Association between sports participation, factor VIII levels and bleeding in hemophilia A


Affiliations below.

DOI: 10.1055/a-1983-0594

Conflict of Interest: O.V. has received speakers fees from Novo Nordisk and received research support from Bayer. M.H.C. has received investigator-initiated research grants over the years from the Netherlands Organization for Scientific Research (NWO), the Netherlands Organization for Health Research and Development (ZonMw), the Dutch “Innovatiefonds Zorgverzekeraars,” Bayer/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 and Bayer. All grants, awards, and fees go to the Erasmus MC as institution. M.O.K. received grants from Bayer, Roche and Merck. R.A.A.M. reports grants from Bayer, grants from Shire, grants from Merck Sharpe Dome, grants from CSL Behring, other from Bayer, other from Shire, outside the submitted work. K.F. has received speaker’s fees from Bayer, Baxter/Shire, Sobi/Biogen, CSL Behring, Octapharma, Pfizer, and Novo Nordisk, and has performed consultancy for Bayer, Baxter, Biogen, CSL Behring, Freeline, Novo Nordisk, Pfizer, Roche, and Sobi. She and/or her institution has received research support from Bayer, Pfizer, Baxter/Shire, and Novo Nordisk. The remaining authors declare no competing financial interests. All unrestricted research grants, awards, educational grants, and consultancy fees have been forwarded to the respective institutions.

Trial registration: NTR6769, Netherlands National Trial Register (http://www.trialregister.nl), observational, prospective, single-center study

Abstract:
Background
Little is known how sports participation affects bleeding risk in hemophilia. This study aimed to examine associations between sports participation, factor VIII (FVIII) levels and bleeding in persons with hemophilia A.

Methods
In this observational, prospective, single-center study, persons with hemophilia A who regularly participated in sports were followed for 12 months. The association of patient characteristics, FVIII levels, and type/frequency of sports participation with bleeding were analyzed by repeated time-to-event (RTTE) modelling.

Results
One hundred twelve persons (median age 24 years [IQR: 16 – 34], 49% severe, 49% on prophylaxis) were included. During follow-up, 70 bleeds of which 20 sports-induced were observed. FVIII levels were inversely correlated with the bleeding hazard; a 50% reduction of the baseline bleeding hazard was observed at FVIII levels of 3.1 and a 90% reduction at 28.0 IU/dL. The bleeding hazard did not correlate with sports participation. In addition, severe hemophilia, pre-study annual bleeding rate and presence of arthropathy showed a positive association with the bleeding hazard.

Conclusions
This analysis showed that FVIII levels were an important determinant of the bleeding hazard, but sports participation was not.
This observation most likely reflects the presence of adequate FVIII levels during sports participation in our study. Persons with severe hemophilia A exhibited a higher bleeding hazard at a similar FVIII levels than non-severe, suggesting that the time spent at lower FVIII levels impacts overall bleeding hazard. These data may be used to counsel persons with hemophilia regarding sports participation and the necessity of adequate prophylaxis.

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Supplementary Methods

Data

In this observational, prospective, single-center Sports Participation and Injuries in people with hemophilia (SPRAIN) study from University Medical Center Utrecht (The Netherlands), persons with hemophilia who regularly participated in sports were followed for one year. For the present analysis, data from 13 people with hemophilia B were excluded, as the exposure-effect relation of factor VIII (FVIII) and factor IX concentrates could be different. Injuries and bleeds were assessed proactively, i.e. participants were contacted bi-weekly, and information about nature, involvement of sports participation, mechanism of injury leading to a bleed and, in case of prophylactic treatment, last factor concentrate dose and timing of dosing and event were recorded. Bleeding was defined according to the ISTH definitions. A bleed was classified as occurring during sports, when the bleed developed following a sports injury and required treatment with factor concentrates with or without a consultation with the hemophilia treatment center. Participation in high-risk sports was based on a National Hemophilia Foundation (NHF) score >2. The hemophilia joint health score (HJHS) was assessed at study initiation.

Repeated time-to-event model (RTTE)

An RTTE model is able to characterize the occurrence of time-varying events (bleeding over time) together with event predictors (e.g. factor activity levels and sports activities). In an RTTE model, the
bleeding probability over time is described by the hazard function. First, a median bleeding hazard was estimated which describes the bleeding hazard for a median person using data from the whole population simultaneously. Differences in bleeding hazard between persons were evaluated by inclusion of the inter-individual variability on the hazard (IIV).

Exponential (equation 1), Gompertz (equation 2) and Weibull (equation 3) hazard functions were tested to describe the distribution of time to bleeding. An exponential hazard function describes a constant hazard over time, while Gompertz and Weibull hazard functions can describe increasing or decreasing bleeding hazards over time. The final individual hazard function was described by equation 4.

\[ h(t) = \lambda \] (1)

\[ h(t) = \lambda e^{\gamma t} \] (2)

\[ h(t) = \lambda \gamma (\lambda t)^{\gamma - 1} \] (3)

\[ h_i(t) = \lambda \left( 1 - \frac{\text{FVIII}(t)}{\text{FVIII}(t)+\text{IC}_{50}} \right) e^{\eta i} \] (4)

in which the bleeding hazard of the \(i\)th patient at time \(t\) is described by \(h_i(t)\). \(\lambda\) describes the scale, \(\gamma\) the shape, FVIII the FVIII activity level at time \(t\), \(\text{IC}_{50}\) the FVIII activity level at which 50% of the maximal inhibition on the bleeding hazard occurs and \(\eta_i\) the inter individual variability in bleeding hazard with mean 0 and variance \(\omega^2\).

