we demarcated a PS >3 of one or more joints as radiologic joint changes indicating arthropathy.(26) Arthropathy was defined as a HJHS ≥10 or PS >3 of one or more joints in accordance to the Willebrand Arthropathy Study.(13) The PS was assessed by two different observers in the VWD and haemophilia studies. High agreement between these two observers was previously established (intra-class correlation 0.88; 0.32–0.97).(30)

The HAL asks about a wide variety of functional activities, including items on participation.(31);(21) The normalized total score ranges from 0-100, a score of 100 means that the participant does not experience functional limitations. For statistical analyses, we dichotomized the total HAL score into ‘no limitations in activities’ (HAL ≥95) and ‘some limitations in activities’ (HAL <95), based on the median HAL score in patients with severe haemophilia.(14)

Statistical analyses

We used IBM SPSS version 23 for the statistical analyses. To analyse differences in the HJHS between VWD and HA we used negative binomial regression analysis because of the skewed distribution of the HJHS and the excess of zeroes.(32) To compare the HAL total and sub-scores between VWD and HA we used the Mann-Whitney U (MWU) test. To analyse differences in the cumulative number of joint bleeds, radiological joint changes and limitations in activities between VWD and HA we used logistic regression with the cumulative number of joint bleeds >5, PS >3 and total HAL score <95 as dependent variables and diagnosis as independent variable with VWD as reference category.

We performed multivariable analysis to adjust for age on all outcome parameters and to correct for VWF inhibitors in the analysis of the primary endpoint. We did not account for the use of prophylaxis in the analyses to reflect joint outcome in current clinical practice. Rate ratios and odds ratios (RR and OR) are presented with 95% confidence intervals.

We considered missing data (Figure 1) as missing completely at random and did not use imputation methods. X-ray data were missing from a large proportion of HA patients, because only X-rays performed within 2.5 years before or after assessment of the HJHS were included.(17;23) We performed sensitivity analysis to explore differences in joint status (HJHS) between HA patients with and without available PS.

A planned subgroup analysis was performed to explore differences in HJHS, HAL and PS between the patients with type 3 VWD and moderate or severe HA. Within the VWD patients we explored whether very low VWF activity <5 IU/dL or FVIII levels <10 IU/dL were associated with worse HJHS scores.

RESULTS

Baseline characteristics and medical file data

In total 146 patients with a history of verified joint bleeds were included in the analyses (Figure 1). The study cohort consisted of 48 patients with VWD (38% with historically lowest VWF activity <5

IU/dL, 46% with historically lowest FVIII levels <10 IU/dL), 39 patients with moderate HA and 59 patients with severe HA. The baseline characteristics of these patients are depicted in Table 1. The patients with VWD were older during joint assessment compared to those with HA (median age 47 in VWD vs. 39 in moderate HA vs. 25 years in severe HA). The VWD cohort included 40% females and 8 type 1, 21 type 2 and 19 type 3 VWD patients. The type 2 VWD patients mainly had subtype 2A (n=15) or 2B (n=5) (Table 1). A large majority of the severe HA patients used prophylaxis (85%) and home treatment with clotting factor concentrates, in contrast to the VWD and moderate HA patients.

The joint outcome data are summarized in Table 2 and 4. Overall, a significantly smaller proportion of VWD patients had a history of more than five joint bleeds in the same joint (52%) compared to both moderate and severe HA patients, independent of age differences (77% and 98% respectively; OR 0.2[0.1-0.7] and 0.1[0.1-0.4] compared to VWD). Orthopaedic surgery because of arthropathy after joint bleeds took place in approximately one in five patients across all three patient groups. The first joint bleed occurred at a significantly higher age in VWD compared to HA (median age 10 vs. 4 vs. 2 years, p<0.01 compared to both moderate and severe HA, respectively).

