Long-term secondary prophylaxis in children, adolescents and young adults with von Willebrand disease

Results of a cohort study

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Summary

In patients with von Willebrand disease (VWD) replacement therapy with factor VIII/von Willebrand (VWF) concentrates is increasingly applied as prophylactic regimen. Since 2000, 82 consecutively enrolled patients with clinically relevant bleeding episodes (spontaneous, peri- or postoperative) were diagnosed with VWD [type 1: 42/82; type 2: 24/82; type 3: 13/82; acquired: 3/82]. In all patients, decision for initiating prophylaxis was based on a bleeding score > 2 prior to diagnosis, concomitant with recurrent bleeds associated with anaemia in patients with on-demand VWD therapy. We report results on secondary prophylactic VWF replacement therapy applied in 32 patients [children n=13; adolescents n=7; adults n=12] with VWD [type 1: 4; type 2: 15; type 3: 13], 15 of which were females, and nine of these at the reproductive period. Eight patients were treated with Humate P® or Wilate® (n=24). Median [min-max] dose [vWF:RCo] was 40 [20–47] IU/kg, 23 patients were given substitution therapy twice weekly, seven patients three times a week, and two children four times per week. Within a 12-month-period haemoglobin concentrations returned to normal values. Median duration of prophylaxis was three years. Recurrent bleeding episodes stopped in 31 of 32 patients, whereas inhibitors developed in one. Following a 12-month observation period the monthly bleeding frequency and the bleeding score was significantly reduced [3 vs. 0.07; 3 vs. 0: p< 0.001], compared to the pre-prophylaxis/pre-diagnostic values. The use of secondary prophylactic VWF replacement therapy is an effective tolerated treatment modality, highly beneficial for patients with VWD, who present with recurrent bleeding events during on-demand therapy.

Keywords

von Willebrand Disease, children, young adults, long-term prophylaxis, inhibitor development

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Introduction

Von Willebrand disease (VWD) is the most common inherited haemostasis disorder in humans with an estimated yearly incidence of 1 per 800–1,000 subjects (1). VWD is characterised by either a quantitative or a qualitative deficiency in von Willebrand factor (VWF) molecule and is divided into three categories; types 1, 2, and 3. Whereas type 1 VWD is characterised by a mild reduction in the amount of a functionally normal VWF, type 2 is characterised by the production of a dysfunctional protein, in which the ability to participate in mediating platelet adhesion, to bind to platelets or to act as a carrier protein for factor VIII in plasma is impaired. Type 3 is characterised by the virtual absence of VWF (2–4). Although most patients with VWD have only mild bleeding symptoms (type 1 VWD being the most common among all types), independent of the type of VWD, some patients with substantially reduced VWF levels may experience severe bleeding symptoms. In these patients, there is a risk of long-term complications such as the development of target joints and consequent arthropathy, recurrent gastrointestinal bleeds and severe anaemia (5–8). Similar to long-term prophylaxis using factor VIII replacement therapy in haemophiliacs, which has been practiced since the 1960s, prophylaxis has also been adopted in certain VWD patients (9–13). Unlike haemophilia, prophylaxis in VWD is not very common, and apart from short-term prophylaxis used in patients with VWD undergoing surgery only few studies have evaluated and discussed the long-term secondary approach (9–18).

The aim of the present study was to investigate the impact of secondary long-term VWF replacement therapy on bleeding frequency and clinical outcome in VWD in a variety of age groups.

Methods

Ethics

The present cohort study of consecutively recruited paediatric and adult patients with VWD was performed in accordance with the ethical standards laid out in a relevant version of the 1964 Declaration of Helsinki and was approved by the Medical Ethics Committee of the University of Münster, Germany.

Inclusion criteria

Caucasian children, adolescents and adults with VWD (all types), who have been admitted for treatment of their first severe bleeding episode to the medical centers in either Duisburg or Münster were enrolled. Patients qualifying for prophylaxis were those who: *i)* were diagnosed as type 3 VWD; *ii)* were diagnosed as type 2 or type 1 VWD and had severe bleeding symptoms prior to diagnosis [bleeding score > 2 points (modified bleeding score 0 to 3 points: 18)]; *iii)* had either of the following: recurrent joint bleeds, gastrointestinal bleeds or clinically significant bleeds during the previous 12 months on-demand therapy leading to iron deficiency and clinically relevant anemia.

