The role of pharmacokinetics in optimizing HA treatment: from theory to practice.

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- Professor and Chair at the department of Health Research Methods, Evidence, and Impact at McMaster University Canada
- Director of the Health Information Research Unit (HiRU) of the Hamilton-Niagara Hemophilia Program *http://hiru.mcmaster.ca/hiru*
- Chair of the Canadian Bleeding Disorders Registry Committee (CBDR)
- Principal Investigator of the Web Application for Population Pharmacokinetic in Hemophilia (WAPPS) project *www.wapps-hemo.org*
  Co-investigator of the Patient Reported Outcomes, Burden, and Experiences (PROBE).
- Past-chair of the WFH Data and Demographics committee
  Co-chair of the World Bleeding Disorders Registry (WBDR)

Educational learning for the talk

1) **A) Provide the foundational elements for the role and value of individualized population PK profiling**

   B) Discuss the practicalities of performing population PK profiling with WAPPS-Hemo

2) A) Present evidence supporting the clinical results you can expect to see by adopting WAPPS-Hemo based hemophilia treatment

   B) focusing on switching patients to EHL factor VIII

Note: Main focus on prophylaxis based on factor concentrates

WFH 2020 Guidelines – 3rd edition

Recommendations

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"For patients with haemophilia A or B with a severe phenotype (may include patients with moderate haemophilia), the WFH strongly recommends that such patients be on prophylaxis sufficient to **prevent bleeds at all times**."

Recommendation 6.1.1

"**Prophylaxis should be individualised**, taking into consideration

patient bleeding phenotype, joint status,

individual pharmacokinetics, and

patient self-assessment and preference."

Recommendation 6.3.1

Srivastava A, et al. Haemophilia 2020;00:1–158

Minimal PK evaluation

TABLE 6-6 Tailoring prophylaxis to patient needs

Tailoring approach
Pharmacokinetics • Involves undertaking at least a minimal PK evaluation of patients and then adjusting the dose/frequency of factor infusions in order to achieve in each patient a predetermined factor trough level. • Can be estimated with population PK modeling (e.g., WAPPS-Hemo)[a] using Bayesian analysis

