





Social participation is reduced in type 3 Von Willebrand disease patients and in patients with a severe bleeding phenotype

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Abstract

Introduction: The negative impact of haemophilia on social participation is well established in previous studies, however, the impact of Von Willebrand disease (VWD) on social participation has not been studied.

Aim: To compare the social participation of a large cohort of VWD patients in the Netherlands with the general Dutch population. In addition, to identify factors associated with social participation in VWD.

Methods: Patients participating in the "Willebrand in the Netherlands" study completed an extensive questionnaire on educational level, absenteeism from school or work, and occupational disabilities.

Results: Seven-hundred and eighty-eight VWD patients were included (mean age 38.9 years, 59.5% females), of whom 136 children < 16 years. Adult patients with type 3 VWD more often had a low educational level (52.9%) compared to type 1 (40.2%), type 2 VWD (36.8%) and the general population (36.4%) ($p = .005$). Moreover, in patients aged ≥ 16 years the days lost from school and/or work in the year prior to study

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inclusion differed significantly between the VWD types ($p = .011$). Using negative binomial regression analysis, the occurrence of bleeding episodes requiring treatment in the year preceding study inclusion was significantly associated with the number of days lost from school and/or work among patients aged ≥ 16 years. Multivariable logistic regression analysis showed that a higher total bleeding score, older age and presence of at least one comorbidity were significantly associated with occupational disability in patients aged ≥ 16 years.

Conclusion: Our study shows that social participation was lower in type 3 VWD and VWD patients with a more severe bleeding phenotype.

KEYWORDS

absenteeism, bleeding, cross-sectional studies, educational status, social participation, von Willebrand Diseases

1 | INTRODUCTION

Von Willebrand disease (VWD) is the most common inherited bleeding disorder.¹ Type 1 VWD is caused by a partial quantitative deficiency of Von Willebrand factor (VWF), type 2 by qualitative VWF defects and type 3 by a complete absence of VWF.² VWD is characterized by mucocutaneous bleedings, such as menorrhagia, post-partum haemorrhage, cutaneous bleeding, epistaxis and oral cavity bleeding.^{3,4} While more rare, joint and muscle bleeds and gastrointestinal bleeding can also occur.³ Bleeding is most often mild to moderate, but can be severe.³ The phenotype is heterogenous, but generally depends on VWD type as well as residual plasma VWF and factor VIII (FVIII) activity levels.³

It is well known that the health-related quality of life of adults and children with VWD is lower compared to that of the general population.^{5,6} In addition, 51% of adult patients with bleeding disorders, including haemophilia and VWD, reported that having a bleeding disorder had a negative impact on their school education.⁷ Moreover, a survey among type 3 VWD patients in the United States demonstrated that 40% of patients reported lost days from school and/or work caused by bleeds or other VWD complications. The mean number of days lost amounted to 4.7 days per year.⁸

Studies in patients with severe haemophilia show lower social participation, as patients were less likely to be employed full-time when compared to the general male population (patients aged 31–64 years 50% vs. 73%, respectively; patients aged 16–30 years 34% vs. 52%, respectively). Moreover, 36% of severe haemophilia patients aged 31–64 years reported complete occupational disability, compared to 11% of the general Dutch male population.⁹ However, much less is known about social participation in VWD patients. Although the bleeding disorder is overall milder, it is also more prevalent and occurs in both men and women, with women more prone to bleeding due to the menstrual cycle and child delivery.¹

Therefore, the aim of this study was to evaluate social participation of a large cohort of VWD patients in the Netherlands and to compare this with the general Dutch population. In addition, we aimed to identify factors associated with social participation in VWD patients. Social

participation was defined similarly as in a previous study performed in haemophilia patients in the Netherlands, that is, the ability to participate in work and education.⁹

