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Association of Peak Factor VIII Levels and Area Under the Curve with Bleeding in Patients with Hemophilia A on Every Third Day Pharmacokinetic-Guided Prophylaxis

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Running title: Peak FVIII Levels, AUC, and Bleeding on PK-Guided rAHF-PFM Prophylaxis

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Abstract

Introduction: We previously showed that pharmacokinetic-guided prophylaxis (PKP) allows the dosing interval to be extended while maintaining a specific trough level. However, the associations of peak factor (F) VIII levels and area under the curve (AUC) with breakthrough bleeding have not been investigated.

Aim: Analyze data from the PKP arm to determine whether peak FVIII levels, AUC, and time with FVIII levels in a hemostatically effective range are independent predictors of bleeding during prophylaxis.

Methods: *Post hoc* analysis of the association of FVIII levels and AUC with annualized bleeding rate in 34 patients on PKP.

Results: During 1 year of PKP, 131 bleeding episodes occurred in 24/34 patients. Average peak FVIII levels ranged from 24 to 168 IU/dL, with higher values associated with a decreased risk for all bleeding (joint and non-joint; $P<0.01$) and joint bleeding ($P<0.01$). Following rFVIII infusion, median percent of time spent with FVIII levels >20 IU/dL was 22%; median AUC was 1363. Both values were significantly associated with a lower ABR when targeting a 1% trough at 72 hours.

Conclusion: When PKP was administered every third day, higher peak FVIII levels, higher AUC, and more time spent per week with FVIII levels >20 IU/dL provided increased protection from joint and non-joint bleeding. These data highlight the potential impact

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of variability in individual PK and bleeding risk and support the need for high peak levels and AUC in some patients treated every third day. The findings do not necessarily apply to alternate-day or other prophylactic dosing regimens.

Introduction

Prophylaxis is considered optimal care for children and adults with severe hemophilia A [1, 2] because of its proven ability to reduce joint and other bleeding episodes [3-7]. On the basis of experience from Sweden, where prophylaxis was pioneered in the late 1950s [8], target FVIII trough levels for prophylaxis have traditionally been set at ≥1 IU/dL above baseline, with the intent of converting the severe bleeding phenotype into the less frequent bleeding pattern of moderate hemophilia [9]. Yet 1 IU/dL is an arbitrary value above which neither all hemorrhages are prevented nor below which bleeding inevitably occurs [10, 11]. Some patients, including those with arthropathy or who have active lifestyles, may require higher FVIII trough levels [12], while others may have trough levels lower than 1 IU/dL but do not bleed [3]. Furthermore, peak FVIII levels, area under the curve (AUC), and time spent with FVIII levels >15 IU/dL [13]) may also be important in protecting against hemarthroses and other bleeding episodes, particularly during periods of high activity, when patients are at increased risk for traumatic bleeding.

A “one size fits all” approach to prophylaxis is not necessarily ideal, possibly leading to inefficient or unnecessarily costly dosing. Using an individual’s pharmacokinetic (PK) response to factor VIII (FVIII) infusions to calculate dose and dosing frequency is one strategy for personalizing the prophylactic regimen [12, 14, 15]. In the study of prophylaxis with ADVATE Antihemophilic Factor (Recombinant), Plasma/Albumin Free Method (rAHF-PFM) (NCT00666406), PK-guided prophylaxis (PKP) given every third day was comparable to standard weight-based every-other-day prophylaxis (SP) [6]. In both arms, the annualized bleeding rate (ABR) [6] and the median annualized joint bleeding rate (AJBR) [16] were significantly reduced as compared with on-demand therapy (OD), and the PKP arm had the advantage of requiring 1 less infusion weekly [6].

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Here we report the results of a *post hoc* analysis of data for the intent-to-treat PKP group to determine whether peak FVIII levels, AUC, and time with FVIII levels >20 IU/dL are independent predictors of prophylactic efficacy for patients using PKP every third day.

Methods

Clinical study summary

The details of the rAHF-PFM prophylaxis study (NCT00243386) have been described [6]. To summarize, 66 previously on-demand-treated males with moderately severe to severe hemophilia A (FVIII ≤2%) aged 7 to 59 years (median: 26 years) who experienced ≥8 joint hemorrhages in the previous year were treated OD for 6 months. These patients (the intent-to-treat population) were then randomly assigned to 12 months of SP (20-40 IU/kg every other day) or PKP (20-80 IU/kg every third day), with the PKP regimen intended to maintain FVIII trough levels ≥1 IU/dL. All prophylactic doses were to be infused in the morning. The characteristics of the study patients were similar for the 2 prophylaxis arms, with all but 1 patient in the SP arm and 2 patients in the PKP arm having 1 to 10 target joints (defined as ≥4 bleeds into the same joint within a 6-month period or >20 lifetime bleeds into a joint) at the start of prophylaxis. (Five of 32 [16%] patients in the SP arm and 13/34 [38%] in the PKP arm had experienced ≥3 joint bleeds in the year preceding study randomization.) No information was collected with regard to patients' lifestyle or physical activity.