Haemophilia, *26*(S6), 1–158. https://doi.org/10.1111/hae.14046

British Journal of Haematology, bjh.16704. https://doi.org/10.1111/bjh.16704

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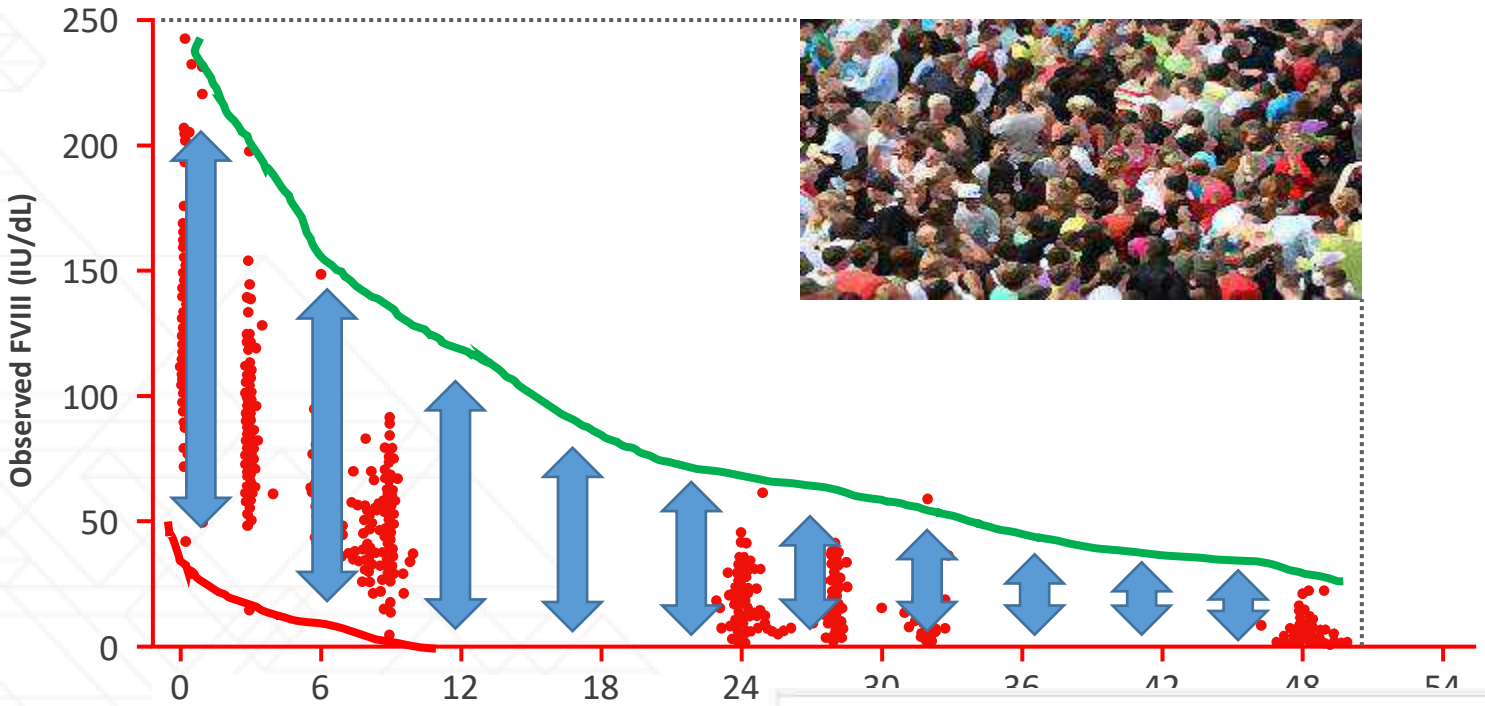
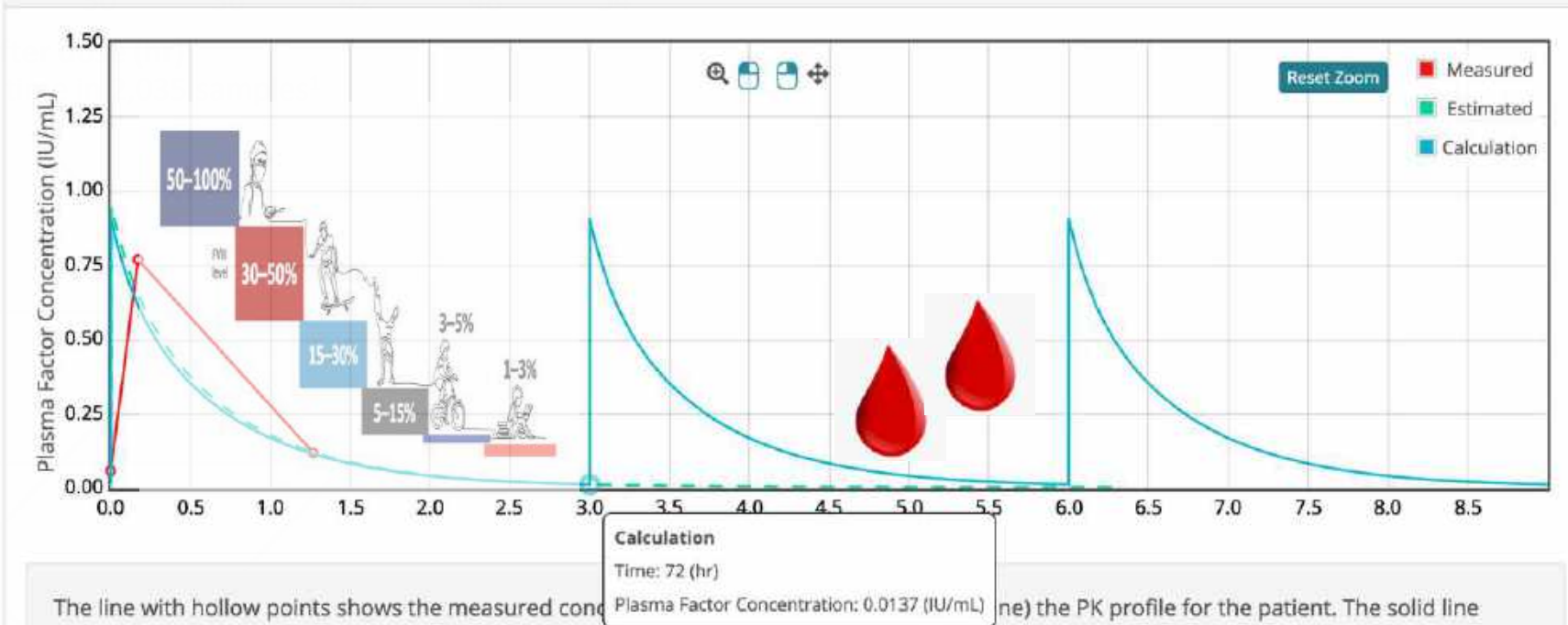
One size does NOT fit all.