Primary outcome parameter: joint health at physical examination and occurrence of arthropathy

HJHS results were available in 47 VWD, 32 moderate and 58 severe HA patients with verified joint bleeds (Figure 2). Table 3 shows the results of the multivariable analyses. Joint health was comparable between the patients with VWD and those with moderate HA (median HJHS 5 vs. 6; age adjusted RR 0.9[0.5-1.4]). Patients with VWD scored better on the HJHS than the younger and more intensively treated severe HA patients (median HJHS 5 vs. 9; age adjusted RR 1.8[1.1-2.9]). This difference hardly changed after correction for the three VWF inhibitor patients (Table 3).

Secondary outcome parameter: radiologic joint changes

X-ray Pettersson scores (PS) were available from 115 joints of 46 patients with VWD, 34 joints of 10 patients with moderate HA and 187 joints of 40 patients with severe HA (Table 4). Sensitivity analysis demonstrated that the moderate and severe HA patients with and without available X-rays had

comparable HJHS scores (age adjusted RR 0.9[0.4-2.4] and 1.3[0.7-2.3], respectively). Patients with VWD less often had arthropathy on X-ray (PS >3 of at least one joint) compared to those with severe HA (26% vs. 68%, age adjusted OR 0.1[0.0-0.3]), particularly in the ankles (Table 4). In contrast, arthropathy on X-ray after verified joint bleeds was observed in a similar proportion of patients with VWD and moderate HA (Table 3A). A PS >3 was strongly associated with a history of > 5 joint bleeds across all patient groups; only one VWD patient and none of the HA patients had a PS >3 and a history of 5 or less joint bleeds.

Secondary outcome parameter: functional impact of arthropathy

HAL results were available from 48 VWD, 35 moderate and 46 severe HA patients with verified joint bleeds and are depicted in Table 2. Self-reported limitations in activities, according to the HAL total score, did not differ between the patients with VWD and moderate HA, nor between VWD and severe HA patients (p=0.14 and 0.09, respectively). This similarity in the HAL total scores occurred independent of age differences (Table 3).

Subgroup analyses

The results of the 19 included type 3 VWD patients are provided in Table 2. More than five joint bleeds in the same joint occurred in 84% of them, a proportion comparable to the moderate and severe HA patients (77% and 98% respectively). The first diagnosed joint bleed occurred later in type 3 VWD, compared to severe and moderate HA patients (median age at first joint bleed 9 vs. 2 vs. 4 years respectively; statistical significance only reached between type 3 VWD and severe HA).

The HJHS of patients with type 3 VWD appeared to be comparable to the young adults with severe HA (median HJHS 14 vs. 9; age adjusted RR 1.1[0.6-2.0]) and worse compared to moderate HA (median HJHS 14 vs. 6; age adjusted RR 0.6[0.3-1.0])(Figure 2). The use of prophylaxis was as often associated with arthropathy in type 3 VWD as in severe HA patients (age adjusted OR 1.8[0.5-6.6], Table 2).

Similar to the results in the whole cohort, there was a trend towards less arthropathy on X-ray in type 3 VWD compared to severe HA (PS >3: 47% vs. 68%; age adjusted OR 0.3[0.1-1.1]). In contrast, PS >3 appeared to occur as frequent in type 3 VWD as in moderate HA patients with verified joint bleeds (PS >3: 47% vs. 50%; age adjusted OR 1.0[0.2-5.2]). Type 3 VWD patients appeared to have radiological joint damage most often, as shown in Table 4. Due to the small numbers no statistical analyses were performed at joint level.

Type 3 VWD patients reported more limitations in activities compared to those with moderate or severe HA (HAL total score: 77 vs. 95 and 95, p=0.03 and p=0.01, respectively).

Within the whole group of VWD patients with a history of joint bleeds, FVIII levels showed a stronger association with joint status than VWF levels: a very low VWF activity <5 IU/dL had no impact on HJHS scores (median HJHS 4 vs. 5, p=0.97). But a very low FVIII level <10 IU/dL was associated with worse joint outcome (median HJHS 3 vs. 13, p=0.02).