2 | PATIENTS AND METHODS

2.1 | Participants

Patients with type 1, 2, and 3 VWD from all ages who participated in the “Willebrand in the Netherlands” (WiN) study were included in the current study. The WiN study is a nationwide cross-sectional study among VWD patients in the Netherlands performed between 2007 and 2009.^{3,5} The inclusion criteria of the WiN study were haemorrhagic symptoms or a family history of VWD and historically lowest levels of VWF antigen (VWF:Ag) ≤ 30 IU/ml and/or VWF ristocetin cofactor activity (VWF:RCo) ≤ 30 IU/ml and/or FVIII activity (FVIII:C) ≤ 40 IU/ml (for type 2N VWD patients). Patients with concomitant haemostatic disorders were excluded. Patients who were originally diagnosed with type 3 VWD, were reclassified as type 1 VWD if VWF propeptide was ≥ 0.05 IU/ml and the diagnosis type 3 VWD was maintained if VWF propeptide was < 0.05 IU/ml.^{10,11} The study was approved by the Medical Ethical Committees of all participating centres and written informed consent was obtained from all patients aged 12 years and older and in children younger than 16 years also from their legal representative(s) (i.e., both parents or guardian), according to Dutch guidelines. Patients in whom data on all questions regarding social participation were missing, were excluded from the current study.

2.2 | Assessment tools and definitions

The assessment tools and laboratory measurements utilized in the WiN study have been described in detail previously.^{3,5,6} Participants completed at the time of inclusion an extensive self-administered questionnaire, which contained a self-administered version of the condensed Tosetto bleeding score (BS).^{12,13} In addition, questions on bleeding episodes and treatment of VWD in the year prior to study inclusion,

comorbidities, educational level, absenteeism from school or work, and occupational disability were incorporated into this questionnaire. The Tosetto BS grades 12 different bleeding symptoms based on their frequency and severity on a scale ranging from -1 to 4 points. The total BS results from summing the scores of all 12 items, which can range from -3 to 45.^{3,12} Comorbidity was used as dichotomous variable (at least one comorbidity present or not) and was defined as any disease or condition other than VWD that requires medical attention from a general practitioner or specialist.^{6,14} Patients were asked to report the total number of days lost from school and/or work in the year that preceded the survey and the number of days lost attributed to VWD. Occupational disability and the degree of incapacity for work were self-reported by the patients. In the Netherlands, the degree of incapacity for work is determined by an insurance physician based on the subject's earning capacity. According to article 4(1) of the law on Work and Income in Accordance with Capacity for Work (WIA), complete occupational disability is defined as being only capable of earning at most 20% of earning capacity.¹⁵ We subdivided occupational disability into complete ($\geq 80\%$) and partial ($< 80\%$) disablement according to a previously published study among haemophilia patients.⁹ Patients who reported to be occupationally disabled were additionally asked whether this was completely or partially due to VWD. Furthermore, we classified the highest educational level attained of patients based on the International Standard Classification of Education 2011 (ISCED, 2011),¹⁶ which we aggregated into three levels according to the standard educational format (in Dutch: *Standaard Onderwijsindeling*) 2016: lower, medium, and higher educational level.¹⁷ Lower educational level refers to primary education and lower secondary education, medium educational level to upper secondary education, and higher educational level to bachelor, master, doctoral or equivalent.^{16,17} Data from the general Dutch population in 2008 were provided by the national statistical office, Statistics Netherlands.¹⁸⁻²⁰ Data on complete occupational disability in the general population were based on the number of occupational disability benefits in 2008.

2.3 | Statistical methods

Categorical data are presented as frequencies and percentages. Continuous data are presented as mean and standard deviation if normally distributed and median and interquartile ranges (IQR) if not normally distributed. Chi-squared test was used to compare proportions of categorical data. Not normally distributed continuous data were compared between the different VWD types using the Kruskal-Wallis test. Patients who reported to be completely occupationally disabled ($\geq 80\%$) and patients aged ≥ 65 years were excluded from the analysis of days lost from work, because the age of retirement in the Netherlands was 65 years when the WiN study was performed.

