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Full Length Article

Clinical outcomes in hemophilia A patients undergoing tailoring of prophylaxis based on population-based pharmacokinetic dosing

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ABSTRACT

Introduction: Standard prophylaxis dosing based on bodyweight may result in over- or under-dosing due to interpatient variability. Adopting individual pharmacokinetic (PK) based tailoring may improve adherence to treatment guideline, and consequently clinical outcomes. Here we report clinical observations performed across the adoption of individual PK based tailoring in a single center in Japan.

Methods: An individual PK study on sparse samples was modeled on myPKFiT or WAPPS-Hemo, depending on concentrate, and used to optimize treatment regimens. Adherence to prophylaxis and bleeding rate were calculated from patient diaries. Radiological joint scores were used to assess arthropathy, and SPSS to perform all the analyses.

Results: Thirty-nine patients underwent PK profiling, and 20 required and accepted a modification of their treatment (8 increases in dose, 5 reductions in frequency, 5 switches to extended half-life (EHL)). Adherence to prophylaxis remained the same in those increasing the dose, whilst increased in all the other groups. Annualized bleeding rate (ABR) and annualized joint bleeding rate (AjBR) decreased in all the groups but reached statistical significance only in those switched to EHL and showed a larger reduction in those patients without baseline arthropathy. Longer time spent above a 1% or 5% threshold was associated with a decrease in the ABR/AjBR.

Conclusions: Our study results suggest that PopPK based tailoring supported changing treatment regimen in nearly half of the patients, and may have contributed to an improvement in the adherence and a reduction in the ABR/AjBR.

1. Introduction

Prophylaxis has become the recommended treatment for persons with hemophilia of all ages. A standard weight-based approach to regular prophylaxis sometimes causes under- or overdosage. It has been recommended that both the dose and infusion frequency should be determined by individual pharmacokinetic (PK) studies, because PK profiles present large variability among individual patients [1].Consequently, medical professionals need to set the prophylaxis regimen for their patients according to various individual factors, including PK data [2]. Full PK analysis poses a big burden, especially on children and their families. A full PK study for hemophilia A patients requires a washout period of 72 h and sample collection for a total of 10 time-points after the infusion of the coagulation factor (before, 15 min and 30 min after, and 3, 6, 9, 24, 28, 32 and 48 h after the infusion) [3]. Furthermore, for a full PK analysis, patients are required to be admitted to the hospital or need to visit the outpatient clinic frequently. Blood collection at a total of 10 time-points is not realistic, especially in children. Baxter/Baxalta/Shire recently developed a population-based PK (PopPK) application called myPKFiT® meant to support optimal use of recombinant factor VIII (rFVIII) (Advate®; Shire plc, Dublin, Irland) for treatment of hemophilia patients, using individual PK data which are obtained using ~~just~~ at least two sampling points. The Web-Accessible Population Pharmacokinetic Service - Hemophilia (WAPPS-Hemo, McMaster University), a PopPK web application supporting PK estimation and treatment optimization for all clotting factor concentrates, including extended half-life products (EHL), has also been developed by Iorio et al. as part of a research program [4]. Herein, in order to evaluate the usefulness of these simplified PK tools, we examined how the use of PopPK for profiling patients with hemophilia A receiving prophylaxis

Abbreviations: PK, pharmacokinetic; SHL, standard half-life products; EHL, extended half-life products; rFVIII, recombinant factor VIII; FVIII:C, FVIII activity; ABR, annualized bleeding rate; AjBR, annualized joint bleeding rate

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affected their treatment and adherence, and eventually affected their subsequent bleeding frequencies.

2. Material and methods

2.1. Subjects

PopPK studies were performed for 39 hemophilia A patients who were already receiving prophylaxis between October 2014 to October 2017. For this study, we defined prophylaxis as administration of standard half-life (SHL) or EHL products more than once per week. There was no eligibility restriction on age, severity of hemophilia or type of coagulation product administered. This study was conducted with the approval of the Ethics Committee of our hospital, and written informed consent was obtained from all the patients.