DISCUSSION

Principal findings

In this post-hoc analysis we analysed the results of three cross-sectional studies on long-term joint outcome after verified joint bleeds in adults with VWD (VWF activity ≤30 IU/dL) and moderate and severe HA. Joint health was comparable between patients with VWD and moderate HA, despite fewer joint bleeds and a later onset of joint bleeding in VWD. Joint health at physical examination and on X-ray in VWD patients was only slightly better than in intensively treated young adults with severe HA. Joint outcome after verified joint bleeds in type 3 VWD patients appeared worse than in moderate HA, more comparable to intensively treated young adults with severe HA. Self-reported limitations in activities were similar across VWD and both moderate and severe HA patients.

Strengths and limitations

The strength of this study is that we compared impact of joint bleeds in patients with VWD and HA on all three domains of the WHO's ICF standard.(28) We only included patients with a verified history of joint bleeds, which is estimated to occur in approximately 10% of the WiN cohort.(4) Therefore, the results of our VWD patients cannot be generalized to all VWD patients, but only those with previously documented joint bleeds. Furthermore, our definition of 'verified joint bleeds' is limited: only patients with joint bleeds clinically verified by physicians were included. This may have led to differential misclassification of especially minor bleeds in VWD compared to HA patients.

The main limitation is the use of data from prior studies, which prevented matching for age and year of birth. This is a relevant limitation since arthropathy progresses with increasing age.(33) The differences in joint outcome between VWD and severe HA are relatively small, which may be due to the younger age and more intensive treatment of the included severe HA patients. Adjusting for age in the analyses could only partially deal with this confounder. We were also unable to adjust for BMI because this was not recorded in the haemophilia cohorts. Post-hoc analysis may give rise to information bias. However, structural differences in PS and HJHS rating are unlikely, since agreement between the two radiologists was established as high and a single physiotherapist (PK) performed all HJHS assessments with excellent intra-rater reliability.(16;26;30)

Strengths & limitations in relation to other studies

Joint outcome after joint bleeds has not been compared before between VWD and HA patients. Only one prior study compared joint outcome between unselected patients with type 3 VWD and moderate HA. In this study joint ROM loss was comparable between 100 type 3 VWD and 1815 moderate HA subjects.(34) ROM, however is only one aspect of joint function, and characterized by large variation and thus provides insufficient information on functioning.(28;35) We used joint health (HJHS), X-rays (PS) and activity/participation levels (HAL), which all are more specific instruments as well as validated to assess joint outcome in a broad sense. The observation of worse joint outcome in type 3 VWD, comparable to severe rather than moderate HA, can be explained by the selection of

VWD patients with verified joint bleeds in the current analyses. Furthermore, the HJHS cut-off of 10 for arthropathy was based on a previous publication on haemophilia patients with a median age of 24, whereas the median age of the VWD patient in the current cohort was 47 years.(17)

As in HA, a low FVIII level is an important determinant for joint bleeding in VWD and FVIII <10 IU/dL at diagnosis is predictive for arthropathy.(3;13) Still, the cumulative number of joint bleeds is the most important predictor for arthropathy in both VWD and haemophilia.(10;13;36) In the current study, the number of joint bleeds was categorized with a cut-off of five as more detailed information could not be obtained for all patients with a history of joint bleeding.

Possible explanations for the findings

Compared to HA, the degree of arthropathy after joint bleeds at physical examination is remarkably similar in VWD, despite fewer joint bleeds and a later onset of joint bleeding. This finding could be explained by delayed diagnosis and inadequate recognition of joint bleeding in VWD. Another possible explanation is an increased tendency to develop arthropathy caused by a lack of VWF in addition to low FVIII levels. However, a novel finding in this study is that very low VWF activity does not seem to be associated with worse joint outcome independent of a low FVIII level.