In order to examine the association between total BS and highest educational level attained, logistic regression analysis was performed. For this purpose, highest educational level attained was dichotomized into the levels lower and medium/higher and was used as dependent variable in the logistic regression model. Logistic regression analysis was also performed to assess the association between total BS and

occupational disability (either partial or complete vs. no occupational disability). In these analyses, total BS, age, sex and the presence of at least one comorbidity were included as independent variables. Outcomes of the logistic regression analyses are presented as odds ratio (OR) and 95% confidence interval (CI). Moreover, the total number of days lost from school and/or work in the year preceding study inclusion was used as dependent variable in negative binomial regression analysis, to account for over-dispersion. Total BS, the occurrence of bleeding episodes requiring treatment with desmopressin or factor concentrates in the year prior to study inclusion, sex, age, and comorbidity were used as independent variables. Outcomes of the negative binomial regression analyses are presented as incidence rate ratio (IRR) and 95% CI. Statistical analyses were performed in R version 4.0.3 (2020-10-10), using the packages *foreign* (version 0.8.80), *MASS* (version 7.3.53.1) and *DHARMA* (version 0.4.1).²¹⁻²⁴ A *p*-value below .05 was considered statistically significant.

3 | RESULTS

A total of 834 patients participated in the WiN study, of whom 788 patients were included in the current study. Forty-six patients were excluded because of missing data on social participation. The characteristics of 652 patients aged ≥ 16 years and 136 children aged < 16 years are shown in Table 1. The proportion of patients who reported to have experienced bleeding episodes requiring treatment in the year prior to study inclusion differed significantly between the different VWD types in both age groups ($p = .003$ and $p < .001$ in patients aged < 16 years and ≥ 16 years, respectively) (Table 1). Levels of VWF, FVIII and total BS, stratified by age, VWD type and sex are displayed in Table S1 and Figure S1.

3.1 | Educational level

Figure 1 shows the highest educational level attained in VWD patients aged ≥ 16 years compared to the general population. The distribution of educational level differed significantly between the different VWD types and the general population ($p = .005$). The proportion of patients with a low educational level was higher in type 3 VWD (52.9%) compared to type 1 (40.2%) and type 2 VWD (36.8%) and the general population (36.4%). These results were comparable when we performed this analysis in patients aged ≥ 18 and ≥ 25 years (Tables S2 and S3, respectively).

In multivariable logistic regression analysis with BS, sex, age and comorbidity as independent variables, we found that female sex (OR = 1.60, 95%CI 1.12-2.29) and older age (OR = 1.03, 95%CI 1.01-1.04) were significantly associated with lower educational level (Table S4).

3.2 | Occupational disability

In patients aged ≥ 16 years, the percentage of VWD patients who were completely occupationally disabled ($\geq 80\%$) was 8.4% among

TABLE 1 Patient characteristics

	Children (0–16 years)			Adults (16–99 years)		
	Type 1 (n = 74)	Type 2 (n = 53)	Type 3 (n = 9)	Type 1 (n = 396)	Type 2 (n = 239)	Type 3 (n = 17)
Age (years)	9.0* [6.0–12.8]	6.0* [2.0–10.0]	11.0* [7.0–12.0]	45.0 [34.0–57.0]	46.0 [32.0–59.0]	45.0 [29.0–58.0]
Sex, female (%)	28 (37.8)	23 (43.4)	5 (55.6)	274** (69.2)	131** (54.8)	8** (47.1)
Blood group O (%)	35* (71.4)	16* (48.5)	1* (11.1)	257** (68.5)	108** (49.3)	9** (52.9)
VWF:Ag (IU/ml)	.20** [.09–.31]	.23** [.20–.25]	.00** [.00–.04]	.37** [.23–.53]	.26** [.17–.36]	.00** [.00–.01]
VWF:CB (IU/ml)	.19** [.09–.35]	.06** [.04–.08]	.00** [.00–.02]	.42** [.23–.65]	.08** [.06–.14]	.00** [.00–.00]
VWF:Act (IU/ml)	.22** [.10–.35]	.08** [.02–.09]	.00** [.00–.00]	.45** [.22–.70]	.08** [.04–.17]	.00** [.00–.00]
FVIII:C (IU/ml)	.49** [.26–.63]	.28** [.22–.39]	.02** [.01–.03]	.66** [.48–.87]	.38** [.27–.49]	.01** [.01–.04]
Bleeding score [†]	5** [3–7]	5** [2–10]	18** [11–20]	10** [5–15]	12** [8–17]	23** [16–26]
Comorbidity [‡] (%)	15 (20.3)	11 (21.2)	2 (22.2)	169 (46.0)	89 (39.9)	8 (53.3)
Bleeding requiring treatment [§] (%)	19* (25.7)	23* (43.4)	7* (77.8)	89** (22.5)	100** (41.8)	14** (82.4)