Exclusion criteria

Patients with concomitant bleeding disorders, such as haemophilia A or B [≥2 congenital defects: n=3], patients with VWD and known inhibitor development, and patients with acquired VWD were excluded from the study. In addition, patients with VWD and life-threatening diseases or anticipated non-compliance were not enrolled.

Study population

From October 2000 to December 2008, 32 of 82 consecutively enrolled Caucasian patients aged 0.5 to 38 years with a first symptomatic bleeding episode leading to diagnosis of VWD fulfilled the inclusion criteria for long-term secondary prophylactic therapy (▶Fig. 1). From the entire cohort 13 had type 3 VWD, 24 had type 2, and 42 had type 1. Three cases were diagnosed as acquired VWD and thus were excluded. In 29 of 82 patients the treatment was switched from the "on-demand" to a secondary "prophylactic" regimen and in three type 3 VWD children long-term primary prophylaxis was initiated immediately after diagnosis following the first symptomatic severe bleeding onset, e.g. bleeding manifestations in the liver capsule (n=1) and joints (n=2). Prior to initiation of VWF prophylaxis seven out of 32 patients were pretreated with oral iron substitution over a period of 12 to 15 months: however, none of these patients reached age-dependent normal haemoglobin levels prior to VWF prophylaxis start. Adolescents and women in the reproductive period were treated with oral contraceptives before and during the study period.
Clinical data including physical examination and laboratory results were recorded at entry and at patient follow-up visits on a specifically designed Case Report Form (CRF: face to face interview) and entered into a web-based application.

Bleeding score

The bleeding score (BS) was calculated from the clinical symptoms documented in the CRF/database and was translated into the bleeding questionnaire by Rodeghiero et al. 2005 (modified 0 to 3 point) (19). As a further modification of the score only the most severe bleeding episodes were counted instead of listing all bleeding episodes: thus the highest reachable score was 3 and the lowest 0.

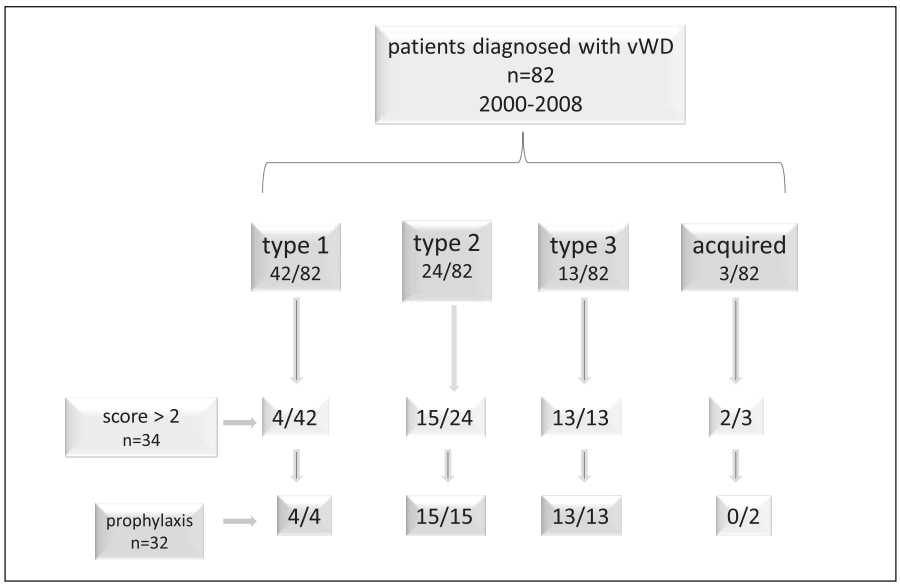

Figure 1: Flow chart: patient enrolment for long-term prophylaxis.

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The BS was *first* determined locally by experienced haematologists at each study site prior to diagnosis of VWD and 12 months after initiation of prophylaxis the BS was retrospectively re-evaluated and further confirmed centrally from the patient database by an independent experienced physician. Apart from joint bleeds, severe bleeding was defined as intracranial, gastrointestinal, spontaneous recurrent bleedings from nose or mouth, menorrhagia leading to clinically relevant anaemia, or bleeding at atypical locations such as intraorbital bleeding.