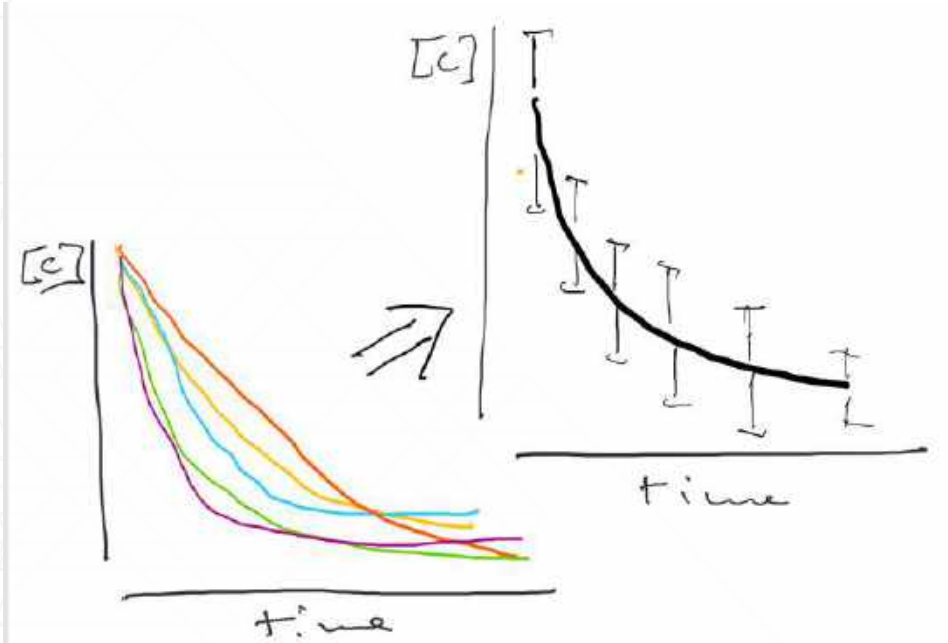
The unmet need

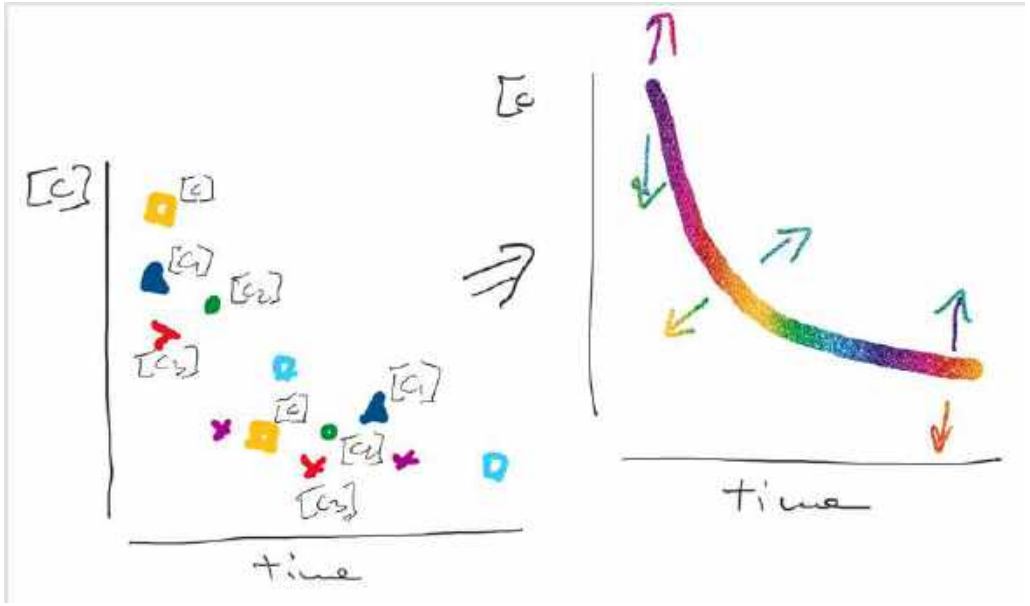


Distribution of observed FVIII levels over



Population pharmacokinetic – basic concepts

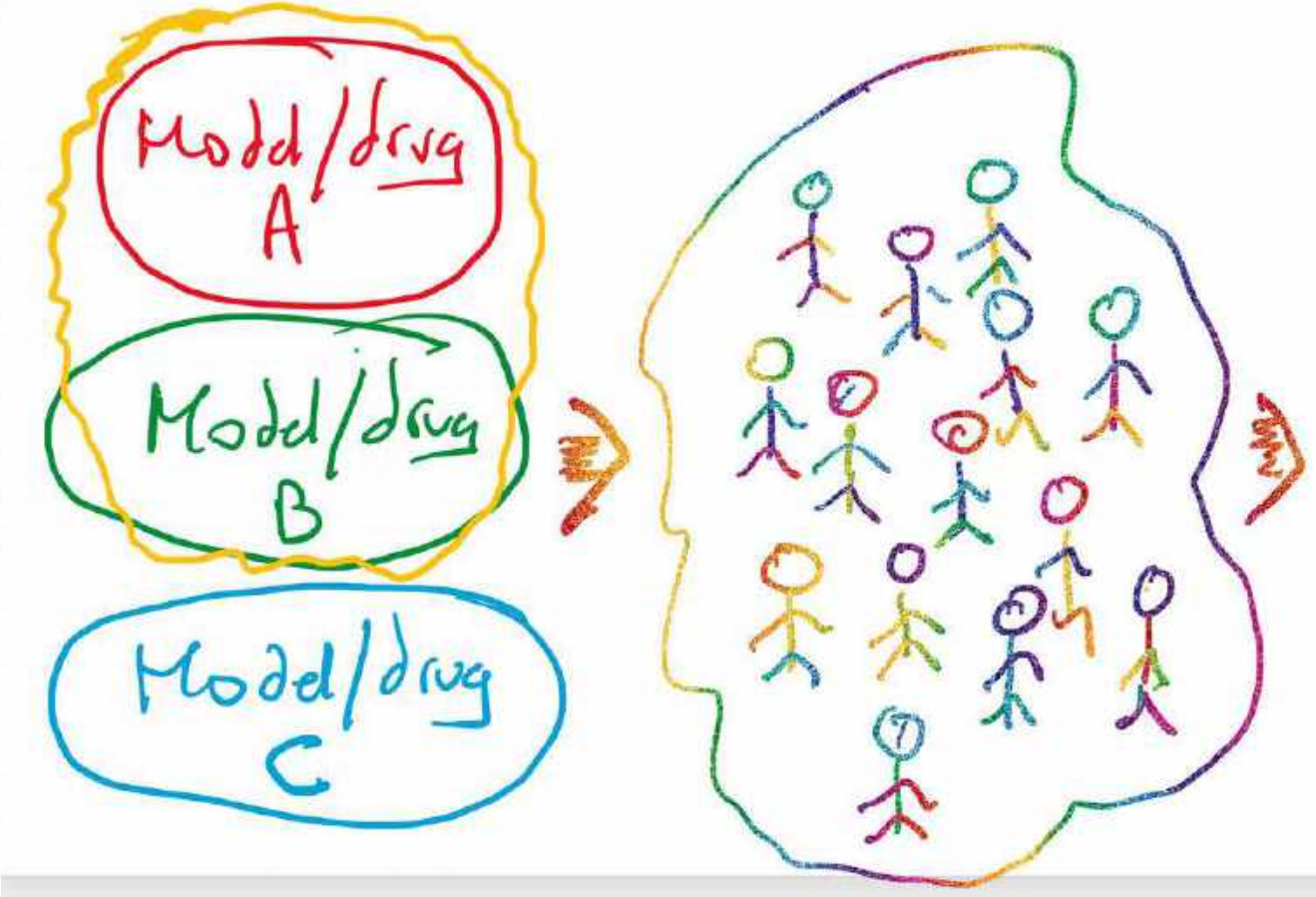




Item	Classical PK Study	Population PK Study
Focus	Drug (and SAMPLED individuals)	Population (and DRUG if enough cases)
Individual profiling	Full set of samples needed	
Pros	Fewer patients; easy math;	[Few] sparse sample; predictive value
Cons	Many draws; no predictive value	Many patients; computationally complex

Population PK – can be used to fairly compare different treatments

In the same real or virtual population



- Individual PK estimates
- Average PK estimates by drug
- Average PK outcomes by regimen by drug
- Fair statistical comparison of different concentrates in the same population

Preijers T et al. Eur J Clin Pharmacol. 2021 Aug;77(8):1193-1200. **Gorkom BAP** et al. Br J Clin Pharmacol. 2021 Jun;87(6):2602-2613. **Bukkems LH** et al. Thromb Haemost. 2021 Jun;121(6):731-740. **Carcao MD** et al. J Thromb Haemost. 2019 Jul;17(7):1085-1096. **Tardy B** et al. Haemophilia. 2022 Jul;28(4):542-547. **Versloot O** et al. Hemasphere. 2022 Mar 21;6(4):e694.

Educational learning for the talk

1) A) Provide the foundational elements for the role and value of individualized population PK profiling

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Note: Main focus on prophylaxis based on factor concentrates

Population pharmacokinetic – Can we trust it? Is it worth?