For persons not receiving a FVIII dose on the day of study initiation, FVIII levels at start of study were calculated based on the previous dose administered prior to study inclusion.

The \(\lambda\) and \(\text{IC}_{50}\) were parameterized to describe the bleeding hazard for a FVIII level of 0.5 and 20 IU/dL following equation 5 and 6.

\[ \lambda = \frac{\lambda_{0.5} \lambda_{20} (0.5 - 20)}{(\lambda_{0.5} - \lambda_{20})} \] (5)

\[ \text{IC}_{50} = \frac{(\lambda_{0.5} - \lambda_{20}) (0.5 - \lambda_{20})}{(\lambda_{0.5} \lambda_{20})} \] (6)

The survival function describes the probability of not having a bleed within a specific time interval. By taking the integral of the hazard the cumulative hazard can be calculated, which is used to calculate the survival function (equation 7).
\[ S_i(t) = e^{-\int_0^t h_i(t) \, dt} \]  

(7)

In which the survival function of the \(i^{th}\) patient within the time interval 0 to \(t\) is described by \(S_i(t)\). In this example 0 is taken as start of the time interval and \(t\) as end of the time interval, \(h_i(t)\) is the individual bleeding hazard.

For some bleeds only the day of the bleeding was known, but not the exact time of the bleeding event. Interval censoring was applied for these bleeds. The probability that these bleeds occurred can be described by the probability that the event occurred between \(t_j\) and \(t_j + 24\)h, following equation 8.

\[ P(t_j < t < t_j + 24) = \left( e^{\int_0^{t_j} h_i(t) \, dt} - \int_0^{t_j} h_i(t) \, dt \right) \left( 1 - e^{-\int_{t_j}^{t_j + 24} h_i(t) \, dt} \right) \]  

(8)

**Covariate analysis**

A full random effects model (FREM) was used to identify covariates with an effect on individual bleeding hazard. This covariate analysis method can characterize the correlation between model parameters - such as the bleeding hazard - and all patient characteristics of interest simultaneously. Herewith, the correlation between the bleeding hazard (including the effect of FVIII levels) and sports activities can be evaluated independently of other patient factors. Furthermore, problems with correlations between covariates and multiplicity are avoided with this method. Covariates are described by the mean and variance, handled as observations into the dataset. The mean is included as fixed effect and the variance as a random effect. The FREM model estimates the random effects of the parameters and covariates and the covariance between those two in a full covariance matrix. The covariance between the parameter and covariates describes the covariate effect. An exponential covariate parameter relationship was used.

During model development we did not evaluate injuries as a covariate, as all bleeds except for 4 spontaneous bleeds, were related to an injury. Furthermore, when an injury occurred without a bleed, the timing of the last concentrate dose was not explicitly recorded.

**Model development and assessment**

The repeated-time to event model was developed in NONMEM (v7.4.1, Icon Development Solutions, Gaithersburg, Maryland, United States). The model was estimated with the Monte Carlo importance sampling assisted by mode a posteriori (IMPMAP) method. R v4.1.1, Pirana v2.9.9. and PsN v5.2.6 were used for data handling, visualization, model management and evaluation.
Supplement Figure 1: Illustration of relationship between factor VIII (FVIII) levels and bleeding hazard for two individuals from the dataset. In the top panels, individual FVIII level over time is plotted, while the bottom panels show the corresponding model predicted individual bleeding hazard. Patient A (10 years, 33 kg, treated with 3x per week 750 IU Elocta) did not experience any bleeds, while patient B (34 years, 73 kg, treated with 3x per week 1000 IU Novoeight) experienced two bleeds (red dots). The bleeding hazard is inversely related to the FVIII levels and is in general higher for patients that experience more bleeds.
**Supplement Figure 2: Kaplan Meier curves of the first, second and third bleed (solid lines)** combined with 2.5\textsuperscript{th} and 97.5\textsuperscript{th} percentile of the model-predicted model predicted Kaplan Meier curves (shaded area, n=500 simulations). The shaded areas cover the Kaplan Meier curves of observed bleeds, demonstrating that the developed model describes the bleeding probability in our data adequately.