2.2. Population PK

FVIII activity (FVIII:C) was determined by the one-stage clotting assay (ACL TOP and HemosIL SynthASil, instrumentation laboratory, Bedford, MA, USA). Individual PK profiles were estimated using myPKFiT® for patients on treatment with Advate®, and using the WAPPS-Hemo program for patients using other factor concentrates. For myPKFiT®, blood samples were accurately collected according by instruction of myPKFiT® (2.5–4.5 h and 22–33 h). For WAPPS-Hemo program, blood sampling times were at 4, 24 and 48 h or at 8 and 30 h after the infusion according to report of Bjorkman et al. [5]. The practical sampling times in our population were 2 points, average 6.8 h (2–42 h) and 27.4 h (7–53 h). However, if there were other sampling points other than recommended time, we added to PopPK to improve the accuracy of predictions. PopPK profiles were presented to the patients by their physicians during an outpatient clinic visit. Since there is simulation function in these 2 PopPK tools, if the FVIII trough level was not sufficient against AjBR, we presented the better dose or interval which was simulated to patients. When patients without bleeding received PopPK, we also presented the better way to prophylaxis.

For the analysis of “time spent above” 0.01 and 0.05 IU/mL of FVIII:C (Fig. 6), we recalculated all the PopPK data using the WAPPS-Hemo program to unify the method of calculation.

2.3. Collected information

2.3.1. Adherence to prophylaxis

All patients were prescribed prophylaxis accordingly to current guidelines. However, they were classified based on the infusion recorded in their bleeding diaries. Patients reporting 3 or more infusions per week for SHL products or one or two infusions per week for EHL products were considered adherent to prophylaxis. Infusion frequencies lower than the above were defined as not adherence to prophylaxis.

2.3.2. Bleeding

The annualized bleeding rate (ABR) and annualized joint bleeding rate (AjBR) were counted from the home records of bleeding for one year before and after the PopPK study. The changes in the ABR and AjBR were defined as follows.

[[ABR (events/time)] **before** PopPK] – [ABR (events/time) **after** PopPK]

[[AjBR (events/time)] **before** PopPK] – [AjBR (events/time) **after** PopPK]

2.3.3. Arthropathy

Target joints were defined as joints with 3 or more spontaneous bleeding episodes during any consecutive 6-month period and were calculated from the individual bleeding records [6]. The stage of hemophilic arthrosis was evaluated by the findings on plain radiographs of the elbows, knees and ankles within one year of the patient enrolment in the study. The X-rays were obtained as part of the medical examination. The X-ray findings were classified by an orthopedic surgeon as representing class I to class V arthropathy (according to the Arnold-Hilgartner scale [7]). Class III or higher arthropathy was defined as end-stage arthropathy.

2.3.4. Cost calculation

We collected total amount of prescription per year before and after PopPK. And total cost per year was calculated by total amount multiply by price per unit. Because the price varies depending on the vials, the highest price per unit was adapted.

2.4. Statistical analysis

All statistical tests were 2-sided, with a significance threshold of 0.05. Fisher's exact test was used for the analyses shown in Fig. 2. Welch's test was used for the analyses shown in Figs. 3, 4 and 5, respectively. Statistical analysis was performed using the SPSS software, version 25.0 (SPSS, Chicago, IL).

3. Results

3.1. Patients

The baseline characteristics of the patients are shown in Table 1. We performed a total of 39 PopPK assessments in 39 patients. All patients were severe hemophilia A patients. A SHL product was used in 35 patients (of whose one was on a plasma-derived product) and an EHL product was used in the remaining 4 patients. The median age of the patients was 19 years (range 2–67). In all, 27 patients received regular prophylaxis, defined as 3 times or more per week in those receiving a SHL product and one or two times a week in those receiving an EHL product. Less frequent infusion frequency was noted in the remaining 12 patients, who were therefore defined as poorly adherent. The most common trigger for the PopPK assessment was uncontrolled breakthrough bleeding under prophylaxis (27 patients). In six of the remaining patients, PopPK analysis was performed for the purpose of confirming the patients' recovery and half-lives of the products immediately after the coagulation product had been switched, mainly from an SHL product to an EHL product or from Kogenate®FS (Bayer AG, Berlin, Germany) to Kovaltry® (Bayer AG, Berlin, Germany). Five patients had a positive history for inhibitors, of whose 3 underwent PopPK assessment to confirm recovery and half-life of the products administered after the Bethesda test turned negative. Moreover, PopPK analysis was also performed in three patients in preparation for a surgical procedure, and the prophylaxis regimen was reviewed at the same time. Ten patients had one target joint and 4 patients had multiple target joints. None of the patients had > 3 target joints. Eighteen patients had one or more joints showing end-stage arthropathy.