The cumulative number of joint bleeds is a major predictor of arthropathy and young cartilage is more vulnerable to blood induced damage.(37;38) Age related knee osteoarthritis may have contributed to the radiologic knee joint changes in the older VWD cohort compared to severe HA, since its incidence increases with age, especially over 50 years of age.(39) However, in our prior nested case control study, VWD patients without a history of verified joint bleeds showed less arthropathy than VWD patients with a joint bleed history, even with matching for age and VWD severity.(13)

The similarity in self-reported limitations in activities between VWD and HA patients could partly be explained by the older age of the VWD patients. Furthermore, it is unknown whether other bleeding symptoms seen in VWD, such as severe nose bleeds, can impact the HAL score. Additionally, a different perspective of VWD patients on their disease-related disabilities compared to HA could be

responsible for this similarity in HAL scores. Differences in self-reported functional abilities in HA only occur between patient groups with large differences in joint health, suggesting that these patients have adapted well to their chronic disease.(14;40;41)

Clinical implications

The current findings clearly show that arthropathy with functional implications occurs in VWD patients after joint bleeds, comparable to haemophilia, especially in type 3 VWD patients. Therefore, the same measurement instruments can be used to assess arthropathy. Importantly, the prevention of arthropathy should also be a treatment goal in VWD patients presenting with recurrent joint bleeds. In addition, VWD patients with arthropathy probably benefit from multidisciplinary care, as advocated by the WFH in haemophilia.(7) Prophylaxis with VWF/FVIII concentrates has proven to be highly effective in reducing the number of joint bleeds in VWD.(42;43) The association of athropathy with the use of clotting factor prophylaxis in type 3 VWD reflects its prescription to the patients with most severe bleeding, but also the inability of secondary prophylaxis to prevent arthropathy. Based on our current and prior study results, VWD patients and their physicians should be aware of joint bleeding, especially in VWD patients with FVIII <10 IU/dL, and consider early treatment.(4;13) The finding that joint outcome after joint bleeds seems worse in type 3 VWD than in moderate HA and is more comparable to intensively treated severe HA patients, suggests that these VWD patients are candidates for prophylaxis with clotting factor concentrates in case of recurrent joint bleeds.

Future research

Our conclusion that outcome after verified joint bleeds in VWD is similar to moderate HA needs confirmation in future studies. To eliminate confounding by age and treatment intensity, future studies should compare joint outcome in age- and birth year matched patients with VWD and HA, preferably with prospective follow up. Furthermore, the relationship between arthropathy and age-related osteoarthritis could be subject of further study. Variations in other coagulation proteins than

FVIII possibly contribute to the phenotypic variation of arthropathy in severe HA patients.(44) Analyses on the occurrence of arthropathy in VWD versus haemophilia, adjusted for the exact number and severity of joint bleeds at joint level might elucidate a possible role for low VWF, superposed on low FVIII, in the development of blood-induced arthropathy. Finally, it remains to be determined whether more intensive treatment of joint bleeds and/or prophylaxis can prevent limitations in activities, preserve quality of life and social participation in VWD patients with joint bleeds.

In conclusion, we show that outcome after joint bleeds in VWD is similar to moderate HA independent of age differences, despite fewer reported joint bleeds and later onset of joint bleeding in VWD. Type 3 VWD patients have worst joint outcome, comparable to younger intensively treated severe HA patients. Furthermore, VWD patients report similar limitations in activities after joint bleeds as both moderate HA patients and young adults with severe HA. The clinical implication is that patients and physicians should be aware of joint bleeds in VWD and that proper treatment is necessary to prevent arthropathy, similar to haemophilia. More research is needed to identify those patients at the highest risk for developing arthropathy.

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Table 1: Baseline characteristics

	VWD type 1	**VWD type 2†**	**VWD type 3**	**Moderate HA**	**Severe HA**
Number of patients	8	21	19	39	59
Age (median, IQR)	58 (35-65)	45 (33-64)	40 (21-58)	39 (24-49)	25 (20-30)
Sex (n, % male)	7 (88%)	16 (76%)	6 (32%)	39 (100%)	59 (100%)
Age at diagnosis (yrs, median IQR)	26 (1-38)	3 (0-18)	1 (0-4)	2 (0.5-7)	<1 (0-1)
FVIII (IU/dL, median IQR)¥	33 (14-39)	48 (34-53)	2 (1-4)	3 (2-4)	0 (0-0)
VWF:RCo (IU/dL, median IQR)¥	4 (4-21)	9 (6-11)	7 (2-7)	81 (64-104)	78 (65-98)
Annual CFC (U FVIII/kg/yr, median, IQR)*	3 (0-42)	59 (0-103)	253 (30-840)	219 (64-462)	1995 (1491-3110)
Age first treatment (yrs, median, IQR)	34 (6-40)	15 (4-35)	4 (2-10)	4 (0-39)	1 (0-4)
Home treatment with clotting factor	2 (25%)	5 (24%)	14 (74%)	22 (56%)	58 (98%)
History of prophylaxis#	1 (13%)	1 (5%)	11 (58%)	4 (10%)	50 (85%)
Inhibitor (current or past)	0	0	3 (16%)	1 (3%)‡	8 (14%)‡