Prophylactic treatment protocols

For patients presenting with severe bleeding at VWD onset, an intensified treatment protocol was introduced, followed by a long-term prophylactic treatment regimen. All other patients were treated individually two to four times per week after two to three bleeds requiring on-demand factor replacement following diagnosis. For factor replacement therapy all concentrates which were available on the German market were qualified: Unless indicated otherwise patients switched from on-demand to prophylaxis were aimed to receive the same VWF concentrate administered during on-demand therapy. Patients were treated with Humate P® [CSL Behring (FVIII/VWF concentrate), n=8; in one of these eight patients treatment was switched to Willfact®, LFB, (highly purified VWF concentrate with low FVIII content)] or Wilate® [Octapharma (human FVIII/VWF complex), n=24]. Median [min-max] dose administered was 40 [20–47] IU/kg based on ristocetin cofactor activity baseline and 24-hour (h) trough levels (14). In addition, patients' weight and commercially available packages were considered. Based on the individual frequency of bleeding episodes 23 patients were substituted twice weekly, seven were treated three times, and two children four times per week. A 21-year-old female with type 3 VWD additionally carrying the heterozygous factor V G1691A mutation was switched from Humate P® to Willfact® due to factor VIII:C accumulation of > 3 $IUml^{-1}$ during surgery. Since then, factor VIII:C levels in this patient were found within the scheduled range for prophylaxis. Apart from contraindications to long-term secondary prophylaxis with VWF concentrates (see also exclusion criteria; adverse events such as allergic reactions, thromboembolism, myocardial infarction or stroke) duration of prophylaxis was not limited in the present study.

Routine patient follow-up

During the first two years after confirmed diagnosis of VWD routine face to face follow-up was scheduled every three months in symptomatic patients with type 1 and 2 VWD, and at least monthly in patients with ongoing bleeding episodes or type 3 VWD. Depending on the course of the disease, on a patient-based level, after two years follow-up face to face clinical visits were prolonged to six months intervals in on-demand treated patients. All patients who were switched to prophylactic treatment were revisited at least at three months intervals.

Primary outcomes

All patients were monitored for *i)* frequency of bleeding episodes, *ii)* change in the bleeding score (calculated from the database including only the most severe monthly bleeding episode prior to diagnosis and at 12 months following onset of prophylaxis), and *ii)* change in haemoglobin concentrations during the prophylaxis period. These outcomes were assessed prior, during and after a 12-month period of prophylactic long-term replacement therapy.

Secondary outcomes

We also monitored for adverse events, such as allergic reactions, anaphylaxis, or inhibitor development, as well as the need for additional medications such as desmopressin (DDAVP) or tranexamic acid.

Laboratory analysis

VWD was diagnosed using standard laboratory methods including the investigation of multimeric pattern in all patients. The mutation analysis of VWD was done as described elsewhere in selected subjects who gave written consent for genetic analysis (20–22). In patients on secondary prophylaxis blood samples for determination of factor VIII:C activity and VWF levels were drawn 24 h following factor replacement therapy.

Statistics

All statistical analyses were performed using the StatView 5 software package (SAS Institute Inc., Cary, USA). Continuous data were presented as median and minimum-maximum [min-max] values and evaluated by non-parametric statistics using the Wilcoxon-Mann-Whitney U test, Kruskal-Wallis test including the Bonferroni/Dunn as post-hoc test, and the Wilcoxon-signed rank test in cases of dependent samples. A correlation analysis was performed using the Spearman rank correlation test. The degree of agreement beyond chance between first and second reader (bleeding score) was measured with the kappa statistics. P-values < 0.05 were considered significant unless otherwise indicated (Bonferroni/Dunn).

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	Type 3 (n=13) male/female: 4/9	Type 2* (n=15) male/female: 9/6	Type 1 (n=4) male/female: 4/-	P-value
Age at start of prophylaxis (years) median [min-max]	8.9 [0.6–34]	19.8 [8–44]	26 [1.8–46]	0.01 [KW] 2 vs. 3: 0.011 [BD]
Duration of prophylaxis (months): median [min-max]	42 [17–108]	26 [13–48]	15 [14–30]	0.029 [KW] 1vs 3: 0.028 [BD: n.s.]
Bleeding frequency (per year) prior prophylaxis	4 [1–30]	2.3 [1–14]	1 [1–3]	0.024 [KW] BD: n.s.
Bleeding frequency (per months) on prophylaxis	0 [0–2*]	0 [0–0]	0 [0–0]	0.54 [KW]
Bleeding score prior to diagnosis	3 [1–3]	3 [1–3]	3 [3–3]	0.45 [KW]
Bleeding score on prophylaxis	0 [0–1**]	0 [0–0]	0 [0–0]	0.22 [KW]
Factor VIII/VWF concentrates				
Humate P® 1x switch Willfact®	5 → 1	3	-	not calculated
Wilate®	8	12	4	

BD: Bonferroni/Dunn post hoc test; KW: Kruskal-Wallis test; n.s: not significant. *2A (n=8: contraindications for DDAVP); 2B (n=3); 2N (n=2); 2M (n=1); not classified [n=2). **Patient with high responding inhibitor: VWF: 5.3 BU/ml; factor VIIIC: 106 BU/ml.