Median (interquartile range [P25, P75]) ABR during prophylaxis was 1.0 (0.0, 3.5) and 2.0 (0.0, 6.9) for the SP and PKP arms, respectively, whereas the median ABR (IQR) during OD was 43.9 (34.6, 56.5), a statistically significant difference (P<0.0001) [6]. Twenty-two patients (33.3%) were hemorrhage-free while receiving prophylaxis (either regimen), whereas all patients experienced bleeding during the OD period. Similarly, the AJBR was significantly lower for per protocol patients (n=53) treated with SP (55 total

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hemarthroses; AJBR median: 0.48 [1.96]) or PKP (72 total hemarthroses; AJBR median: 1.00 [4.07]), as compared with OD (1164 total hemarthroses; AJBR median: 38.65 [24.81]; P<0.0001) [16]. Median (range) FVIII trough levels were 3.0 IU/dL (0.5-45.0) during SP (56 observations in 24 patients) and 1.0 IU/dL (0.5-10.0) during PKP (52 observations in 23 patients). FVIII consumption and adverse event rates for both prophylactic regimens were equivalent, and no patient developed a hypersensitivity reaction related to rAHF-PFM or a FVIII inhibitor while on study.

Data for all 34 patients in the every third day intent-to-treat PKP arm were evaluated. A total of 4089 prophylactic infusions were administered during a median of 364 treatment days (range: 97–394). The median dose per infusion was 43.0 (range: 13.0–107.1) IU/ kg, and the median number of units administered per patient was 2979 (range: 1073-5600). Bleeding episodes were recorded in patient diaries and verified by the investigator. Data collected included time and date of bleeding, anatomical site(s), identification of bleeding as joint or non-joint, etiology (spontaneous, traumatic, or undetermined), and severity.

Statistical analyses

The predicted concentration level (IU/dL) at the time of bleeding was projected on the basis of individual PK parameters, assuming that each patient was at his natural baseline. Average peak FVIII levels were estimated using individual in vivo recovery values and average dose/prophylactic infusion.

A negative binomial multivariate regression model was used to evaluate the association between ABR and 1) average peak FVIII level (IU/dL), 2) time spent >20 IU/dL FVIII activity (%), and 3) weekly AUC (IU x hr/dL); age and body mass index were covariates [17]. ABR was calculated as the number of bleeding events divided by the length (in years) of the treatment regimen. Average peak FVIII level was calculated as the average dose (IU/kg) during the study multiplied by incremental recovery (IU/dL/IU/kg). Time

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spent and weekly AUC above 5, 10, 15, 20, 30, and 40 IU/dL FVIII activity were estimated from each patient's infusion log and time per week together with his PK parameters. Correlation between 2 variables was described using nonparametric spearman method.

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Results

A total of 845 bleeding episodes (188 traumatic, 657 spontaneous; 750 joint, 95 non-joint) occurred in the 34 patients during 6 months of OD that preceded PKP. The mean ± SD (range; median) ABR and AJBR during on-demand treatment was 49.2 ± 20.7 (13-90.8; 44.8) and 43.5 ± 21.3 (6.5-90.8; 39.0), respectively.

Number of hemorrhages and time of bleeding

During PKP, 131 bleeding episodes occurred in 24/34 patients (70.6%). Among the 121 episodes of joint bleeding, 4 (all spontaneous) occurred within the first 12 hours after infusion, 20 (6 spontaneous) occurred 12-24 hours post-infusion, 49 (21 spontaneous) occurred 24-48 hours post-infusion, and 40 (20 spontaneous) occurred 48-72 hours post-infusion (Table 1). No significant increase was observed in the number of bleeding episodes occurring more than 48 hours after infusion as compared with those occurring within the first 48 hours.

Pattern of spontaneous and traumatic bleeding

The median predicted concentration (range) at the time of bleeding among patients in the PKP arm was 2.71 IU/dL (0-26.55) for 57 spontaneous hemorrhages, 3.57 IU/dL (0-41.6) for 74 traumatic hemorrhages, 3.43 IU/dL (0-41.67) for 121 hemarthroses, and 2.87 IU/dL (0-11.26) for 10 non-joint bleeding events (Figures 1 and 2). No statistically significant difference in predicted FVIII levels was observed either between spontaneous or traumatic or joint and non-joint hemorrhages. Traumatic joint bleeding occurred with predicted FVIII levels as high as 42%, but most hemarthroses occurred at levels <10 IU/dL (median predicted value 3.43 [IQR = 7.18 [1.33-8.51]).