* $p < .05$ between types 1, 2, and 3 VWD. ** $p < .001$ between types 1, 2, and 3 VWD. Continuous variables are presented as median and interquartile ranges.

[†]Total bleeding score can range from -3 (i.e., no spontaneous bleeding symptoms, no bleeding after surgeries, teeth extractions and deliveries) to 37 or 45 (i.e., major bleeding for all symptoms) in males and females, respectively.^{3,12} An abnormal bleeding score is defined as a total bleeding score ≥ 4 in both males and females.³⁰ Higher scores correspond to more severe or frequent bleeding.³

[‡]Comorbidity indicates the presence of at least one comorbidity defined as any disease or condition other than VWD that required medical attention from a general practitioner or specialist.^{6,14}

[§]The occurrence of bleeding episodes requiring treatment with desmopressin or factor concentrates in the year preceding inclusion in the study.

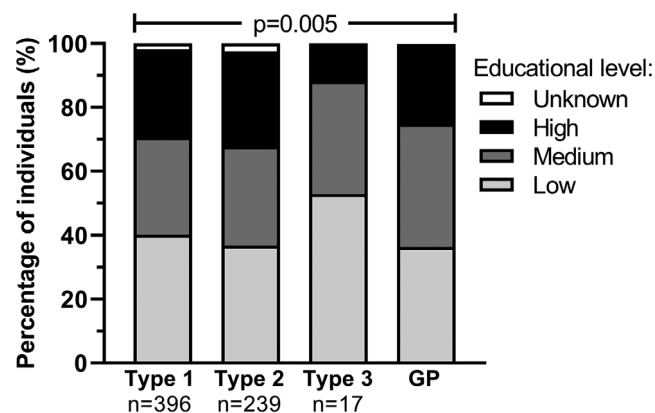


FIGURE 1 Educational level of VWD patients compared to the general Dutch population. Data are presented as percentages. The distribution of educational level among patients aged ≥ 16 years differed significantly between the different VWD types and the general population ($p = .005$). Data considering educational level of the general Dutch population were provided by Statistics Netherlands and collected in 2008.¹⁸ GP = general population

type 1, 7.9% among type 2, and 11.8% among type 3 VWD patients (Table 2) compared to 3.5% of the general Dutch population.^{19,20} The results were comparable when we performed this analysis in patients aged ≥ 18 years (Table S5). In patients who reported occupational disability (either partial or complete), 5.1% of type 1, 10.7% of type 2, and 20.0% of type 3 VWD patients reported that this was

TABLE 2 Occupational disability

Occupational disability	VWD		
	Type 1	Type 2	Type 3
No	325 (85.1)	201 (87.8)	13 (76.5)
<25%	8 (2.1)	3 (1.3)	0 (.0)
25–49%	10 (2.6)	3 (1.3)	2 (11.8)
50–79%	7 (1.8)	4 (1.7)	0 (.0)
$\geq 80\%$	32 (8.4)	18 (7.9)	2 (11.8)

Occupational disability, both complete, partial and not attributed to VWD. Data are presented as frequency and percentages. The proportion of occupational disabled patients (partial and complete) did not differ significantly between the different VWD types ($p = .340$).

completely related to VWD, whereas in 15.3% of type 1, 25.0% of type 2, and 20.0% of type 3 VWD patients this was partly due to VWD.