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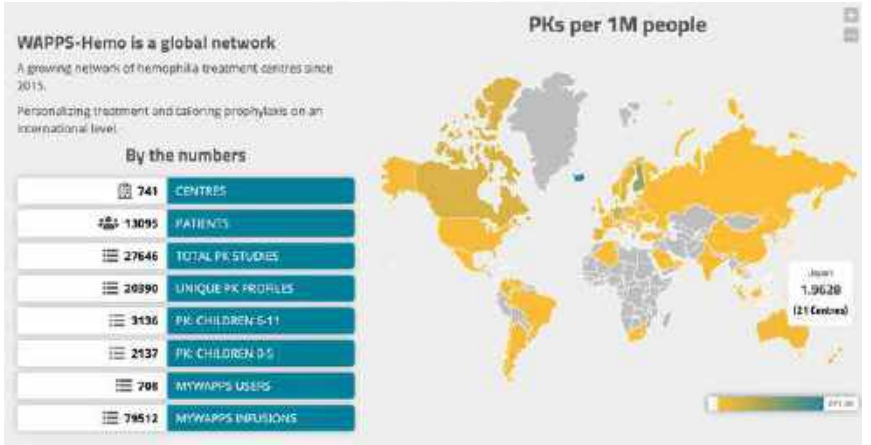
PopPk with

- 2 sample including pre-dose and info on previous infusion retains 85% of the precision of a classical individual profile
- >5 sample consistently beats the classical approach

Benefits when used at the POC:

1. It does not require wash out
2. Can precisely estimate a regimen, of any complexity
3. Can precisely predict the impact of changing dose/frequency
4. Can “merge” samples obtained after different infusion
5. Can model the changes associated with changes in age, weight, height, (VWF levels)



WAPPS-Hemo: worldwide usage

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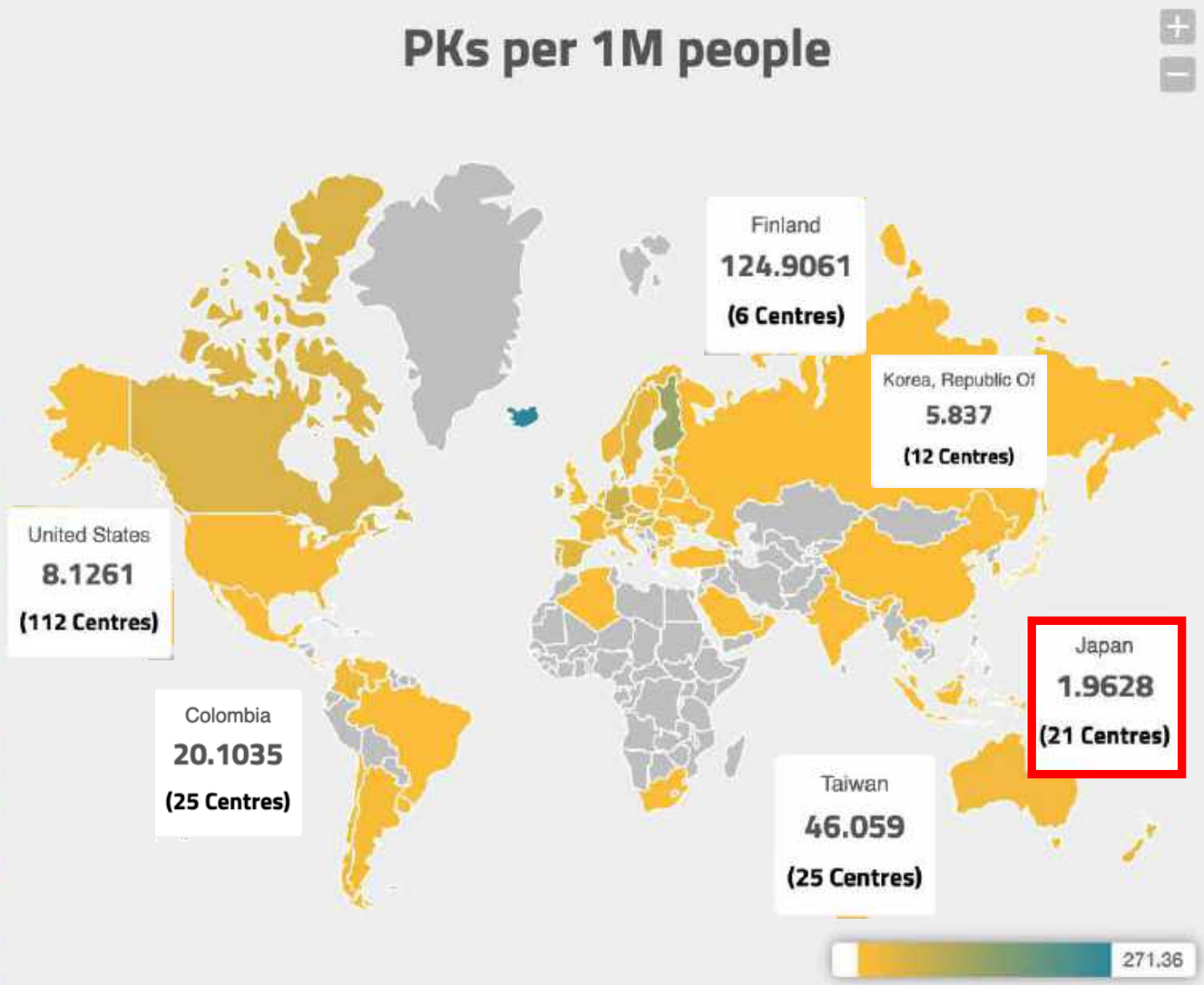
WAPPS-Hemo is a global network