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Peak levels and bleeding risk

Average peak FVIII levels (IVR x average dose) in the PKP arm ranged from 24.3 to 167.5% (median: 70.9%), with lower values associated with an increased risk for all bleeding (P=0.0004) and joint bleeding (P=0.0013) (Figure 3).

AUC and peak FVIII levels in non-bleeding and bleeding patients

The average predicted AUC was 136 between 24-48 hours and 33 between 48-72 hours post-infusion. To further examine the possible relationship between high AUC, peak FVIII levels, and bleeding risk in the immediate hours following infusion, we compared the weekly AUC 0-12 hours post-infusion for patients who did and did not report bleeding (Table 3). No significant difference was observed between the 2 groups, likely attributable to the small sample size. Nonetheless, patients who had no bleeding during the 12-month study period appeared to have higher post-infusion AUC 0-12 hours as well as higher peak FVIII levels.

Time spent at FVIII levels >20 IU/dL *and bleeding risk*

Among patients in the PKP arm, the median percent of time spent with FVIII levels >20 IU/dL was 22.3% (range: 2.9-46.1), resulting in a median AUC of 1363 (range: 130-4265). Both values were significantly associated with a lower ABR, and during the period that the FVIII concentration was ≥27 IU/dL, PKP-treated patients experienced no spontaneous bleeding. This relationship was even more pronounced when a higher percentage of time was spent with FVIII levels >30 IU/dL (Figure 4) or higher peak levels (Figures 1 and 2) were achieved. The modeled data showed a consistent and strong positive correlation among peak level, time above percent, and weekly AUC (Table 2).

Discussion

In this *post hoc* analysis of the rAHF-PFM prophylaxis study data, patients receiving PKP every third day were dosed to maintain a target trough FVIII level of ≥1 IU/dL [6], thereby eliminating time spent <1 IU/dL as a variable contributing to bleeding risk.

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Evaluating PK parameters in relation to the reported bleeding events led to 3 observations. First, higher peak FVIII levels and AUC provided increased protection against joint and non-joint bleeding. Specifically, spontaneous bleeding was prevented when patients in the PKP arm had a FVIII concentration ≥27 IU/dL.

Broderick and colleagues similarly recognized the link between high peak levels and a reduction in bleeding [18]. In a case-crossover study nested within a prospective cohort study that included 104 children and adolescents with hemophilia, they found the transient increase in bleeding risk associated with vigorous physical activity was mitigated with estimated peak factor concentrations of 70 to 100 IU/dL. Conversely, low peak levels may have contributed to the increase in bleeding events observed by Lindvall et al in some patients who crossed over to daily low-dose prophylaxis designed to maintain at least the same FVIII trough level as obtained with their standard prophylactic regimens [19].

Second, ABR declined as the percent of time spent weekly with FVIII levels >20-30 IU/dL rose. Specifically, among 8 patients who spent ≥20% of time about 30 IU/dL, only 2 had an ABR >2. Nearly 40 years ago, Aronstam described a 60% reduction in bleeding frequency in boys with severe hemophilia A treated with FVIII-containing “materials” to increase their factor levels to 15% to 30% of normal [20]. In 2011, den Uijl observed that patients with hemophilia A who had a baseline FVIII activity exceeding 15 IU/dL experienced no joint bleeding [13]. This result is not directly equivalent to the situation observed in our study, however, as a steady state of 15 IU/dL differs from the peaks and troughs we described. Additionally, our FVIII level data are modeled on the basis of estimated PK parameters and patient-reported infusion and bleed event (including etiology) records, which may introduce some degree of error. Nevertheless, Broderick also noted the connection between higher FVIII levels and bleed reduction, reporting that the risk of bleeding decreased by 2% for each 1% increase in factor activity [18].

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When factor levels were maintained at approximately 50 IU/dL during physical activity, bleeding risk was lower than that for inactive patients treated on-demand.

Finally, while traumatic bleeding occurred throughout the range of predicted FVIII plasma levels (as high as 58 IU/dL), most occurred at FVIII levels <10 IU/dL. These observations are consistent with those reported by den Uijl [13].

In patients with hemophilia A, joint bleeding results in increased morbidity, decreased health-related quality of life, and higher treatment costs associated with the management of chronic arthropathy [21-24]. Prophylaxis is highly effective in preventing joint and other serious bleeding episodes [3-6, 25], but a personalized approach to treatment [15] that takes into consideration an individual's PK—FVIII peaks and AUC as well as troughs—may have the potential to optimize the treatment regimen.