**Supplement Table 1: Parameter estimates and their 95% CI of the RTTE model in different patient groups**

<table>
<thead>
<tr>
<th></th>
<th>All patients (n=112)</th>
<th>Prophylaxis patients with available FVIII levels (n=23)</th>
<th>Prophylaxis patients with no available FVIII levels (n=32)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bleeding hazard at FVIII 1 IU/dL (year\textsuperscript{-1})</td>
<td>1.14 (0.56-1.72)</td>
<td>1.49 (0.18-2.8)</td>
<td>1.23 (0.42 – 2.03)</td>
</tr>
<tr>
<td>Bleeding hazard at FVIII 20 IU/dL (year\textsuperscript{-1})</td>
<td>0.20 (0.10-0.30)</td>
<td>0.25 (-0.01 -0.51)</td>
<td>0.43 (0.02 – 0.84)</td>
</tr>
<tr>
<td>Inter-individual variability of bleeding hazard (CV%)</td>
<td>92.4 (48.9-135.9)</td>
<td>89.0 (-1.7-179.7)</td>
<td>79.0 (15.5-142.5)</td>
</tr>
</tbody>
</table>

**References**


Abstract

Background

Little is known how sports participation affects bleeding risk in hemophilia. This study aimed to examine associations between sports participation, factor VIII (FVIII) levels and bleeding in persons with hemophilia A.

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In this observational, prospective, single-center study, persons with hemophilia A who regularly participated in sports were followed for 12 months. The association of patient
characteristics, FVIII levels, and type/frequency of sports participation with bleeding were analyzed by repeated time-to-event (RTTE) modelling.

Results

One hundred twelve persons (median age 24 years [IQR:16 – 34], 49% severe, 49% on prophylaxis) were included. During follow-up, 70 bleeds of which 20 sports-induced were observed. FVIII levels were inversely correlated with the bleeding hazard; a 50% reduction of the baseline bleeding hazard was observed at FVIII levels of 3.1 and a 90% reduction at 28.0 IU/dL. The bleeding hazard did not correlate with sports participation. In addition, severe hemophilia, pre-study annual bleeding rate and presence of arthropathy showed a positive association with the bleeding hazard.

Conclusions

This analysis showed that FVIII levels were an important determinant of the bleeding hazard, but sports participation was not. This observation most likely reflects the presence of adequate FVIII levels during sports participation in our study. Persons with severe hemophilia A exhibited a higher bleeding hazard at a similar FVIII levels than non-severe, suggesting that the time spent at lower FVIII levels impacts overall bleeding hazard. These data may be used to counsel persons with hemophilia regarding sports participation and the necessity of adequate prophylaxis.

Keywords: bleeding, hemophilia A, prophylaxis, repeated time-to-event, sports

Introduction

Persons with hemophilia A suffer from factor VIII (FVIII) deficiency and impaired hemostasis, resulting in spontaneous and/or trauma-related bleeding. Bleeding characteristically occurs in joints and muscles and eventually results in hemophilic arthropathy. Most severe and some moderate persons with hemophilia A are treated
prophylactically with FVIII replacement therapy. For mild and most moderately affected persons, on demand treatment is usually used. Recently, also non-replacement therapies have been introduced.\textsuperscript{1}

Historically, only low impact sports were recommended for persons with hemophilia due to a perceived increased bleeding risk when engaging in high-risk sports activities.\textsuperscript{2} This advice has contributed to poor exercise performance and impaired muscle strength in persons with hemophilia as reported in early studies.\textsuperscript{3–5} The widespread availability of factor concentrates in well-resourced countries and the introduction of prophylaxis has however enhanced the ability for sports participation for all persons with hemophilia. This is of importance as adequate physical activity overall reduces risk of chronic diseases and all-cause mortality.\textsuperscript{6,7} Later studies conducted in settings in which adequate prophylaxis and on demand treatment were available have demonstrated similar sports participation, physical fitness and muscle strength in persons with hemophilia in comparison to the general population.\textsuperscript{8–10} However, whether similar sports participation in persons with hemophilia as in the general population leads to a higher bleeding risk remains unanswered. Presumably, the risk of bleeding during sports participation is dependent on the achieved factor level. Only a few studies have assessed the relationship between bleeding risk and physical activity.\textsuperscript{11,12} Ross et al\textsuperscript{11} observed no impact of athletic participation on joint outcomes. Tiktinsky et al\textsuperscript{12} reported a higher bleeding rate during vigorous exercise in persons with severe hemophilia who were treated on demand. Only Broderick et al\textsuperscript{13} examined the effect of factor levels and sports participation on bleeding risk and reported a moderate relative increase in bleeding risk for vigorous physical activities together with a reduction of bleeding at increasing FVIII levels. This study included only children with severe and moderate hemophilia, leaving a knowledge gap for both adult and mild hemophilia patients.
The association between sports participation, FVIII levels and bleeding hazard can be modeled with a parametric repeated time-to-event (RTTE) model. This technique can characterize the occurrence of repetitive events (bleeding) over time and can be used to examine the association of various patient factors with the bleeding hazard. The aim of this study was to examine the influence of sports participation and FVIII levels on the bleeding hazard in persons with hemophilia A in the current treatment setting in the Netherlands using an RTTE analysis. **Methods**

A detailed method description is presented in the supplementary material.

**Data**

In this observational, prospective, single-center study from University Medical Center Utrecht, persons with hemophilia who participated in sports at least once weekly were followed for 12 months (SPRAIN study). Participants were contacted bi-weekly to enquire about bleeds and injuries, including information on nature, mechanism, involvement of sports participation and details of last factor concentrate administration. Data on prophylactic treatment regimen, body mass index (BMI), presence of arthropathy and pre-study annual bleeding rate (ABR) were extracted from electronic patient files. Physical activity was assessed using a one-week training diary and activity tracker. The sports described were assumed to be constant during the entire study period, with exception of summer and winter recess.