A growing network of hemophilia treatment centres since 2015.

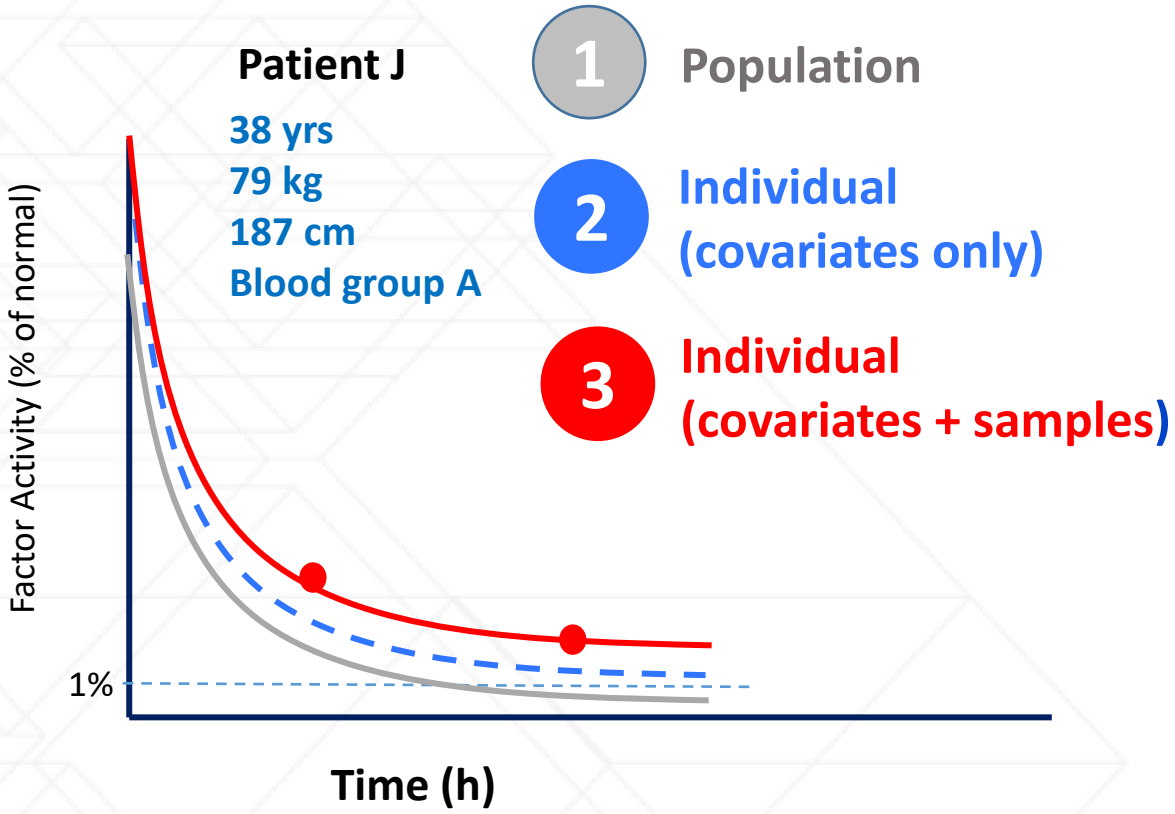
Personalizing treatment and tailoring prophylaxis on an international level.