In multivariable logistic regression analysis with BS (as a continuous variable), sex, age and comorbidity as independent variables, we found that a higher BS (OR = 1.07 for one point increase in total BS, 95%CI 1.04, 1.11), older age (OR = 1.03, 95%CI 1.01–1.05) and the presence of at least one comorbidity (OR = 3.33, 95%CI 1.88, 6.12) were significantly associated with occupational disability (Table S6). When excluding type 3 VWD patients, BS remained significantly associated with occupational disability (OR = 1.08, 95%CI 1.04–1.12).

TABLE 3 Days lost from school and/or work in the year prior to study inclusion

	Children (0–16 years)			Adults (16–99 years)		
	Type 1	Type 2	Type 3	Type 1	Type 2	Type 3
Total days lost from school and/or work	1.0 [.0, 3.0]	1.5 [.0, 4.0]	6.0 [2.3, 9.0]	.0 [.0, 2.0]*	.0 [.0, 4.0]*	4.0 [.0, 10.0]*
Days lost attributed to VWD	.0 [.0, .8]*	.0 [.0, 1.0]*	3.0 [2.0, 4.0]*	.0 [.0, .0]*	.0 [.0, 1.0]*	4.0 [.0, 10.0]*

Data are presented as median and interquartile ranges. * $p < .05$ between types 1, 2, and 3 VWD.

3.3 | Absenteeism from school or work in patients aged 16 years and older

The total number of days lost from school and/or work in the year prior to study inclusion and the number of days lost attributed to VWD among patients aged 16 years and older are shown in Table 3.

In negative binomial regression analysis with BS, sex, age, comorbidity and bleeding requiring treatment as independent variables, we found that the occurrence of bleeding episodes requiring treatment in the year preceding study inclusion was significantly associated with the number of days lost from school and/or work in the year prior to inclusion (IRR = 6.7, 95%CI 3.5–13.2) (Table S7). When excluding type 3 VWD patients, the occurrence of bleeding episodes requiring treatment in the year preceding study inclusion remained significantly associated with the number of days lost from school and/or work (IRR = 6.8, 95%CI 3.5–13.8).

3.4 | Absenteeism in children

The number of days lost from school in the year prior to study inclusion and the number of days lost attributed to VWD in children aged < 16 years are shown in Table 3.

In negative binomial regression analysis with BS, sex, age, comorbidity and bleeding requiring treatment as independent variables, we found that the presence of at least one comorbidity was significantly associated with the number of days lost from school in the year prior to study inclusion (IRR = 3.7, 95%CI 1.7, 9.3) (Table S8).

3.5 | The association between bleeding score items and social participation

In female patients with four points on the BS item of menorrhagia (corresponding to the need of blood transfusion, replacement therapy, desmopressin, or hysterectomy) 57.9% had a low educational level, whereas 42.6% of women with three points on the menorrhagia item (corresponding to dilation and curettage, iron therapy or ablation), and 38.1% of women with two points (corresponding to antifibrinolytics or oral contraceptives). In comparison, among women reporting no menorrhagia this percentage was 34.5% ($p = .015$). Among female patients with one point on the BS item of menorrhagia (corresponding to con-