Table 1: Patients' characteristics (type VWD, gender distribution, age at prophylaxis start, prophylaxis duration, bleeding frequency, bleeding score and factor concentrates administered) are shown.

Results

Patients on prophylaxis

Thirty-three VWD patients (9.5% of type 1, 63% of type 2 and 100% of type 3) were finally treated with a prophylactic regimen. Apart from the prophylaxis criteria given, indications for prophylactic factor replacement therapy in type 1 and type 2 patients were based on contraindications to DDAVP in three children with recurrent bruising/soft tissue bleeding and the presence of a target joint in a male adult. The cohort, 13 children, seven adolescents and 12 young adults, comprises of 15 females, nine of whom within the reproductive age, and 17 males. ►Tables 1 and 2 summarise the characteristics of the patients on long-term prophylaxis. Patients with VWD started long-term secondary prophylaxis with a median age of 15.9 years [type 3: 8.9 years; type 2: 19.8 years, type 1: 26 years] and in

	Type 3 (n=13) male/female: 4/9	Type 2 (n=15) male/female: 9/6	Type 1 (n=4) male/female: 4/-	P-value
HB [g/dl] prior prophylaxis	10.8 [6.7–13.8]	12.8 [11–15]	13.3 [11.5–15]	0.009 [KW] 2 vs. 3: 0.003 [BD]
HB [g/dl] on prophylaxis	13.3 [8.8–15.2]	15 [11.3–17.2]	14.4 [12.2–15.8]	0.10 [KW]
FVIII:C [IU ml^{-1}] prior to prophylaxis: median [min-max]	0.02 [0.0–0.04]	0.42 [0.21–0.5]	0.5 [0.43–0.6]	0.0017 [KW] 1vs. 3: 0.0003 2 vs. 3: 0.001 [BD]
FVIII:C [IU ml^{-1}] on prophylaxis: median [min-max]	0.24 [0.04–0.64]	0.52 [0.29–0.73]	0.77 [0.61–0.79]	0.0028 [KW] 1 vs. 3: 0.0008 2. vs. 3: 0.003 [BD]
VWF:RCO [IU ml^{-1}] prior to prophylaxis	0.02 [0–0.04]	0.18 [0.01–0.4]	0.29 [0.08–0.47]	0.012 [KW] 1 vs. 3: 0.02: [BD: n.s.]
VWF:RCO [IU ml^{-1}] on prophylaxis	0.09 [0–0.77]	0.26 [0.01–0.60]	0.55 [0.21–0.56]	0.022 [KW] 1 vs. 3: 0.3 [BD: n.s.]

BD: Bonferroni/Dunn post hoc test; HB: haemoglobin; KW: Kruskal-Wallis test; n.s: not statistically significant; VWF:RCO: von Willebrand factor ristocetin cofactor activity.

Table 2: Laboratory values prior and post long-term prophylaxis (median values of 12-month observation time point).

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total, 20 out of 32 (64%) started before the age of 18 years. Median [min-max] duration of prophylaxis was three years [1.0–9.0] at the time of data analysis. As expected, differences with respect to the age at start of long-term prophylaxis were observed between the different types of VWD. Similarly differences were observed for the haemoglobin levels prior to prophylaxis, and the factor VIII:C activity levels [prior to and on prophylaxis: 24-h trough levels]. In contrast, no differences were found for bleeding frequency, bleeding scores, haemoglobin on prophylaxis, and ristocetin cofactor activity prior to and on prophylaxis (Kruskal Wallis test with ad hoc Bonferroni/Dunn correction). Apart from a bleeding score > 2, major bleeding symptoms qualifying for prophylaxis were as follows: joint bleeds (n=9), soft tissue bleeding (n=3), recurrent spontaneous haemorrhage from the mouth and nose (children: n=11), gastrointestinal bleeds without association of helicobacter pylori infection (n=2), menorrhagia necessitating blood transfusion and intensive VWF replacement therapy (n=7). In addition, in 12 female adolescents and young adults intravenous iron substitution was necessary prior to long-term prophylaxis. Patients with initial joint bleeds were additionally treated with intensive physiotherapy.