3.2. PopPK based tailoring

We performed PopPK analysis to reconsider the prophylactic regimen in all 39 patients. Based on the results of the PK assessment the patients were grouped according to the required action (Fig. 1). For 20 patients, 8 patients required a higher dosage of the factor concentrate. Five patients required a shorter interval of infusions. Five patients underwent a change of the coagulation factor from a SHL product to an EHL product. Two patients required a reduction of their prophylactic doses. In group A, median dose 24.7 IU/kg (19.2–37.7 IU/kg) changed to median 43.2 IU/kg (37.3–57.6 IU/kg). In all subjects, maximum dosing interval was every other day. Therefore, prophylaxis of all patients was consistent with the recommendations provided in the products' labelling or guidelines. Of remaining 19, there was either no need to modify the prophylactic regimens (16 patients) or the patients refused to change their regimens (3 patients). Former 13/16 patients had

Table 1
Baseline characteristics of the patients.

Patient population characteristics	*N* = 39
Age (year)	Median 19 (range 2–67)
Body weight (kg)	Median 51.9 (range 13–87)
Medical history of inhibitors	5
Frequency of prophylaxis before application of PopPK	
Three times a week or over with an SHL	25
Recommended as the attached document[a] with an EHL	2
Lower frequency than the above	12
Frequency of prophylaxis after application of PopPK	
Three times a week or over with an SHL	25
Recommended as the attached document[a] with an EHL	7
Lower frequency than the above	7
Reason for PK testing	
Uncontrolled bleeding under prophylaxis	27
After change of product	6
Follow-up after disappearance of inhibitors	3
Before surgery	3
Number of target joints[b]	
None	25
One joint	6
Two joints	3
Three joints	1
Unknown	4
Number of joints showing end-stage hemophilic arthrosis[c]	
None	21
One joint	3
Two joints	3
Three joints	3
Four joints	1
Five joints	4
Six joints	4

PopPK: Population PK; SHL: standard half-life product; EHL: extended half-life product.

[a] Eloctate®(Bioverative): twice (25 IU/kg to 50 IU/kg) per week or once (65 IU/kg) per week for Japanese patients. Adynovate®(Shire plc, Doublin, Ireland): twice (40 to 60 IU/kg) per week for Japanese patients.

[b] More than 3 bleeding episodes during a 6-month period according to the ISTH guideline.

[c] More than Arnold Hilgartner scale III.

good FVIII trough level with PopPK. Of remaining 3/16 patients had lower FVIII trough level (< 1% of FVIIIa:c) but good AjBR. The latter 3 patients had lower trough level and high AjBR but refused to change.

EHL: extended half-life product; ABR: annualized bleeding rate; AjBR: annualized joint bleeding rate.

3.3. Adherence to prophylaxis

We investigated the change in the adherence in each of the groups (Fig. 2). There was no change in the adherence in the group that needed an increase of the infusion doses, which originally consisted mostly of patients showing good baseline adherence (7/8 before and 7/8 after). Improved adherence was observed in the group requiring shortening of the infusion interval (1/5 before and 4/5 after) and in the group switching to an EHL product (3/5 before and 4/5 after). No diaries were available for the 2 patients requiring a dose reduction. The difference did not reach statistical significance in any of the groups. Adherence also improved (14/19 before and 15/19 after) in the patients that required no change of their prophylactic regimens or refused to change.