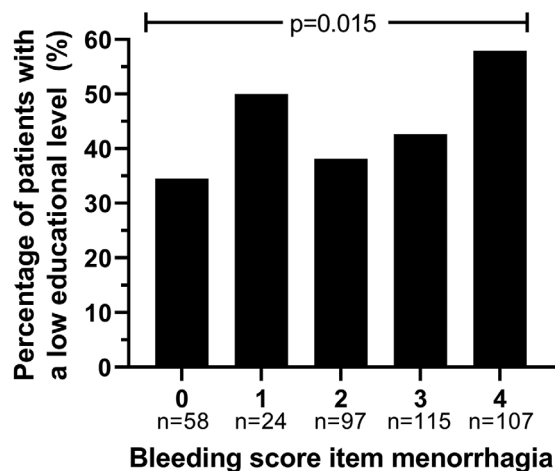


FIGURE 2 Percentage of female VWD patients with a low educational level for different points on the bleeding score item of menorrhagia. Data are presented as percentages. The proportion of female patients with a low educational level differed significantly between the different severities of menorrhagia (as measured by points on the bleeding score item of menorrhagia) ($p = .015$)

sultation only), 50.0% had a low educational level, however, only 24 patients were included in this group (Figure 2).

In total, 84 patients (12.9%) reported to have ever experienced joint bleeds requiring treatment, either spontaneous or traumatic. Among these patients, 26.2% reported complete or partial occupational disability, whereas this was only 12.3% among patients who had never experienced joint bleeds requiring treatment ($p = .001$).

4 | DISCUSSION

In this cross-sectional study, we have examined the social participation of a large cohort of VWD patients in the Netherlands. Type 3 VWD patients more often had a low educational level compared to type 1 and type 2 VWD patients and the general population. We found that each point increase in total BS, older age and the presence of at least one comorbidity were significantly associated with occupational disability. Moreover, in patients aged ≥ 16 years the days lost from school and/or work in the year prior to study inclusion differed significantly between the VWD types, with highest absenteeism in type 3 VWD. We found that the occurrence of bleeding episodes requiring treatment was

significantly associated with the number of days lost from school and/or work in patients aged ≥ 16 years. In children aged < 16 years the presence of at least one comorbidity was significantly associated with the number of days lost from school in the year preceding study inclusion.

Our results suggest that type 3 VWD and a more severe bleeding phenotype in type 1 and type 2 VWD are associated with less social participation, since total BS and bleeding requiring treatment in the year preceding inclusion remained significantly associated with less social participation, even after excluding type 3 VWD patients. In line with our findings, a similar study in haemophilia patients in the Netherlands found that the percentage of completely occupationally disabled patients was 26% for severe haemophilia and 16% for moderate haemophilia, but only 1% for mild hemophilia.⁹ Furthermore, we found that a significantly higher proportion of patients who ever experienced joint bleeds requiring treatment reported occupational disability compared to patients who never experienced joint bleeds requiring treatment. It was described previously that VWD patients who experienced joint bleeds more often had joint pain and joint damage compared to patients who did not report joint bleeds.²⁵ Moreover, VWD patients with joint bleeds and arthropathy reported less social participation compared to patients without arthropathy.²⁶

It is well known that the prevalence of menorrhagia in women with VWD is high.²⁷ In a recent study VWD patients reported that heavy menstrual bleeding negatively impacted their academic lives, that they missed school and were afraid to leave home.²⁸ We found an association between severity of menorrhagia, based on the BS item, and educational level, however, we cannot exclude potential confounding bias. Future research should focus on the impact of menorrhagia on school performance and social participation among female VWD patients. We also found that female sex was significantly associated with lower educational level. However, this could also reflect the distribution of highest educational level attained in the general Dutch population in 2008, as the percentages of females with lower, medium, and higher educational level were 40.2%, 37.2%, and 22.0%, respectively, and among males these were 32.6%, 39.8%, and 26.8%, respectively.¹⁸ In order to eliminate the effect of reduced education opportunities among older females, we performed a sensitivity analysis among patients aged < 50 years, in which female sex and older age were not significantly associated with lower educational level (data not shown).

In total, 28 (20.6%) children reported at least one comorbidity. Most often reported comorbidities among children were asthma, atopic dermatitis and allergies. Our results suggest that among children, the impact of comorbidities on absenteeism from school may be more important than VWD.