It is important to recognize that the findings from our analyses are specific to patients with severe hemophilia A (baseline FVIII ≤2%) receiving PKP administered every third day. The results cannot necessarily be extrapolated to other regimens and may not be applicable to alternate-day dosing. Indeed, we have previously reported that AUC was not associated with breakthrough bleeds in patients receiving prophylaxis 3 to 4 times per week [26]. Furthermore, , almost all patients had pre-existing joint disease, with nearly 40% having ≥3 target joints at study initiation. The impact of joint status on FVIII levels at the time of bleeding is unclear. Finally, consistent with the results of den Uijl et al [13], the influence of peak FVIII levels is likely to diminish as baseline FVIII levels approach the normal range.

The observation that lower peak levels were associated with increased bleeding in the PKP arm has interesting implications. Patients with the longest-half-lives required the lowest FVIII doses to sustain a level >1 IU/dL by 72 hours and, therefore, also had the lowest peaks. Thus, paradoxically, those with the longest half-lives appeared to do less

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well on every third day prophylaxis targeted at a trough of 1 IU/dL than did those with shorter half-lives. In addition, owing to the shape of the PK curves in people with longer half-lives, those with lower peaks also spent more time with low FVIII levels between infusions. Whether these findings have implications for more frequent dosing intervals and/or for treatment with extended half-life molecules require further investigation.

Limitations to the analysis

Our analysis has several limitations. First, the data set is comprised of only 34 patients receiving PKP, and the analysis was performed *post hoc*. Second, information about FVIII activity at the time of each bleeding episode was extrapolated from PK data obtained at study entry and was calculated using patient-reported time of infusion and time of hemorrhage without adjustment for potential residual FVIII from prior dose. Third, the impact of a patient's lifestyle and participation in sports activities on bleeding could not be ascertained, as these data were not collected, but it is possible that they may have influenced bleeding in some patients. Finally, the possibility that some joint pain-related events may have been misclassified as hemarthroses, and that some bleeding episodes may not have been recognized or were misclassified as traumatic (versus spontaneous) cannot be ruled-out.

In conclusion, the findings from this *post hoc* analysis of data for the PKP arm of the rAHF-PFM prophylaxis study add to previous observations that time spent with FVIII levels <1% positively correlates with bleeding risk by demonstrating that in patients receiving every third day prophylaxis targeting a trough of 1 IU/dL, peak FVIII levels, AUC, and time spent at high FVIII plasma levels are also associated with the risk for joint and non-joint bleeding. The data highlight the potential impact of variability in individual PK and the likelihood for hemorrhage and may support the need for higher peak levels and AUC in some patients on every third day dosing, such as those with underlying joint disease or during periods of increased activity. These conclusions do not necessarily

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apply to patients receiving alternate-day dosing, and further studies in this group are needed.

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Addendum

Myungshin Oh performed the statistical analyses; L. A. Valentino, S.W. Pipe, P.W. Collins, V.S. Blanchette, E. Berntorp, K. Fischer, B. Ewenstein, and G. Spotts analyzed and interpreted data; L. A. Valentino and S.W. Pipe prepared the manuscript, which was critically reviewed by the other coauthors.

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Disclosure of Conflict of Interest

L.A. Valentino: During the preparation of this manuscript, LAV became an employee of Baxalta US, Inc. but continues in an academic capacity as a Rush University Medical Center (RUMC) faculty member. RUMC received grant support on behalf of LAV from Baxter Healthcare Corporation, Bayer Healthcare, Biogen, CLS Behring, GTC Biotherapeutics, Inspiration Bioscience, Novo Nordisk, and Pfizer. RUMC received payments on behalf of LAV for his participation in advisory boards and serving as a consultant to Baxter Healthcare Corporation, Bayer Healthcare, Biogen, CLS Behring, GTC Biotherapeutics, rEVO Biologics, Inspiration Bioscience, Novo Nordisk, and Pfizer.

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B. Ewenstein, M. Oh, and G. Spotts are employees of Baxalta US, Inc., the sponsor of the study.

References

1. Srivastava A, Brewer AK, Mauser-Bunschoten EP, Key NS, Kitchen S, Llinas A*, et al.* Guidelines for the management of hemophilia. *Haemophilia* 2013; **19:** e1-47.
2. National Hemophilia Foundation. MASAC [Medical and Scientific Advisory Council] Recommendation 179. MASAC recommendation concerning prophylaxis (regular administration of clotting factor concentrate to prevent bleeding). Adopted November 4, 2007. Available at: http://www.hemophilia.org/NHFWeb/MainPgs/MainNHF.aspx?menuid=57&contentid=1007.