3.4. Bleeding

The ABR and AjBR before and after the PopPK profiling were compared for each group (Fig. 3). Both the ABR and AjBR tended to decrease in all groups. A tendency towards decrease, although not statistically significant, was observed in the groups in which the dosing regimen changed, but the product used remained the same (increase of the dose required or shortening of the interval between doses). On the other hand, a significant decrease in the ABR and a trend towards decrease in the AjBR were observed in the group in which the product was changed from an SHL to an EHL product. Both the ABR and AjBR decreased in the patients that required no change of the prophylactic regimen. We examined the changes in the AjBR for subgroups of patients with or without arthropathy (Fig. 4). A significant decrease of the AjBR was observed after adoption of the PopPK based regimen in the group without but not in the group with end-stage arthropathy.

The degree of improvement of the ABR/AjBR according to adherence is shown in Fig. 5. Improvement is represented by the increase in the difference of bleeding episodes from before to after adoption of PopPK. A tendency towards improvement of the ABR was noted in the adherent group as compared to the non-adherent group; however, the difference was not statistically significant. The correlation between the AjBR and the time above 1% and 5% of FVIII:C (as hour per week) before and after application of PopPK in patients with or without arthropathy is shown in Fig. 6. Longer times spent above either 1% or 5% were associated with a decrease in the AjBR.

From the view of cost, the total amount of the cost in group A and B (dose up and interval shortage) became expensive after PopPK. In group C (SHL to EHL), there were 3 Eloctate®(Bioverativ, Waltham, MA, US) users. The cost was same in 2 of 3 and became half price in 1 of 3. However, the cost in remaining 2 Adynovate® users increased > 3 times before PopPK. In the 2 patients in group D (dose down), the cost went down almost half price after PopPK.

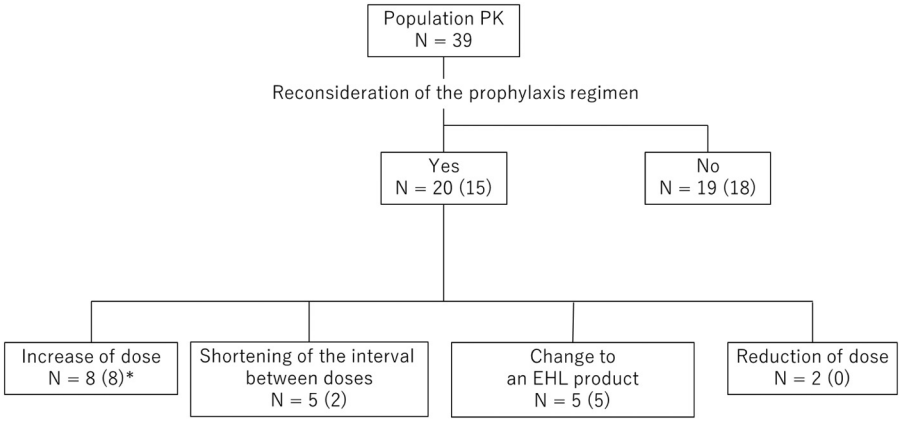

Fig. 1. Flow chart and grouping according to of the results of reconsideration of the prophylaxis after application of PopPK.
Footnote; * the number in brackets indicates the patients in which we could count the ABR/AjBR from the infusion notes.

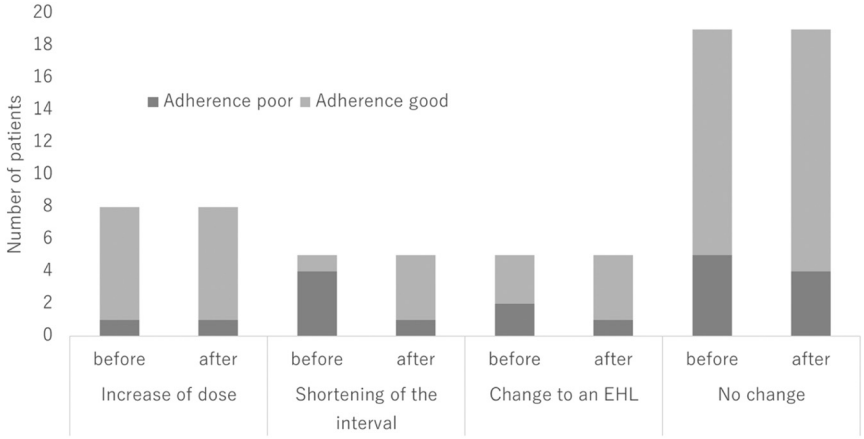

Fig. 2. Improvement of adherence after application of PopPK.
Footnote; EHL: extended half-life product.