By the numbers

741	CENTRES
13095	PATIENTS
27646	TOTAL PK STUDIES
20390	UNIQUE PK PROFILES
3136	PK: CHILDREN 6-11
2137	PK: CHILDREN 0-5
708	MYWAPPS USERS
79512	MYWAPPS INFUSIONS

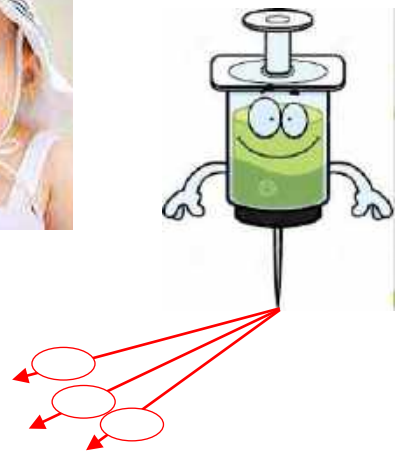


Estimating an individual PK profile with pop PK approach



New ISTH guidelines

(popPK + sparse sampling)



Washout

Iorio A, Blanchette V, Blatny J, Collins P, Fischer K, Neufeld E
J Thromb Haemost. 2017 Oct 12. doi: 10.1111/jth.13867.

Iorio A, et al. Performing and interpreting individual pharmacokinetic profiles in patients with Hemophilia A or B: Rationale and general considerations.
Res Pract Thromb Haemost. 2018 Jul 20;2(April):1–14. doi. 10.1002/rth2.12106