The study was registered in the Dutch Trial register under NTR6769 (www.trialregister.nl). The Medical Ethical Committee approved the study (IRB number: 181-41). Informed consent was obtained from all study participants and data was collected in accordance with the declaration of Helsinki.

**Development of repeated-time-to-event (RTTE) model**
The modelling process is visualized in Figure 1. The probability of bleeding over time was analyzed using an RTTE model, which is a parametric survival method.\textsuperscript{14,15} In the RTTE model, the bleeding probability over time is estimated by the parametric hazard function. Exponential, Gompertz and Weibull hazard functions were evaluated to describe how the hazard varied over time. Inter-individual variability on the overall bleeding hazard was considered.

The effect of FVIII levels on the bleeding hazard was assessed by a maximum inhibition (Imax) model (Step 2 in Figure 1). FVIII level was assumed to be constant for persons treated on demand, and was described by the lowest measured endogenous FVIII level. For persons treated prophylactically with data on FVIII levels available, individual PK parameters were estimated with the Web Accessible Population Pharmacokinetic Service (WAPPS) online tool using Bayesian forecasting.\textsuperscript{18–20} For people lacking information on FVIII levels, individual PK parameters were estimated based on FVIII concentrate, age, bodyweight and blood group using the population PK models applied by WAPPS.\textsuperscript{18}

The association between bleeding and sports participation was evaluated using two different methods. Firstly, sports participation was incorporated as a time-varying covariate (set to 1 or 0 depending on exposure or not) in the data set, and the effect of sports participation on the bleeding hazard was evaluated (Step 3a in Figure 1).

Secondly, a full random effects model (FREM) was used (Step 3b in Figure 1). The FREM characterizes the correlation between the bleeding hazard and all covariates of interest independently.\textsuperscript{21} Examined covariates in the FREM were: BMI, ABR, presence of arthropathy, endogenous FVIII level, sports frequency per month and participation in high-risk sports.\textsuperscript{22}

\textbf{Model development and assessment}
Model building was performed using non-linear mixed effect modelling in NONMEM v7.4.1. Model evaluation was performed based on comparison of the observed and model-simulated Kaplan Meier curves, scientific plausibility of the parameter estimates, their standard error and the objective function value (OFV) via the likelihood ratio test.

Results

Data

Patient and treatment characteristics are presented in Table 1. One hundred and twelve persons with hemophilia A of which 13 children <12 years were included. Fifty-five had severe- (endogenous FVIII <1 IU/dL), 8 moderate- (endogenous FVIII ≥1 and ≤5 IU/dL) and 49 had mild hemophilia (endogenous FVIII >5 IU/dL). In total, around half of the study population (49%) was treated prophylactically with FVIII concentrate, while the others used on demand treatment. One person with moderate hemophilia was treated with prophylaxis and one person with severe hemophilia was treated on demand. FVIII levels were available for 23 (42%) persons on prophylaxis, for the other 32 persons on prophylaxis FVIII levels were unavailable. Sports activities were performed a median of 13 times per month (range: 2 - 33) and 59% participated in high-risk sports. During the follow up period, 167 injuries and 70 bleeds were reported, of which 35 (50%) were joint bleeds and 20 (29%) were sports-induced bleeds. Bleeds were mostly self-diagnosed by study participants, but 25 bleeds (36%) were evaluated by a medical professional.

Development of repeated-time-to-event (RTTE) model

An exponential hazard function described the bleeding data best, indicating a constant bleeding hazard over time. For 18 bleeds (26%, all not sports-induced) the exact time of bleed was unknown therefore interval censoring over the day was applied. The effect of FVIII level on the bleeding hazard was statistically significant (p<0.001) and was described
with an Imax model, showing a higher bleeding hazard at lower FVIII levels (Supplement Figure 1). The final individual hazard function was described by Equation 1.

\[
 h_i(t) = \lambda \left( 1 - \frac{FVIII(t)}{FVIII(t) + IC_{50}} \right) e^{\eta_i} \tag{1}
\]

in which \( h_i(t) \) describes the individual bleeding hazard at time \( t \), \( \lambda \) the bleeding hazard in absence of FVIII, FVIII the FVIII level at time \( t \), \( IC_{50} \) the FVIII level at which 50% of the maximum inhibition on the bleeding hazard occurs and \( \eta \) is a random effect describing the inter individual variability in bleeding hazard.

The parameter estimates of the model are presented in Table 2. The estimated bleeding hazards can be interpreted as the estimated annual bleeding rate when a person has a constant FVIII level. As a result, a median person with a constant FVIII level of 0, 1, 10 or 20 IU/dL will experience 1.5, 1.1, 0.4 or 0.2 bleeds per year, respectively. The estimated bleeding hazards for other FVIII levels are visualized in Figure 2.