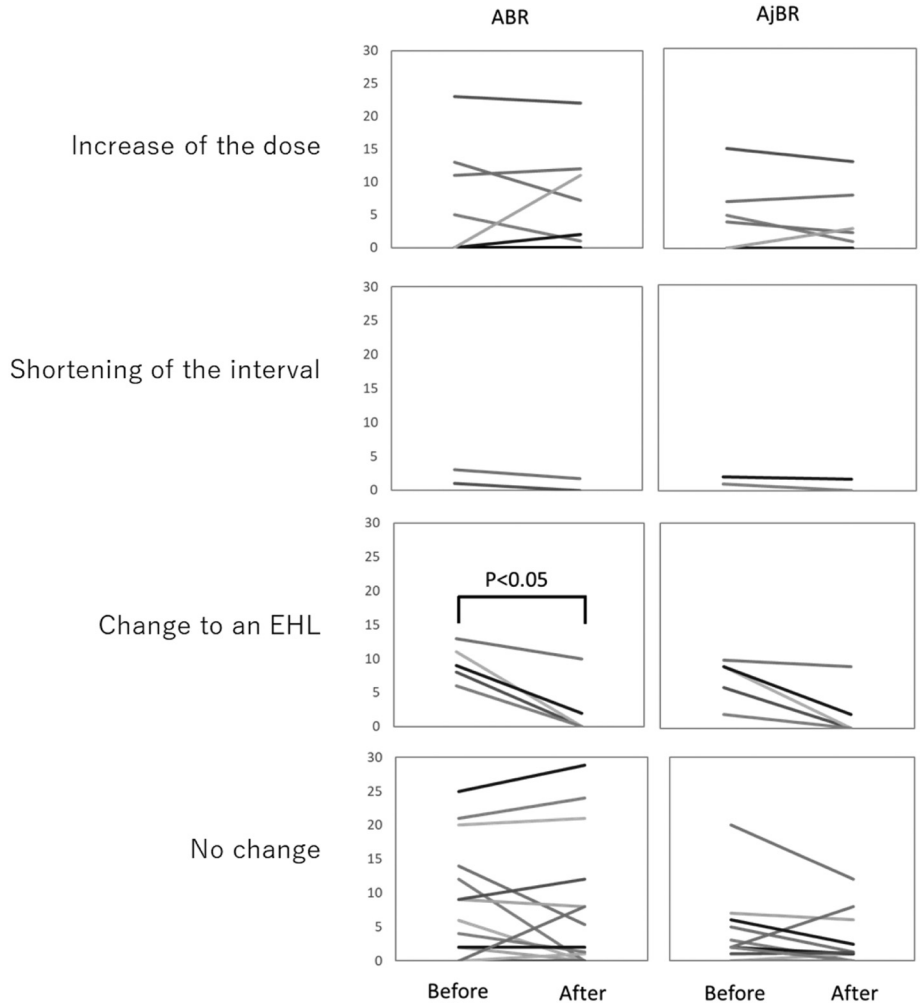

Fig. 3. ABR and AjBR in each group before and after application of PopPK.
Footnote; EHL: extended half-life product, ABR: annualized bleeding rate, AjBR: annualized joint bleeding rate.

4. Discussion

Our study showed that the PopPK profiling using myPKFiT® or the WAPPS-Hemo program led to reconsideration of the prophylactic regimen in 20 of the 39 patients. The impact of adopting PopPK based treatment as measured by changes in treatment adherence and bleeding rate was modest, but the study power was limited by the characteristics of the study population.