VWD type 3 patients with joint bleedings (descriptive analysis]

Six of 13 patients with VWD type 3 (male: n=2) developed joint bleedings before initiating secondary prophylaxis. Apart from identical low baseline VWF:RCo activities and age at first bleeding onset, FVIII:C levels were lower in children with joint bleeds compared to type 3 children without affected joints (0.05 vs. 0.25 IU/ml^{-1}). In addition, five out of six children with affected joints carried blood group 0 compared with one out of five in children without joint haemorrhage (blood group not done in two out of seven type 3 patients). On long-term prophylaxis, however, children with and without initial joint bleeds did not show any differences with respect to bleeding score, haemoglobin, weekly application intervals and VWF concentrate dosing.

Primary study endpoints

The overall median bleeding frequency calculated as the number of bleeding events per month (primary outcome) after 12 months long-term prophylaxis (►Fig. 2A) was significantly lower compared to those prior to long-term prophylaxis (entire cohort: 3 vs. 0.07; p < 0.001). In addition, the modified bleeding score (median values) determined from the database on the most severe bleeding episode following VWD diagnosis and falling in the 12-month observation period (►Fig. 2B) was significantly reduced, compared to pre-diagnostic values (entire cohort: 3 vs. 0; p <0.001). The degree of agreement beyond chance between first and second reader measured with the kappa statistics was 90.6% (kappa 0.75, 95% confidence interval [CI]: 0.45–1.0; z= 4.96; p< 0.001).