Compared to persons with severe hemophilia and no measurable FVIII level, the annual bleeding rate was reduced by 50% at a FVIII level of 3.1 IU/dL, by 75% at a FVIII level of 9.3 IU/dL and by 90% at a FVIII level of 28.0 IU/dL. The inter-individual variability of bleeding hazard was high (coefficient of variation of 92.4%), demonstrating that people with similar FVIII levels presented with a varying number of bleeds. For instance, ABR for persons with a constant FVIII level of 1 IU/dL is median 1.1 per year but the 95% prediction interval was 0.2 – 5.3 per year.

In Supplement Figure 2, the observed Kaplan Meier curves of the first, second and third bleed combined 2.5\(^{th}\) and 97.5\(^{th}\) percentile of the model simulated Kaplan Meier curves are presented. The simulated shaded areas cover the observed Kaplan Meier curves, demonstrating that the model describes the bleeding probability observed in our data adequately. As described in the method section, we used two different strategies to estimate the individual PK parameters since FVIII levels were not available for every person. To
analyze if these different strategies affected the estimates of the RTTE model, we developed RTTE models including only the prophylaxis patients with FVIII levels or only the prophylaxis patients without FVIII levels available. The results showed similar parameters estimates for patients on prophylaxis, indicating that these different methods did not affect the results (Supplement Table 1).

**Sports participation**

During the study, 20 sports-induced bleeds occurred during 14,162 sport exposures. On average subjects presented with a 21% higher FVIII level during sports than their average FVIII levels. The median estimated FVIII level during sports-induced bleeds was 5.9 IU/dL (range: 0 – 20 IU/dL) while these were 11.0 IU/dL (range: 0 - 95 IU/dL) during sports activities without occurrence of bleeding. When the median FVIII levels between sports-induced bleeds and during sport activities were compared for severe, moderate and mild hemophilia patients seperately, the difference was larger for persons with severe hemophilia (4.5 IU/dL during sport induced bleeds and 8.6 IU/dL during sports activities without bleeding) than for for mild hemophilia (14.0 IU/dL during sport induced bleeds and 15.0 IU/dL during sports activities without bleeding).

In the first covariate analysis, sports participation was related to the bleeding hazard. Results showed that during sports participation the bleeding hazard did not change statistically significantly, as inclusion of this covariate did not improve the goodness-of-fit (p>0.05).

The results of the second covariate analysis using the FREM methodology, estimated weak, statistically non-significant, correlations between bleeding hazard and both i) sports frequency per month, and, ii) participation in high-risk sports, as illustrated in Figure 3. In this figure, the 90% confidence interval whiskers cross the solid reference line of a mean participant, indicating that when sports frequency per month and participation in high-risk sports differ from this mean, there is no strong association with the bleeding hazard.
Covariates that showed strong correlations with bleeding hazard and indicated an increased bleeding hazard were: high ABR, presence of arthropathy and severe hemophilia. For instance, pre-existing arthropathy resulted in a median 4.6 times higher bleeding hazard when compared to persons without pre-existing arthropathy. Consequently, persons with pre-existing arthropathy required a 4.6 times higher FVIII level to achieve a similar ABR as persons without pre-existing arthropathy.

Discussion

This study is the first to evaluate the association of sports participation and FVIII levels with bleeding hazard in both severe and non-severe hemophilia A in a wide age range. Bleeding hazard was predominantly determined by FVIII levels. A FVIII level of 3.1 IU/dL was found to reduce the ABR in absence of FVIII by 50%, while a FVIII level of 28.0 IU/dL reduced this baseline ABR by 90%. No association between sports participation and bleeding hazard was observed in our study population, as neither frequency nor intensity of sports participation (low versus high-risk) showed an independent association with bleeding hazard. Other covariates independently associated with the bleeding hazard were: ABR before study inclusion, presence of arthropathy and hemophilia severity.

Possible explanations for observed results

How can we explain the lack of association between sports participation and bleeding hazard? We presume two main reasons may play a role. Firstly, prophylactic treatment is personalized according to an individual’s sports schedule and other physical activities, consciously targeting higher FVIII levels during sports. The median estimated FVIII levels during sports-induced bleeds were lower than the median FVIII levels observed during sports activities in which no bleeding occurred (5.9 vs 11.0 IU/dL), which suggests that higher FVIII levels protected against bleeding during sports activities. Secondly, as our study population regularly participated in sports, increased muscle mass and strength may also have
protected against sports-induced bleeds, as physical fitness and muscle strength resulting from regular sports participation may help prevent bleeding.\textsuperscript{24,25}

In the covariate analysis, additional covariates showed independent associations with the bleeding hazard. As expected, a higher ABR before study inclusion and presence of arthropathy predicted a higher bleeding hazard. Hemophilia severity and thus endogenous FVIII levels were negatively associated with bleeding hazard, indicated a higher bleeding hazard for persons with lower endogenous FVIII levels. This suggests that persons with severe hemophilia have a higher bleeding hazard than persons with non-severe hemophilia when similar FVIII levels are achieved. For example, when a person with severe hemophilia reaches a FVIII level of 20 IU/dL with the use of prophylaxis, his bleeding hazard will be higher at this time point than when a person with mild hemophilia has a FVIII level of 20 IU/dL. This finding seems to contradict the general view that prophylaxis is able to convert severe hemophilia into moderate hemophilia.\textsuperscript{26} However, this study observation may be explained by the fact that persons with non-severe hemophilia solely treated on demand in majority have stable endogenous FVIII levels. Contrastingly, persons with severe hemophilia on prophylaxis experience fluctuating FVIII levels, often returning to FVIII levels under or around 1 IU/dl, not seen in persons with non-severe hemophilia A. These repetitive low FVIII trough levels, seen before administration of prophylaxis are expected to increase the overall bleeding hazard. This observation is in accordance with the observation of Collins et al., which observed that increased time periods spent with FVIII levels $<1$ IU/dL were associated with an overall higher bleeding risk, and emphasizes the importance of FVIII trough levels and/or time spent under a certain FVIII level during prophylactic treatment.\textsuperscript{27}