Many of the subjects presented end-stage arthropathy (18/39 patients) and target joints (14/39 patients), implying that the population mainly consisted of patients with severe bleeding phenotype; many of the patients (29/39 patients) had breakthrough bleeding whilst on prophylaxis, which in 31% (12/39) of them were not performed according to the guideline-recommended regimens or the package inserts,

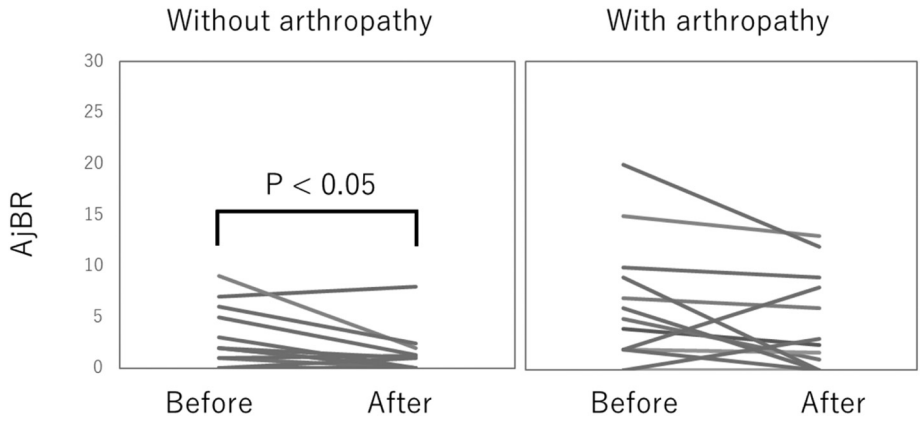

Fig. 4. Comparison of the AjBR between patients with/without end-stage arthropathy before/after application of PopPK.
Footnote; ABR: annualized bleeding rate; AjBR: annualized joint bleeding rate.

as confirmed by the home infusion records.

Adherence is an important consideration for success of prophylaxis [8]. In our study, application of PopPK led to improved adherence, especially in patients in whom the administration interval was shortened, and in patients in whom the product was changed from an SHL to an EHL product, and in one of the 18 patients in whom the prophylactic regimens was not modified. Overall, 5 out of 12 patients (41.6%) who showed poor adherence before, improved their adherence after the PopPK profiling.

Adherence may have a direct influence on the ABR/AjBR, even if Schrijvers et al. reported that low adherence was not always associated with frequent joint bleeding [9] and Pérez-Robles reported the absence of any significant correlation between adherence and the number of bleeding episodes [10]. In our study population, the degree of adherence at baseline did not appear to have a large effect on the ABR/AjBR (Fig. 5). On the other hand, the level of pre-existing arthropathy may affect the impact of PopPK tailoring, as a significant improvement of the AjBR was observed after application of PopPK in patients without but not with arthropathy. Therefore, assessing the impact of tailoring PopPK in patients with end-stage arthropathy may reduce the chance of observing an effect.

Our study does not allow firm conclusions on the effect of PopPK tailoring on ABR/ABJR, as we could not control for two confounders. The first confounder was the choice of SHL versus EHL. Indeed, a significant improvement of the ABR was observed in the group switching from a SHL to an EHL (Fig. 4, $p < 0.05$), which can be due to EHL as much as to tailoring, most likely to both. However, from the view of cost, the cost may change drastically depending on the choice of the products. The second confounder is the "on study effect". Indeed, the ABR/AjBR improved in some patients despite the absence of any change of the prophylactic regimen. One possible interpretation of our results in this group is that performing and discussing their PopPK profile may have influenced their behavior.

We could not measure any reduction in factor concentration usage as there were two patients in whom the dose of the FVIII product could be reduced, and both of these patients had late-stage arthropathy in both the ankle joints and were on intensive treatment, i.e. daily infusion of 50 IU/kg of factor concentrate. Unfortunately, the two patients were bad diary takers and did not contribute data to our analysis. However, good tendency was obtained from at least the amount of prescription and cost.

5. Conclusion

Our study results suggest that PopPK based tailoring supported changing treatment regimen in nearly half of the patients, and may have contributed to improvement of adherence and reduction of the ABR/AjBR.