This is the largest study to date on the impact of VWD on social participation of a large cohort of well-defined type 1, 2 and 3 VWD patients from all ages. In particular, 80% of patients known with VWD (with historically lowest VWF levels ≤ 30 IU/ml) in the Netherlands participated in this study. Therefore, the risk of selection bias is reduced and our results are generalizable to the total population of VWD patients.

A potential limitation of this study is that data were obtained from 2007 to 2009. Therefore, recent improvements in the management of VWD may have changed the impact of VWD on the social participation of patients.

Another potential limitation of this study is that data on social participation and bleeding episodes in the past were self-reported by the patients. Therefore, due to recall bias, patients may for instance have underreported the number of days lost from work and/or school. However, the misclassification is expected to be nondifferential, that is, unrelated to the BS and the occurrence of bleeding episodes or VWD type.

Furthermore, only type 1 VWD patients with historically lowest VWF levels ≤ 30 IU/ml were included. The clinical bleeding phenotype, and therefore social participation, of type 1 patients might have been more similar to type 2 patients than if we would have also included type 1 patients with VWF levels $< .50$ IU/ml, as is defined in the most recent VWD guideline.²⁹

Finally, only 26 patients (3.3%) with type 3 VWD were included in this study.

5 | CONCLUSION

Our study shows that social participation was lower in type 3 VWD, and VWD patients with a more severe bleeding phenotype. Total BS and bleeding requiring treatment in the year prior to inclusion were important associated factors.

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

AUTHORS CONTRIBUTIONS

E.K. designed the study, performed statistical analysis, interpreted data, and wrote the manuscript. C.K. interpreted data and critically revised the manuscript. J.M., S.S., K.G., K.M., M.C., J.B., K.F., and J.E. designed the study, interpreted data and critically revised the manuscript. F.A. designed the study, interpreted data, revised the statistical analysis, and wrote the manuscript. F.L. conceived of and designed the study, interpreted data, and critically revised the manuscript. All authors gave their consent to the final version of the manuscript.

CONFLICTS OF INTEREST

S.E.M. Schols has received travel grants from Bayer and Takeda, and consultancy grants from Takeda and Novo Nordisk. K.P.M. van Galen received unrestricted research support from CSL Behring and Bayer and speakers fee from Takeda and Amgen. K. Meijer reports speaker

fees from Bayer and Alexion, participation in trial steering committee for Bayer, consulting fees from Uniqure, participation in data monitoring and endpoint adjudication committee for all fees go to the institution. M.H. Crossen has received investigator-initiated research and travel grants over the years from the Netherlands Organisation for Scientific Research (NWO), the Netherlands Organization for Health Research and Development (ZonMw), the Dutch “Innovatiefonds Zorgverzekeraars”, Baxter/Baxalta/Shire, Pfizer, Bayer Schering Pharma, CSL Behring, Sobi Biogen, Novo Nordisk, Novartis and Nordic Pharma, and has served as a steering board member for Roche, Bayer and Novartis. All grants, awards and fees go to the Erasmus MC as institution. J.G. van der Bom has been a teacher on educational activities of Bayer and received consultancy fees from Novo Nordisk, paid to the Leiden University Medical Center. The institution of K. Fijnvandraat has received unrestricted research grants from CSL Behring, Sobi and NovoNordisk and her institution received consultancy fees from Grifols, Takeda, Novo Nordisk and Roche. J. Eikenboom received research support from CSL Behring and he has been a teacher on educational activities of Roche. F. Atiq received the CSL Behring-professor Heimburger Award 2018 and a travel grant from Sobi. F.W.G. Leebeek received research support from CSL Behring and Shire/Takeda for performing the Willebrand in the Netherlands (WiN) study and Sobi and uniQure for studies not related to this manuscript, and is consultant for uniQure, Sobi, Biomarin and Shire/Takeda, of which the fees go to the institution, and has received a travel grant from Sobi. He is also a DSMB member for a study by Roche. None of the other authors has a conflict of interest to declare.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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