**Study strengths and limitations**

Strengths of this study include the bi-weekly contact with participants to gather information on bleeding and injuries, minimizing recall bias. Furthermore for this analysis, RTTE
modelling was used, which is a powerful method to describe time-varying events such as bleeding over time and its association with FVIII levels.

Importantly, we underline that study results cannot be directly extrapolated to all persons with hemophilia A, as this study only included persons who regularly participated in sports. This may have introduced selection bias, as persons experiencing many and severe bleeds due to sports participation may have ended sports activities and could therefore not be included in this study. On the other hand, it has been established that the majority (±70%) of Dutch adults and Dutch children with hemophilia play sports. Furthermore, in settings in which FVIII prophylaxis regimens are not consciously adjusted to sports schedules, an association between sports participation, factor levels and bleeding may be easier identified. Our findings may also be limited due to incomplete data on exact FVIII timing and doses, as well as sports activities during the follow up period as the training diary was only completed for a one-week period due to practical considerations, which may be too short and less representative. Importantly, exact details of the last FVIII dose and details of sports participation were recorded for each bleed. During other periods standard FVIII dosing and sports regimens were presumed. Lastly, bleeds were generally self-reported by study participants and only 36% of the bleeds were evaluated by a medical specialist.

Comparison to other studies

In our study, the bleeding hazard for a constant FVIII level of 0.5 IU/dL was estimated to give 1.3 bleeds per year (95%CI: 0.5 – 2.1), which is lower than the 2.8 bleeds per year with a constant FVII level of 0.5 IU/dL estimated by Abrantes et al in a RTTE analysis of the BAY 81-8973 clinical trial data in severe hemophilia. Concomitantly, the IC50 estimate in this current study of 3.1 IU/dL was also lower than the IC50 value of 10.2 IU/dL reported by Abrantes. These differences may be due to the lower overall number of bleeds observed in our study population, caused by differences in intensity of treatment, different evaluations of
bleeding events as well as the inclusion of persons with non-severe hemophilia. Importantly, the study of Abrantes et al\textsuperscript{16} did not include sports participation as a covariate in the analysis. Broderick et al\textsuperscript{13} examined sports participation and bleeding in 104 boys with severe hemophilia and observed a moderate relative increase in the bleeding risk immediately following vigorous physical activities, while we were not able to identify an association between participation in high-risk sports and bleeding hazard. Possibly, this is caused by the differences in statistical power (436 vs 70 bleeds), population (children versus all ages), different statistical methods and/or a different FVIII treatment regimen.

Conclusions and clinical implications

We conclude that in this study, FVIII levels are an important determinant for the bleeding hazard, while sports frequency, participation in high-risk sports and sports participation were not associated with the bleeding hazard. The low number of sports-induced bleeds, complicated analyses of the association between FVIII levels and bleeding, during sports participation. However, based on the association between FVIII levels and bleeding during the entire study, it could be derived that FVIII levels above 28.0 IU/dL decrease the ABR by at least 90\% compared to when no FVIII level is measureable. Furthermore, a higher bleeding hazard was observed for persons with a high ABR or persons with pre-existing arthropathy, suggesting the need for higher FVIII levels. Moreover, in persons with severe hemophilia a higher bleeding hazard was observed than in non-severe hemophilia at similar FVIII levels. Importantly, this finding suggests that lower FVIII levels in between prophylactic infusions impact the overall bleeding hazard. These data provide important information for counselling regarding sports participation and underline the need for adequate prophylaxis as well as adequate targets for replacement and non-replacement therapy.

SUMMARY TABLE
<table>
<thead>
<tr>
<th>What is known on this topic?</th>
<th>• Even today, with modern treatment options available, uncertainty remains regarding bleeding risk during sports activities in hemophilia patients.</th>
</tr>
</thead>
<tbody>
<tr>
<td>What does this paper add?</td>
<td>• This study examined the influence of sports participation and FVIII levels on the bleeding hazard in both severe and non-severe hemophilia A.</td>
</tr>
<tr>
<td></td>
<td>• FVIII levels, presence of arthropathy and previous annual bleeding rate are important determinants for the bleeding hazard, while sports frequency, participation in high-risk sports and sports participation were not.</td>
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<tr>
<td></td>
<td>• In people with severe hemophilia a higher bleeding hazard was observed than in non-severe at similar FVIII levels, suggesting that time spent at lower trough levels presents additional bleeding risk.</td>
</tr>
</tbody>
</table>

**Acknowledgements**

We thank WAPPS-Hemo for estimating the individual pharmacokinetics of the patients in this study.