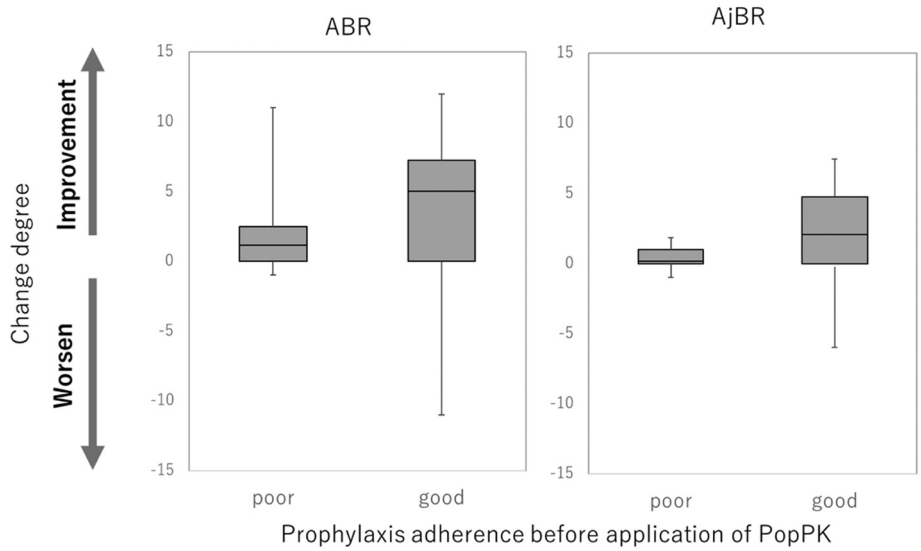

Fig. 5. Changes of the ABR/AjBR depending on the adherence to prophylaxis before application of PopPK.s
Footnote; ABR: annualized bleeding rate; AjBR: annualized joint bleeding rate.

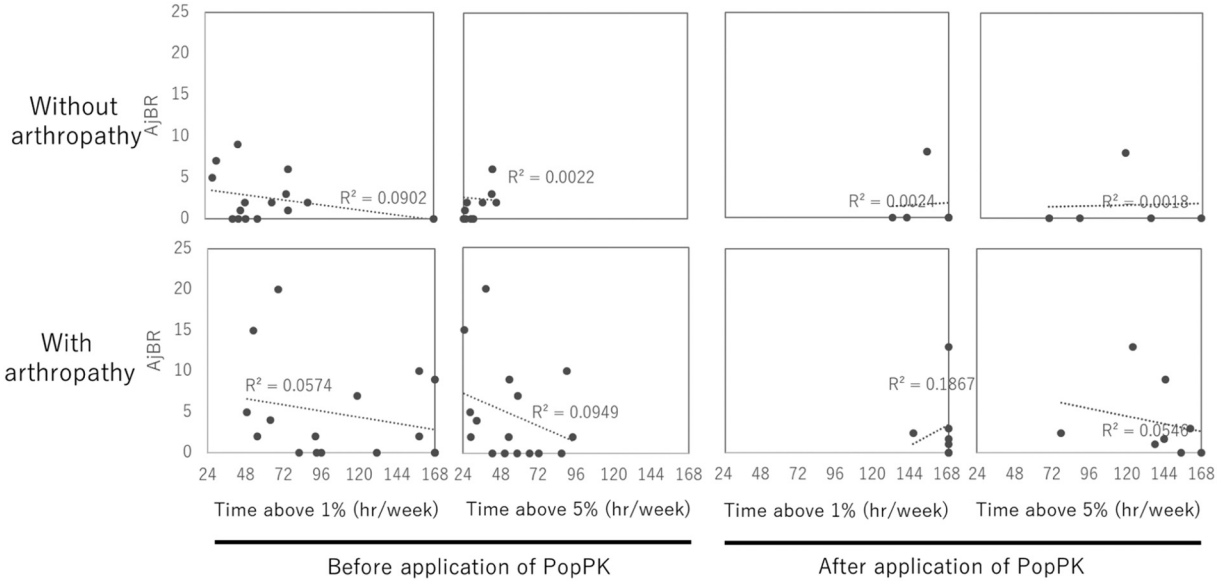

Fig. 6. Correlation between the AjBR and times above 1% and 5% of the factor VIII activity.
Footnote; ABR: annualized bleeding rate; AjBR: annualized joint bleeding rate.

Summary declaration of interest

AN received research grant with no relation of this study from SHIRE.

CY and FG have nothing to declare.

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