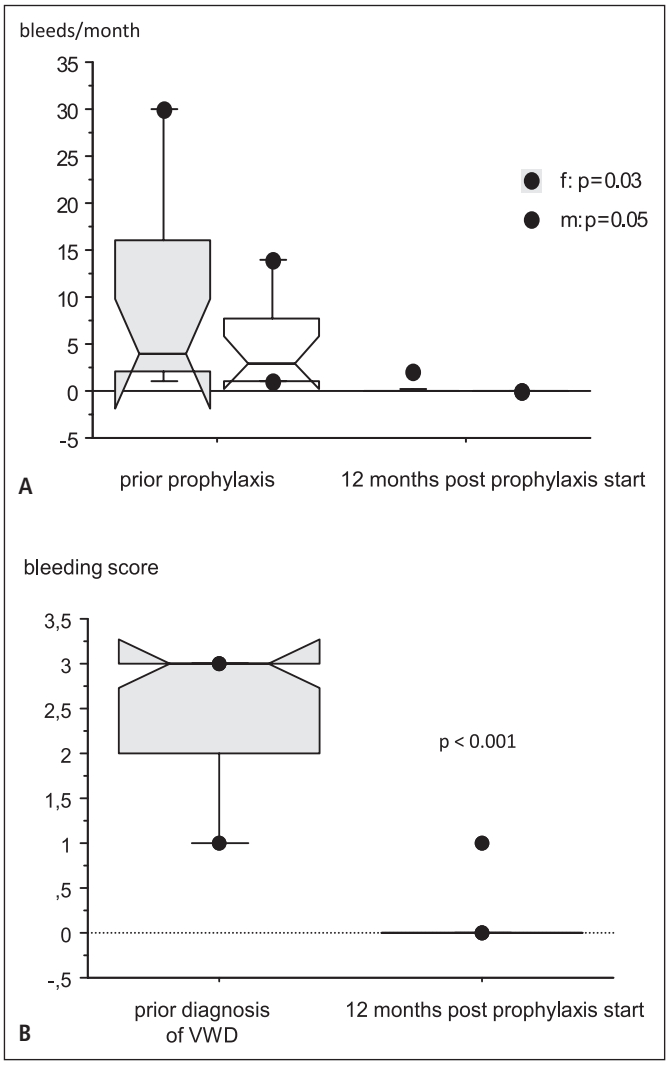

Figure 2: Bleeding frequency (A) and bleeding score (B) before and on prophylaxis. A) Monthly bleeding frequency prior to long-term secondary prophylaxis and at the 12 months observation time point [post] separated by gender [f: female; m=male] is shown. In the box plot 25th, 50th [median values], and 75th percentiles are plotted as horizontal lines, and 10th and 90th percentiles [representing minimum-maximum values] are depicted as points. For both genders, a significant reduction of the monthly bleeding frequency was noted 12 month after start of secondary prophylaxis. B) Modified bleeding score prior to diagnosis of von Willebrand disease compared to the 12 months observation time point (post) is depicted. In the box plot 25th, 50th [median values], and 75th percentiles are plotted as horizontal lines, and 10th and 90th percentiles [representing minimum-maximum values] are depicted as points. At the 12 months observation time a significant reduced bleeding score compared to the onset of the disease is shown.

Accordingly, within a six- to 12-month-period of prophylaxis, the haemoglobin concentrations returned to normal values (►Fig. 3A). In three of the seven patients with haemoglobin levels of 6.7, 7.2 and 9.9 g/dl, respectively, iron substitution was continued during the VWF prophylaxis regimen. In the former three patients haemoglobin increased to 11.2, 9.0 and 14 g/dl, respectively,

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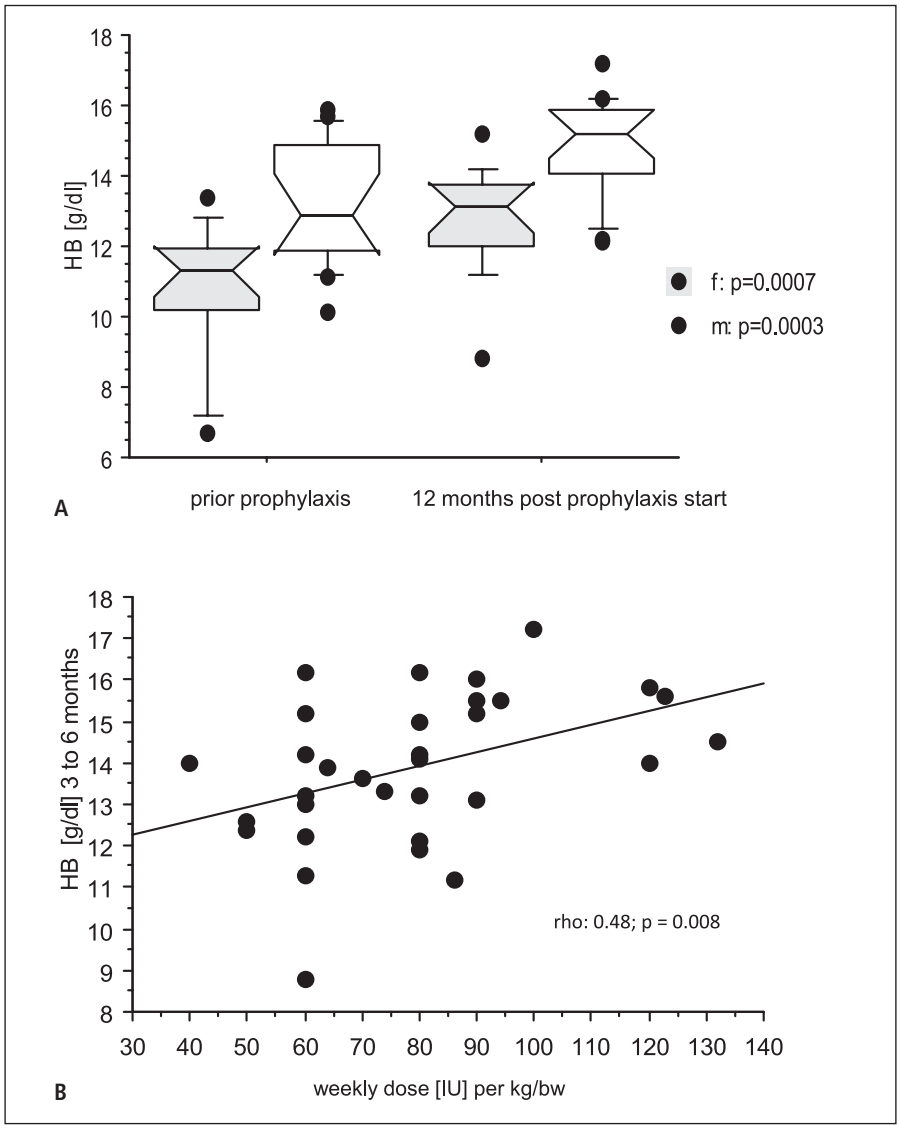