**Funding**

L.H.B is funded by the OPTI-CLOT/ To-WiN studies and the SYMPHONY consortium. The SYMPHONY consortium aims to orchestrate personalized treatment in people with bleeding.
disorders, and is a unique collaboration between patients, health care professionals and translational & fundamental researchers specialized in inherited bleeding disorders, as well as experts from multiple disciplines. It aims to identify best treatment choice for each individual based on bleeding phenotype. In order to achieve this goal, workpackages have been organized according to three themes e.g. Diagnostics (workpackage 3&4); Treatment (workpackages 5-9) and Fundamental Research (workpackages 10-12). This research received funding from the Netherlands Organization for Scientific Research (NWO) in the framework of the NWA-ORC Call grant agreement NWA.1160.18.038. Principal investigator: Dr. M.H. Cnossen; project coordinator: Dr. S.H. Reitsma.

Beneficiaries of the SYMPHONY consortium: Erasmus University Medical Center-Sophia Children’s Hospital, project leadership and coordination; Sanquin Diagnostics; Sanquin Research; Amsterdam University Medical Centers; University Medical Center Groningen; University Medical Center Utrecht; Leiden University Medical Center; Radboud University Medical Center; Netherlands Society of Hemophilia Patients(NVHP); Netherlands Society for Thrombosis and Hemostasis (NVTH); Bayer B.V., CSL Behring B.V., Swedish Orphan Biovitrum (Belgium) BVBA/SPRL.

**Conflict of Interest**

O.V. has received speakers fees from Novo Nordisk and received research support from Bayer. M.H.C. has received investigator-initiated research grants over the years from the Netherlands Organization 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 and Bayer. All grants, awards, and fees go to the Erasmus MC as institution. M.O.K. received grants from Bayer, Roche and Merck. R.A.A.M. reports grants from Bayer, grants from...
Shire, grants from Merck Sharpe Dome, grants from CSL Behring, other from Bayer, other from Shire, outside the submitted work. K.F. has received speaker’s fees from Bayer, Baxter/Shire, Sobi/Biogen, CSL Behring, Octapharma, Pfizer, and Novo Nordisk, and has performed consultancy for Bayer, Baxter, Biogen, CSL Behring, Freeline, Novo Nordisk, Pfizer, Roche, and Sobi. She and/or her institution has received research support from Bayer, Pfizer, Baxter/Shire, and Novo Nordisk. The remaining authors declare no competing financial interests. All unrestricted research grants, awards, educational grants, and consultancy fees have been forwarded to the respective institutions.

**Literature**


25. Heijnen L. The role of rehabilitation and sports in haemophilia patients with inhibitors. Haemophilia 2008;14:45-51


**Figure 1:** Visual description of the workflow to develop the repeated time-to-event (RTTE) model to evaluate the association between sports participation, FVIII levels and bleeding. In the example equations, $h_i(t)$ describes the individual bleeding hazard at time $t$, $\lambda$ the baseline bleeding hazard, FVIII, FVIII activity level at time $t$, IC$_{50}$ the FVIII activity level at which 50% of the maximum inhibition on the bleeding hazard occurs, ‘sport effect’ describes the change in bleeding hazard during sports and ‘sport’ is equal to 1 during a sports exposure and zero when not participating in sports.

**Figure 2:** Relationship between factor VIII (FVIII) level and estimated annual bleeding rate (ABR). The solid blue line gives the median relation (based on the estimated model parameters) and the shaded area the 95% confidence interval (based on the relative standard errors of the parameter estimates). The IC$_{50}$ and IC$_{90}$ depict the FVIII level at which 50% or 90% of the maximal protective effect occur, respectively. A median patient in this dataset with a constant FVIII level of 3.1 IU/dL will experience 0.75 bleeds per year.

**Figure 3:** Effect of the examined patient characteristics (covariates) on the bleeding hazard. The change in bleeding hazard (dots, point estimate) relative to a patient with mean covariate values is described for the 5th and 95th percentiles of the distribution of the examined covariates. The error bars present the uncertainty around the 5th and 95th percentiles point estimates, given by the 90% confidence interval. The solid line at 1.0 indicates no change in the bleeding hazard relative to a patient with mean covariate values. The mean study patient presented with an annual bleeding rate of 0.8 per year, experienced no
arthropathy, had an endogenous FVIII level of 7.1 IU/dL, did not participate in high-risk sports, played sports 13.6 times per month and had a body mass index of 22.9 kg/m².

Covariates are ranked from covariates with the strongest correlation with bleeding hazard on top (based on point estimates) to no correlation with the bleeding hazard on the bottom.