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3. Aledort LM, Haschmeyer RH, Pettersson H. A longitudinal study of orthopaedic outcomes for severe factor-VIII-deficient haemophiliacs. The Orthopaedic Outcome Study Group. *J Intern Med* 1994; **236:** 391-9.
4. Manco-Johnson MJ, Abshire TC, Shapiro AD, Riske B, Hacker MR, Kilcoyne R*, et al.* Prophylaxis versus episodic treatment to prevent joint disease in boys with severe hemophilia. *N Engl J Med* 2007; **357:** 535-44.
5. Gringeri A, Lundin B, von Mackensen S, Mantovani L, Mannucci PM. A randomized clinical trial of prophylaxis in children with hemophilia A (the ESPRIT Study). *J Thromb Haemost* 2011; **9:** 700-10.
6. Valentino LA, Mamonov V, Hellmann A, Quon DV, Chybicka A, Schroth P*, et al.* A randomized comparison of two prophylaxis regimens and a paired comparison of on-demand and prophylaxis treatments in hemophilia A management. *J Thromb Haemost* 2012; **10:** 359-67.
7. Manco-Johnson MJ, Kempton CL, Reding MT, Lissitchkov T, Goranov S, Gercheva L*, et al.* Randomized, controlled, parallel-group trial of routine prophylaxis vs. on-demand treatment with sucrose-formulated recombinant factor VIII in adults with severe hemophilia A (SPINART). *J Thromb Haemost* 2013; **11:** 1119-27.
8. Ahlberg A. Haemophilia in Sweden. VII. Incidence, treatment and prophylaxis of arthropathy and other musculo-skeletal manifestations of haemophilia A and B. *Acta Orthop Scand Suppl* 1965; **77:** 3-132.
9. Nilsson IM, Hedner U, Ahlberg A. Haemophilia prophylaxis in Sweden. *Acta Paediatr Scand* 1976; **65:** 129-35.
10. Collins PW, Bjorkman S, Fischer K, Blanchette V, Oh M, Schroth P*, et al.* Factor VIII requirement to maintain a target plasma level in the prophylactic treatment of severe hemophilia A: influences of variance in pharmacokinetics and treatment regimens. *J Thromb Haemost* 2010; **8:** 269-75.
11. Ahnstrom J, Berntorp E, Lindvall K, Bjorkman S. A 6-year follow-up of dosing, coagulation factor levels and bleedings in relation to joint status in the prophylactic treatment of haemophilia. *Haemophilia* 2004; **10:** 689-97.

Author Manuscript

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12. Bjorkman S. Prophylactic dosing of factor VIII and factor IX from a clinical pharmacokinetic perspective. *Haemophilia* 2003; **9 Suppl 1:** 101-8; discussion 9-10.
13. den Uijl IE, Mauser Bunschoten EP, Roosendaal G, Schutgens RE, Biesma DH, Grobbee DE*, et al.* Clinical severity of haemophilia A: does the classification of the 1950s still stand? *Haemophilia* 2011; **17:** 849-53.
14. Bjorkman S. Limited blood sampling for pharmacokinetic dose tailoring of FVIII in the prophylactic treatment of haemophilia A. *Haemophilia* 2010; **16:** 597-605.
15. Valentino LA. Considerations in individualizing prophylaxis in patients with hemophilia A. *Hemophilia* 2014; **epublished April 8, 2014**.
16. Valentino LA, Reyes CM, Ewenstein B, Guzman-Becerra N, Wong WY, Schoenig-Diesling C*, et al.* ADVATE prophylaxis: *post hoc* analysis of joint bleeding episodes. *Haemophilia* 2014.
17. Hilbe JM. *Negative Binomila Regression, Second Edition*. UK: Cambridge University Press, 2011.
18. Broderick CR, Herbert RD, Latimer J, Barnes C, Curtin JA, Mathieu E*, et al.* Association between physical activity and risk of bleeding in children with hemophilia. *JAMA* 2012; **308:** 1452-9.
19. Lindvall K, Astermark J, Bjorkman S, Ljung R, Carlsson KS, Persson S*, et al.* Daily dosing prophylaxis for haemophilia: a randomized crossover pilot study evaluating feasibility and efficacy. *Haemophilia* 2012; **18:** 855-9.
20. Aronstam A, Kirk PJ, McHardy J, Culver-James JW, McLellan DS, Turk P*, et al.* Twice weekly prophylactic therapy in haemophilia A. *J Clin Pathol* 1977; **30:** 65-7.
21. Dunn AL, Busch MT, Wyly JB, Sullivan KM, Abshire TC. Arthroscopic synovectomy for hemophilic joint disease in a pediatric population. *J Pediatr Orthop* 2004; **24:** 414-26.
22. Rodriguez-Merchan EC. Aspects of current management: orthopaedic surgery in haemophilia. *Haemophilia* 2011.