Table 1 legend: Abbreviations: IQR: interquartile range; VWD: von Willebrand disease; FVIII: clotting factor VIII; HA: haemophilia A; VWF:RCo: Von Willebrand factor ristocetin cofactor activity; CFC: clotting factor consumption.

†VWD type 2 subtypes: 2A n=15, 2B n=5, 2N n=1, 2M n=0; ¥historically lowest levels; *Data on CFC use available: type 1 VWD n=8, type 2 VWD n=21, type 3 VWD n=15 (all Haemate P®, dose based of FVIII), moderate HA n=39, severe HA n=56; #defined as any history of at least 1 regular clotting factor concentrate infusion per week for at least 45 consecutive weeks; §11/13 because of joint bleeds including two patients still on prophylaxis at the time of the study; ‡Only low titer inhibitors of 0.3-0.6 Bethesda Units or >0.6 BU without decreased FVIII recovery (Supplemental material).

Table 2: Joint outcome according to diagnosis

	VWD type 1	VWD type 2†	VWD type 3	Moderate HA	Severe HA
Number of patients	8	21	19	39	59
>5 joint bleeds in the same joint* (n, %)	4¶ (50%)	5 (24%)	16 (84%)	30 (77%)	58 (98%)
Elbow§ 1-5	3 (38%)	7 (33%)	6 (32%)	20 (51%)	19 (32%)
>5	0 (0%)	0 (0%)	2 (11%)	9 (23%)	35 (59%)
Knee§ 1-5	5 (63%)	17 (81%)	9 (47%)	23 (59%)	41 (70%)
>5	0 (0%)	2 (10%)	5 (26%)	14 (36%)	20 (34%)
Ankle§ 1-5	3 (38%)	10 (48%)	5 (26%)	20 (51%)	14 (24%)
>5	3 (38%)	3 (14%)	13 (68%)	13 (33%)	44 (75%)
Age first JB (median, IQR)**	19 (9-38)	14 (8-42)	9 (4-11)	4 (3-9)	2 (1-3)
Orthopedic surgery# (n, %)	1 (13%)	2 (10%)	8 (42%)	12 (18%)	13 (22%)
HJHS total score‡ (median, IQR)	6 (0.5-13)	2.5 (1-5)	14 (3-21)	6 (0-12)	9 (3-19)
HJHS≥10‡	3 (38%)	4 (19%)	12 (63%)	9 (23%)	28 (48%)
PS >3 in at least one joint (n/n, %)¥	1 (13%)	2 (10%)	9 (47%)	5/10 (50%)	27/40 (68%)
Arthropathy despite prophylaxis (%)‡	1 (13%)	0 (0%)	11 (58%)	3 (8%)	37 (63%)
HAL Total score‡‡ (median, IQR)	85 (69-99)	92 (69-100)	77 (50-95)	95 (81-100)	95 (83-99)
HAL Total <95 (n/total, %)	6 (75%)	12 (57%)	14/19 (74%)	17/35 (49%)	22/46 (48%)

Table 2 legend: Abbreviations: Cum. no.: cumulative number; HA: haemophilia A; JB joint bleeds; HJHS Haemophilia Joint Health Score; IQR: interquartile range; HAL: Haemophilia Activities List.