Table 1: Patient and treatment characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Number (percentage) or median [IQR] (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients</td>
<td>112</td>
</tr>
<tr>
<td>Age (years)</td>
<td>24.1 [16.0 – 33.7] (7.2 - 49.6)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>77.0 [62.8- 85.3] (24.0 - 135.0)</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>22.5 [19.5 – 25.1] (14.2 – 38.5)</td>
</tr>
<tr>
<td>Hemophilia Severity</td>
<td></td>
</tr>
<tr>
<td>Severe (FVIII&lt;1 IU/dL)</td>
<td>55 (49%)</td>
</tr>
<tr>
<td>Moderate (FVIII≥1 and ≤5 IU/dL)</td>
<td>8 (7%)</td>
</tr>
<tr>
<td>Mild (FVIII&gt;5 IU/dL)</td>
<td>49 (44%)</td>
</tr>
<tr>
<td>Endogenous FVIII level non-severe (IU/dL)</td>
<td>15 [10 – 17] (2 – 29.0)</td>
</tr>
<tr>
<td>Sports frequency (per month)</td>
<td>13 [9 – 17] (2 – 33)</td>
</tr>
<tr>
<td>Participation in high-risk sports</td>
<td>66 (59%)</td>
</tr>
<tr>
<td>Follow up (days)</td>
<td>365 [365 – 365] (365 – 365)</td>
</tr>
<tr>
<td>Hemophilia joint health score</td>
<td>0 [0 – 3] (0 – 44)</td>
</tr>
<tr>
<td>Pre-existing arthopathy</td>
<td>22 (20%)</td>
</tr>
</tbody>
</table>

| Treatment specifications         |                                             |
| Prophylaxis                      | 55 (98% of severe patients)                 |
| Median FVIII dose (IU/kg/week)   | 43.1 [36.0 – 53.9] (11.7 – 89.5)            |
**Factor concentrate**

- Standard half-life FVIII*: 40 (73%)
- Extended half-life FVIII**: 15 (27%)

**Bleeding specifications**

- Bleeds (n observed): 70
- Joint bleeds: 35 (50%)
- Sports-induced bleed: 20 (29%)
- ABR before study inclusion: 0 [0 – 1] (0 – 9)
- AJBR before study inclusion: 0 [0 – 0] (0 – 4)
- ABR during study: 0 [0 – 1] (0 – 5)

FVIII: Factor VIII, ABR: annual bleeding rate, AJBR: annual joint bleed rate, *Advate, Kogenate and Novoeight, ** Elocta. ABR describes the number of bleeds observed within 365 days.

**Table 2: Parameter estimates of the final repeated time-to-event (RTTE) model**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Estimate</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bleeding hazard at FVIII 0 IU/dL (derived) (year⁻¹)</td>
<td>1.50</td>
<td>-</td>
</tr>
<tr>
<td>Bleeding hazard at FVIII 1 IU/dL (year⁻¹)</td>
<td>1.14</td>
<td>0.56 – 1.72</td>
</tr>
<tr>
<td>Bleeding hazard at FVIII 10 IU/dL (derived) (year⁻¹)</td>
<td>0.36</td>
<td>-</td>
</tr>
<tr>
<td>Bleeding hazard at FVIII 20 IU/dL (year⁻¹)</td>
<td>0.20</td>
<td>0.10 – 0.30</td>
</tr>
<tr>
<td>IC50 (derived) (IU/dL)</td>
<td>3.12</td>
<td>-</td>
</tr>
<tr>
<td>IC90 (derived) (IU/dL)</td>
<td>28.0</td>
<td>-</td>
</tr>
<tr>
<td>Inter-individual variability of bleeding hazard (CV%)</td>
<td>92.4</td>
<td>48.9 – 135.9</td>
</tr>
</tbody>
</table>

IC50: FVIII activity level resulting in 50% reduction of the baseline bleeding hazard at a FVIII level of 0 IU/dL, IC90: FVIII activity level resulting in 90% reduction of the baseline bleeding hazard.
bleeding hazard at a FVIII level of 0 IU/dL, CI: confidence interval, CV: coefficient of variation calculated as $\sqrt{e^{\omega^2} - 1}$, shrinkage of inter-individual variability of bleeding hazard was 50%. The estimated bleeding hazards at 0, 1, 20 and 20 IU/dL can be interpreted as the median estimated annual bleeding rate when a patient has the respective constant FVIII level. A FVIII level of 3.12 IU/dL was found to reduce the median baseline annual bleeding rate of 1.50 year$^{-1}$ to 0.75 year$^{-1}$. 


Step 1: Description of the bleeding hazard

Step 2: Add effect of FVIII activity levels

Step 3a: Add effect of sports participation to the model

Step 3b: Add effect of sport frequency and high risk sports independently of other covariates

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Input data

Example output

Example of model equation

$$h_i(t) = \lambda$$

$$h_i(t) = \lambda \times \left(1 - \frac{\text{FVIII}(t)}{\text{FVIII}(\text{FVIII}_{\text{pred}})} \right) \times \text{sport effect}$$

Model from step 2 + Sport frequency, high risk sport participation, age, body mass index, arthropathy

Using full covariate effects model (FREM)

Data

- n=112
- Median 24 years (range: 7-50)
- 49% severe hemophilia
- Followed for 365 days
- 70 bleeds
- 14,162 sport moments

Repeated time-to-event analysis

Risk of bleeding in hemophilia A

Determinants

FVIII levels

Sports participation

Severe versus non-severe hemophilia

Presence of arthropathy

Pre-study annual bleeding rate