Figure 3: Haemoglobin concentration before and on prophylaxis (A) and correlation between haemoglobin concentration and weekly dose of factor VIII/ von Willebrand factor concentrate (B). A) Course of haemoglobin concentration separated by gender f: female; m=male] prior start of prophylaxis and 6 to 12 months on prophylaxis. In the box plot 25th, 50th [median values], and 75th percentiles are plotted as horizontal lines, and 10th and 90th percentiles [representing minimum-maximum values] are depicted as points. A significant increase was noted for both genders starting 6 to 12 months after onset of secondary prophylaxis. B) Significant positive correlation between weekly dose of factor VIII/von Willebrand factor concentrate [per kg body weight] and haemoglobin concentration [g/dl] is depicted.

after the combined iron/VWF concentrate regimen. ►Figure 3B shows the increase of haemoglobin in association with the weekly dose of VWF concentrate. In addition, as shown in ►Table 2 a statistically non-significant ristocetin cofactor increase was observed in concomitance with significantly higher factor VIII:C levels at the predefined 12-month observation time point.

No statistically significant differences were found between patients treated with Humate P® or Wilate® with respect to 12-month bleeding frequencies (p=0.60), 12-month bleeding score (p=0.40) and haemoglobin concentrations (p=0.40).

Secondary study endpoints

Within the observation period (long-term prophylaxis) recurrent bleeding episodes stopped in 31 of 32 patients. Two patients received additionally tranexamic acid and an inhibitor developed in one of the 32 patients on long-term prophylaxis (3.1%): This seven-year-old female type 3 patient developed a high responding inhibitor towards ristocetin antigen (5.3 BU/ml; modified Bethesda assay) and factor VIIIC (106 BU/ml; modified Bethesda assay) after a 10-day-treatment period with Humate P® (daily dose 60 to 70 IU/kg body weight daily) for a recurrent joint bleeding (left ankle: Nuss score 9: 23). The girl was treated for a total of 48 exposure days prior to inhibitor development. The inhibitor did not respond to immune tolerance therapy (ITT) with Humate P® as well as to a modified haemophilia B immune tolerance protocol. Since 2008 she has been treated two to three times weekly with recombinant factor VIIa in combination with tranexamic acid. No more spontaneous bleeding episodes have occurred under this regimen. Further adverse events such as allergic reactions or anaphylaxis were not observed.

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Discussion

The treatment of a bleeding episode in VWD patients requires correction of *i)* the VWF deficiency, i.e. the defect in primary haemostasis (platelet adhesion), and *ii)* the impaired secondary haemostasis, i.e. to increase the potentially low FVIII:C level. Apart from administration of DDAVP in mild/moderate cases with satisfactory response to this treatment, replacement therapy with plasma-derived factor VIII/VWF products is the therapy of choice for bleeding situations or for short-term prophylaxis during surgery or clinical interventions (1, 8, 21, 24). Starting in the 1960s few centers in Sweden evaluated an approach of secondary prophylaxis in VWD. First results from the same Swedish cohort on long-term prophylaxis were published by Berntorp 2006, and Lethagen 2006 (9, 10). In this study 37 VWD patients (type 3: n=28; type 2: n=6; type 1: n=3) subjected to a prophylaxis regimen at the age of 13 were reported. The main indications for prophylaxis were joint bleeds, nose and mouth bleeds, and menorrhagia or gastrointestinal bleedings. In this cohort prophylaxis was dosed according to FVIII:C levels and the doses administered ranged from 12 to 50 IU/kg one to four times weekly. With this regimen the number of bleeding episodes was reduced from 11 to one per year. Interestingly, using this former regimen one out of 37 patients (2.7%)] developed an inhibitor against VWF. Subsequently to the Swedish cohort, an Italian study reported 11 patients (type 3: n=5; type 2: n=5; type 1; n=1) enrolled in a prophylaxis regimen where the median age at the start of prophylaxis was 34.5 years with a median duration of 201 days. The VWF concentrate doses were calculated based on ristocetin cofactor activity levels (40 IU/kg: three times weekly) (25). Effectiveness in this Italian cohort study was calculated on reduction/resolution of *i)* bleedings, *ii)* numbers of packed red blood cells and *iii)* days of hospitalisation. In the Italian study on prophylaxis the bleeding was stopped in eight of 11 patients, and reduced hospitalisation for blood transfusion was documented in the remaining three patients.