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23. Khawaji M, Astermark J, Von Mackensen S, Åkesson K, Berntorp E. Bone density and health-related quality of life in adult patients with severe haemophilia. *Haemophilia* 2011; **17:** 304-11.
24. Berntorp E. Joint outcomes in patients with haemophilia: the importance of adherence to preventive regimens. *Haemophilia* 2009; **15:** 1219-27.
25. Manco-Johnson MJ, Kempton CL, Reding MT, Lissitchkov T, Goranov S, Gercheva L*, et al.* Randomized, controlled, parallel-group trial of routine prophylaxis versus on-demand treatment With rFVIII-FS in adults with severe hemophilia A (SPINART). *J Thromb Haemost* 2013.
26. Collins PW, Blanchette VS, Fischer K, Bjorkman S, Oh M, Fritsch S*, et al.* Break-through bleeding in relation to predicted factor VIII levels in patients receiving prophylactic treatment for severe hemophilia A. *J Thromb Haemost* 2009; **7:** 413-20.

Table 1. Number of hemorrhages (patients) and time at which bleeding occurred post-infusion in the PKP arm.

Bleeding Type	12 hr	12-24 hr	24-48 hr	48-72 hr	>72 hr*	All
Spontaneous	4 (4)	7 (4)	21 (13)	22 (12)	3 (3)	57
Traumatic	0 (0)	14 (9)	31 (10)	22 (11)	7 (4)	74
Joint	4 (4)	20 (11)	49 (17)	40 (15)	2 (1)	121
Non-joint	0 (0)	1 (1)	3 (2)	4 (3)	2	10

*Indicates non-adherence to the treatment regimen.

Table 2. Average peak level, time above %, and weekly AUC covariance in the PKP arm: correlation coefficients among the variables.

Variable	PKP (N=34)	
	Time >5%	**AUC >5%**
	Time >10%	**AUC >10%**
	Time >20%	**AUC >20%**
	Time >30%	**AUC >30%**

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	Time >40%	AUC >40%
Average Peak (IU/dL)	---- (ns) 0.43 (s) 0.65 (s) 0.90 (s) 0.94 (s)	0.82 (s) 0.82 (s) 0.87 (s) 0.94 (s) 0.95 (s)
Time >5% **Time >10%** **Time >20%** **Time >30%** **Time >40%**	Not applicable	0.60 (s) 0.81 (s) 0.90 (s) 0.99 (s) 0.99 (s)

Non-parametric correlation coefficient: (s) indicates P <0.05.

Table 3. Peak FVIII and AUC levels within 12-hours post-infusion in non-bleeding and bleeding patients

	Non-Bleeding Patients (N=9)					Bleeding Patients (N=25)					P-value*
	Min	Q25	Median	Q75	Max	Min	Q25	Median	Q75	Max	
Average Peak FVIII (IU/dL)	45.9	66.9	83.6	124.4	150.9	24.3	45.9	56.4	108.3	167.5	0.4793
Weekly AUC for 12 hr after infusion	852.2	1134.5	1263.0	1846.0	2882.0	490.3	774.5	1097.5	1712.1	2353.4	0.3765

*P-value is from t-test.

Figure 1. Spontaneous and traumatic bleeding episodes over time in patients on PKP.

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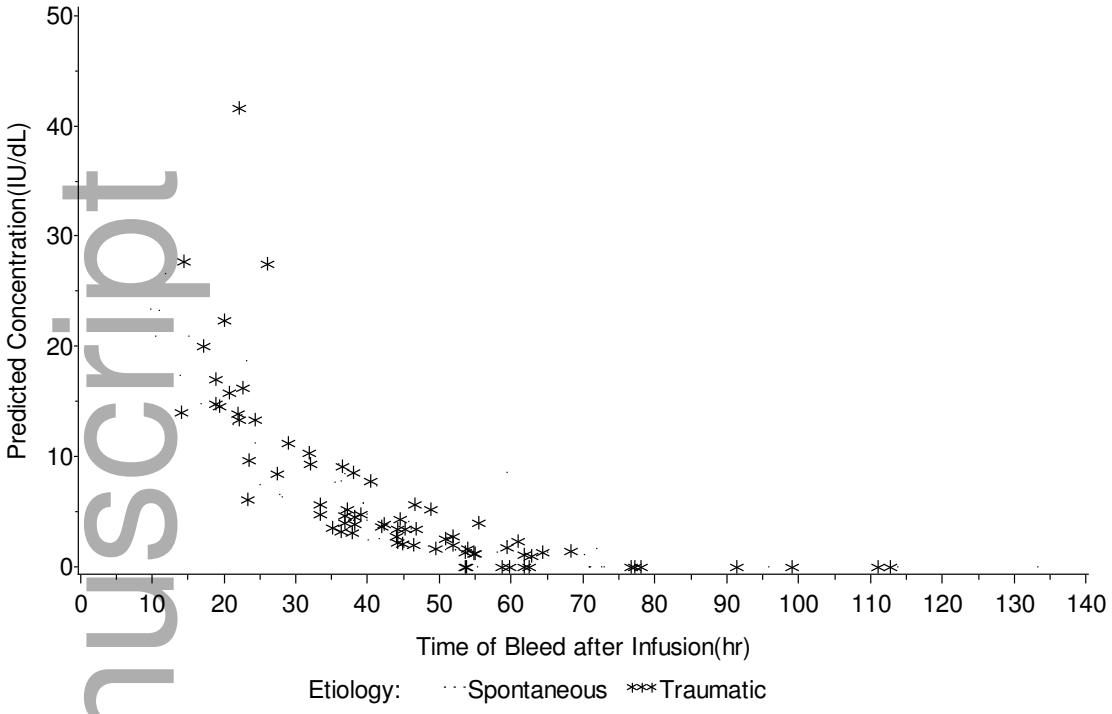