†VWD type 2 subtypes: 2A n=15, 2B n=5, 2N n=1, 2M n=0; *According to the maximum number of joint bleeds per joint (ankles, knees or elbows); ¶includes one patient with >5 joint bleeds in hand joints due to boxing (this patient also had 1-5 JB in several large joints); §according to the maximum number of joint bleeds in left and/or right joint (not added); **Date age 1th JB available: VWD n=48, moderate HA n=33, severe HA n=54; #Because of arthropathy after joint bleeds; ‡Arthropathy defined as a HJHS ≥10 or PS >3 of one or more joints, prophylaxis defined as any history of at least 1

regular clotting factor concentrate infusion per week for at least 45 consecutive weeks;‡‡n=data available see Figure 1; ¥Arthropathy on X-ray, specified according to joint in Table 4.

Table 3A and B: Age adjusted comparison of arthropathy

A. VON WILLEBRAND DISEASE COMPARED TO MODERATE HAEMOPHILIA A			
	Multivariable regression§		
	Negative binomial regression analyses		
Dependent variable	**Rate Ratio¥**	**95% CI**	**p-value**
HJHS	0.9	0.5-1.4	0.60
HJHS corrected for VWF inhibitors	1.0	0.6-1.6	1.0
	Logistic regression analyses		
	Odds Ratio‡	**95% CI**	**p-value**
Cum no. JB >5 overall	0.2	0.1-0.7	<0.01
HAL <95	1.7	0.7-4.5	0.25
PS >3	0.3	0.1-1.4	0.13

B. VON WILLEBRAND DISEASE COMPARED TO SEVERE HAEMOPHILIA A			
	Multivariable regression§		
	Negative binomial regression analyses		
	Rate Ratio¥	**95% CI**	**p-value**
HJHS	1.8	1.1-2.9	0.02
HJHS corrected for VWF inhibitors	2.1	1.3-3.5	<0.01
	Logistic regression analyses		
	Odds Ratio‡	**95% CI**	**p-value**
Cum no. JB >5 overall	0.02	0.002-0.1	<0.01
HAL <95	1.3	0.5-3.5	0.63
PS >3#	0.1	0.03-0.3	<0.01

Table 3A and B legend: Abbreviations: CI: 95% confidence interval; RR: rate ratio; OR: odds ratio; HJHS: Heamophilia Joint Health Score; Cum no. JB: cumulative number of joint bleeds in at least one joint; HAL: Heamophilia Activities List; PS: Pettersson score (X-ray score of ankles, elbows and knees). §all analyses are adjusted for age and with VWD as the reference category; ¥The rate ratio indicates that, as compared to VWD, the HA patients had on average RR times more (of less if RR <1) HJHS points, independent of age differences and ..; ‡The odds ratio indicates that the chance (odds) of VWD patients to have functional limitations or … is OR times higher (or lower if OR <1) than the HA patients, independent of age differences; #arthropathy on X-ray of at least one individual joint.

Table 4: Arthropathy on X-rays of joints with prior bleeds

	VWD	Moderate HA	Severe HA	Type 3 VWD
Knees PS >3/total* (%) Knees JB >5/total (%)	5/46 (11%) 8/96 (8%)	0/10 (0%) 16/78 (21%)	7/56 (13%) 27/118 (23%)	3/10 (30%) 6/38 (16%)
Ankles PS >3/total* (%) Ankles JB >5/total (%)	13/52 (25%) 30/96 (31%)	3/13 (23%) 20/78 (26%)	32/73 (44%) 65/118 (55%)	10/20 (50%) 21/38 (55%)
Elbows PS >3/total* (%) Elbows JB >5/total	3/17 (18%) 3/96 (3%)	6/11 (55%) 12/78 (15%)	11/58 (19%) 44/118 (37%)	3/4 (75%) 3/38 (8%)
Total proportion PS>3 of joints with JB>5 (%)¥	21/41	9/48	50/136	16/30

Table 4 legend: Abbreviations: VWD: Von Willebrand disease; HA: haemophilia A; PS: Pettersson score; JB: joint bleeds; pts: patients.*total is n joints with prior bleeds and an X-ray score available (X-rays were taken from joints with prior bleeds and controls as previously reported(13)); †in the at least one joint; ¥ less X-rays available for analysis in HA compared to VWD.