In our cohort study we report on 17 children and adolescents and 12 adult patients with VWD (type 3: n=10; type 2: n=15; type 1: n=4) who were subjected to a secondary long-term prophylaxis and three children with type 3 VWD on primary prophylaxis. Of note, we have to mention here that the initiation of primary prophylaxis in the latter three children was a physician-parent decision, individually based on the severity of the first bleeding episode. In total, 20 out of 32 patients were children and adolescents. Keeping in mind the higher proportion of VWD type 2 patients in our study, similar to each of the Swedish and the Italian cohort, we included all types of VWD and the dose intervals ranged from 1 to 4 times weekly. Apart from the use of a modified bleeding score prior to diagnosis of VWD, bleeding symptoms varied between recurrent nose, mouth, joint bleeds and severe menorrhagia which could not be improved by factor replacement therapy with the need for further therapy, such as administration of DDAVP or tranexamic acid. Overall, prophylaxis was successful and effective, leading to a notable increase of haemoglobin and factor VIII:C in 31 of 32 patients and subsequently to a significant reduction in the monthly bleeding frequency as depicted by a reduced bleeding score at the 12-month observation time point. We believe that the elevated factor VIII:C may have contributed to the improvement of the spontaneous bruising and the joint bleeds. The seven-year-old female who developed a high responding inhibitor (same incidence compared to the Swedish cohort) presented with clinically important breakthrough bleedings while on ITT treatment. It is known that intensive treatment with coagulation factors (high doses over a prolonged period) is associated with an increased risk for inhibitor development in haemophilia A patients as has been reported by the CANAL study (26). Thus, we also speculate that in this girl, the very high dose of FVIII/VWF concentrate administered (60–70 IU/kg/day for 10 days) to this particular patient for her ankle bleed may have contributed to this severe adverse event.

As a limitation of this cohort study we may consider the possible additive effect of oral iron substitution on haemoglobin increase in three of the 32 patients presented here, who concomitantly received oral iron substitution along with replacement therapy during the study period. However, none of these three candidates, who were additionally pretreated for 12 and 14 months prior to prophylaxis, reached haemoglobin levels normal for their age at

What is known about this topic?

- Von Willebrand disease (VWD) is the most common inherited bleeding disease in humans.
- Most patients with VWD have only mild bleeding symptoms; independent of the type of VWD some patients will experience severe bleeding symptoms along with substantially reduced von Willebrand factor (VWF) levels. In these patients, there is a risk of long-term complications such as the development of target joints, recurrent gastrointestinal bleeds and severe anaemia.
- Apart from administration of desmopressin (DDAVP) in mild/moderate cases with satisfactory response to this treatment, replacement therapy with plasma-derived factor VWF/VIII products is the therapy of choice for bleeding situations or for short-term prophylaxis during surgery or clinical interventions.

What does this paper add?

- Unlike haemophilia, secondary prophylaxis in VWD is not very common, and there is only limited data on such treatment options in patients with VWD.
- We report on 29 children and young adults with VWD with no response or contraindications to DDAVP who were subjected to secondary long-term prophylaxis and three children with type 3 VWD on primary prophylaxis.
- Apart from the monthly bleeding frequency we introduced a modified (Rodeghiero-) bleeding score and haemoglobin concentration as outcome measurements.
- We showed that secondary prophylaxis was successful and effective, leading to a notable increase of haemoglobin and factor VIII:C and subsequently to a significant reduction in the monthly bleeding frequency.
- We speculate that the elevated factor VIII:C may have contributed to the improvement of the spontaneous bruising and joint bleeds.

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the beginning of prophylaxis.

Apart from this limitation and the small number of patients, we believe that our study provides significant data and expands on the few studies available in the literature on application of prophylaxis in certain cases of VWD. The use of secondary prophylactic VWF replacement therapy is an effective tolerated treatment modality, highly beneficial for patients with VWD, who present with recurrent bleeding events during on-demand therapy.

Further prospective international studies are necessary to answer open questions (27), such as what is the optimal dosage, dosing intervals, as well as questions on how to prevent inhibitor development. It would be also useful if larger studies could include appropriate controls and if a bleeding questionnaire was designed and validated for follow-up patients under long-term prophylaxis. There is also a further need for establishing strict criteria for application of prophylactic therapy in VWD patients.

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