Figure 2. Joint/non-joint bleeding episodes over time in patients on PKP.

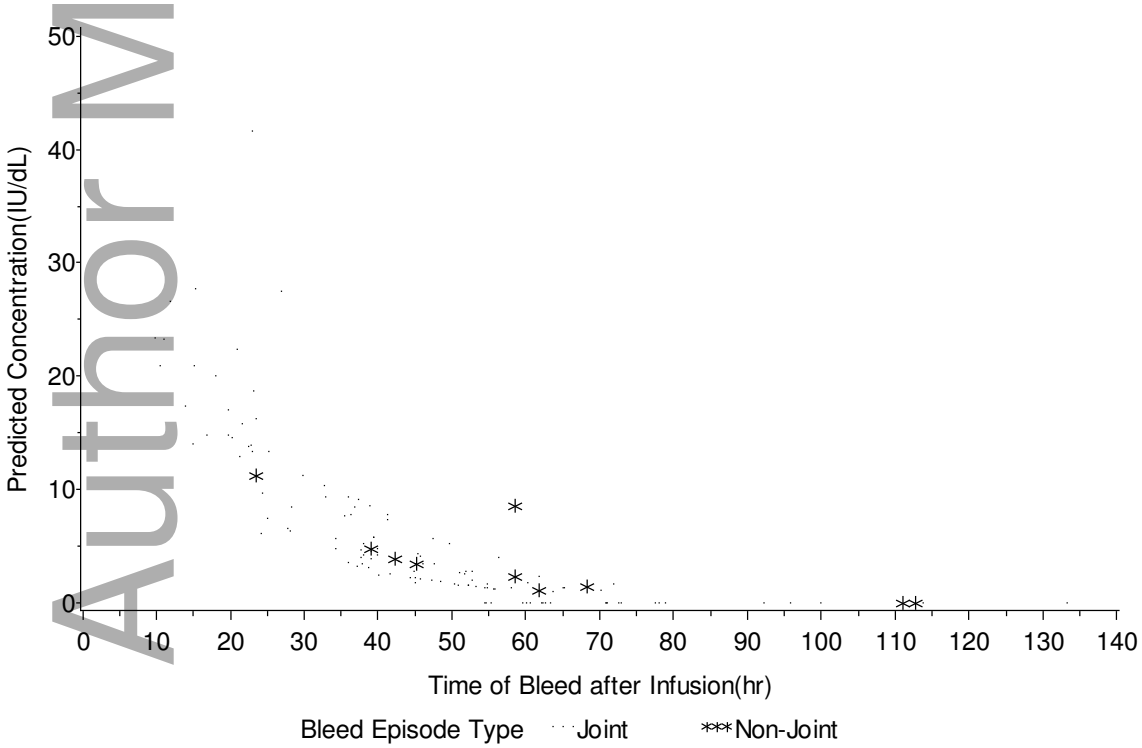

Figure 3. Average peak FVIII levels and risk for bleeding in patients on PKP.

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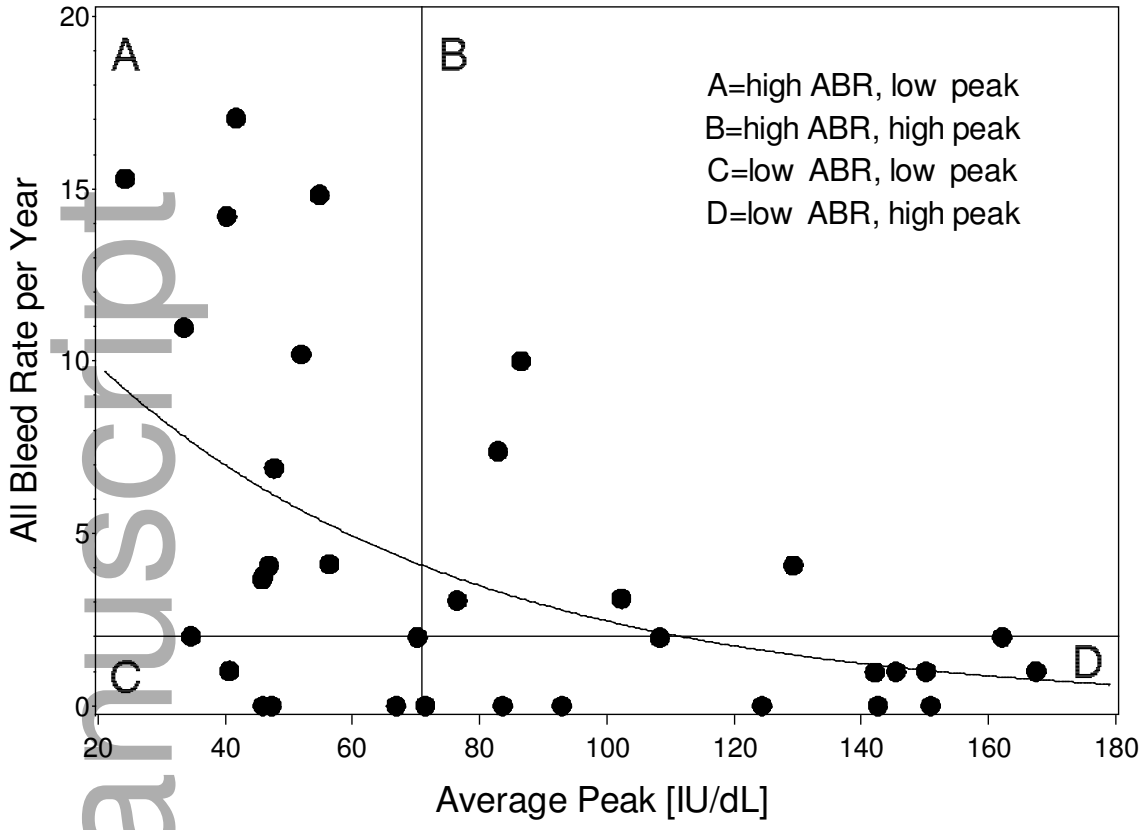

The trend curve presents the predicted ABR derived from the negative binomial multivariate regression model across the average peak FVIII level for an average patient (with regard to age and body mass index).The average peak FVIII levels are related to the risk of all bleeding (P=0.0004; coeff: -0.02) and joint bleeding (P=0.0013; coefficient: -0.02). Four quadrants are identified to signify the relationship between bleeding rates and average peak FVIII levels. The horizontal line represents median ABR (2.0) for the overall population, and the vertical line represents median theoretical peak FVIII level achieved following prophylactic infusion.

Figure 4. Time spent post-infusion with FVIII levels >30% and bleeding risk in the PKP arm.

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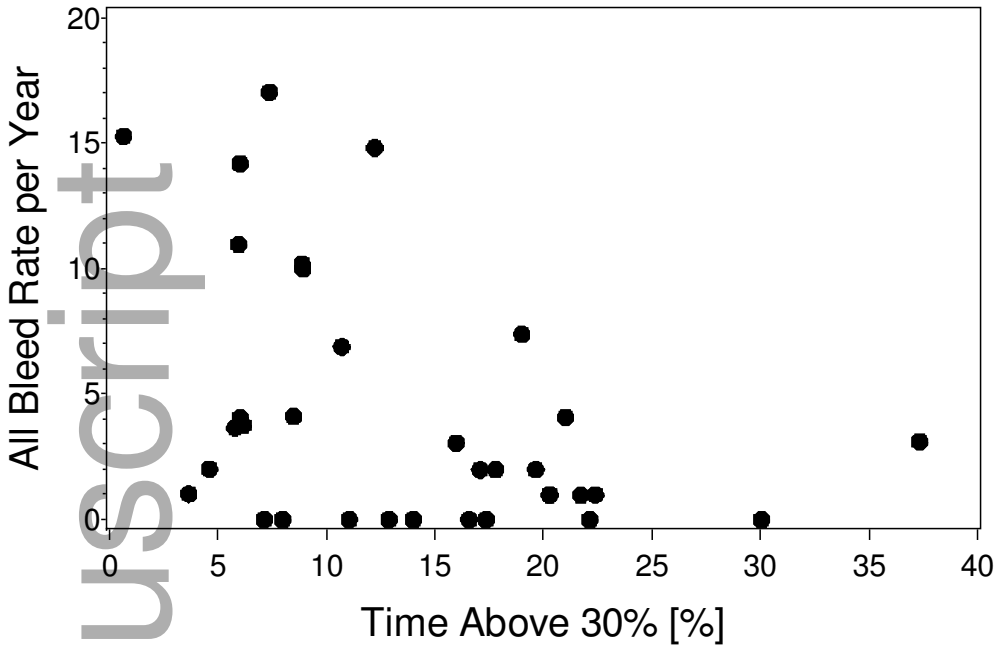

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