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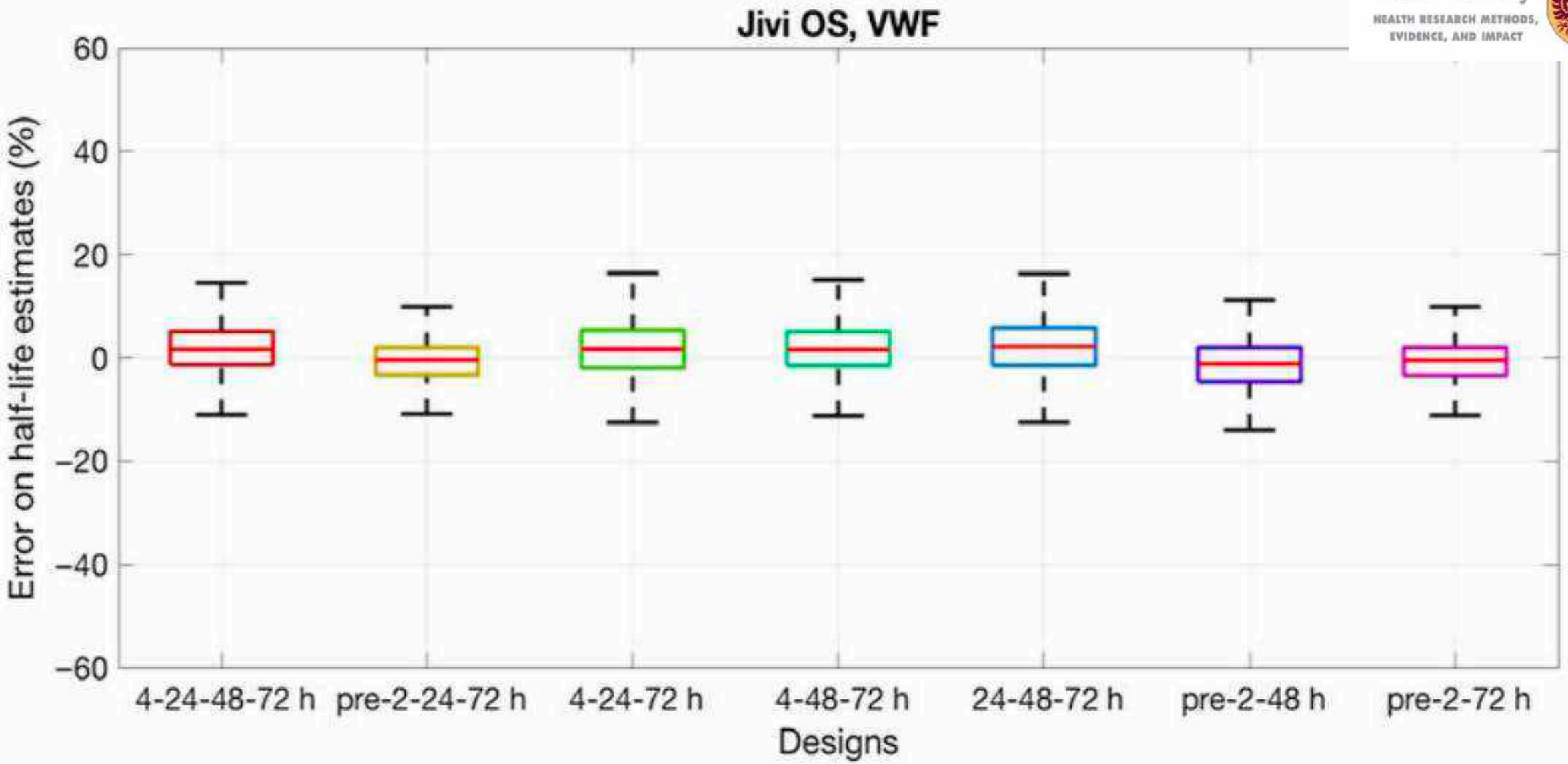
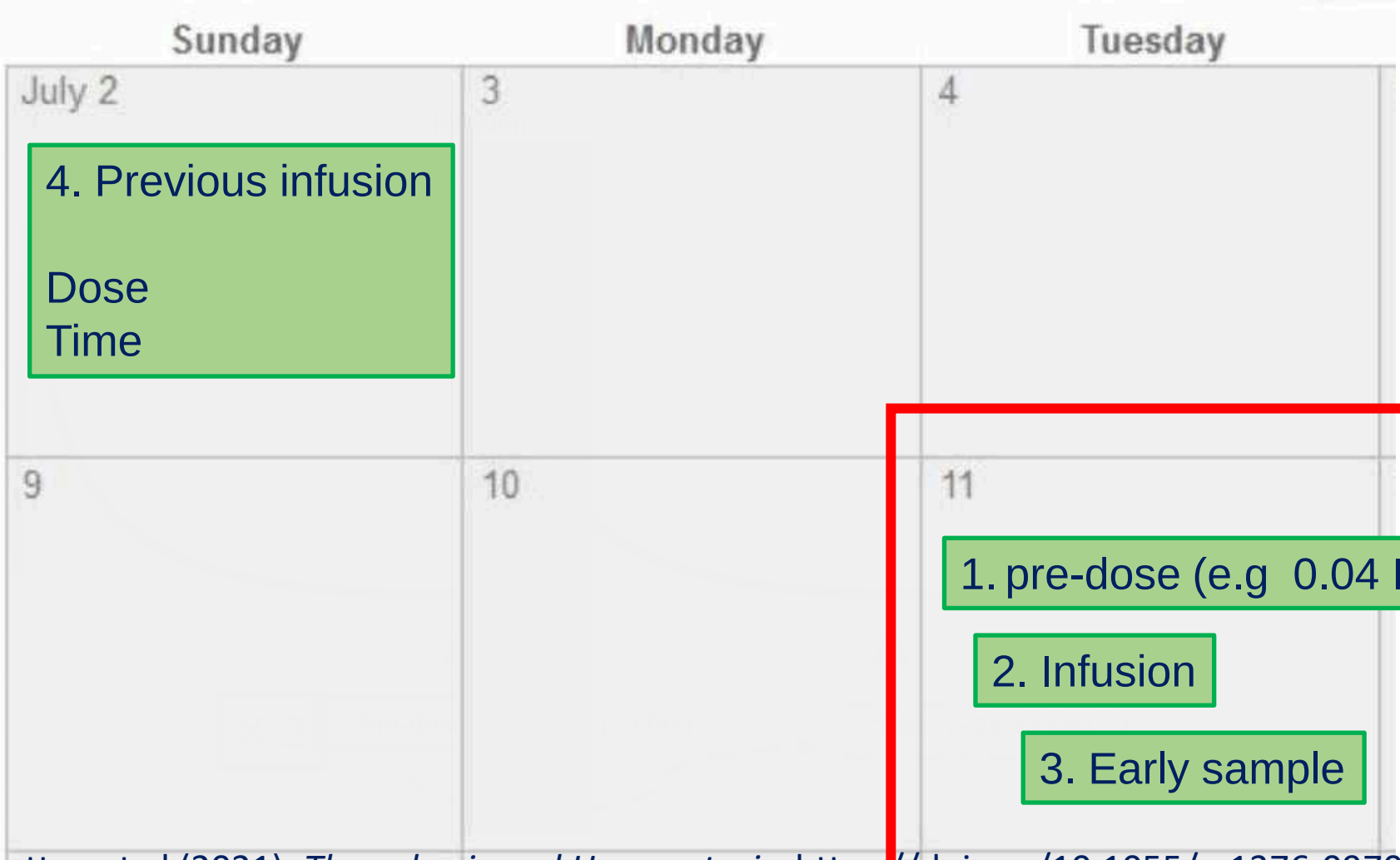


Simplified PK study

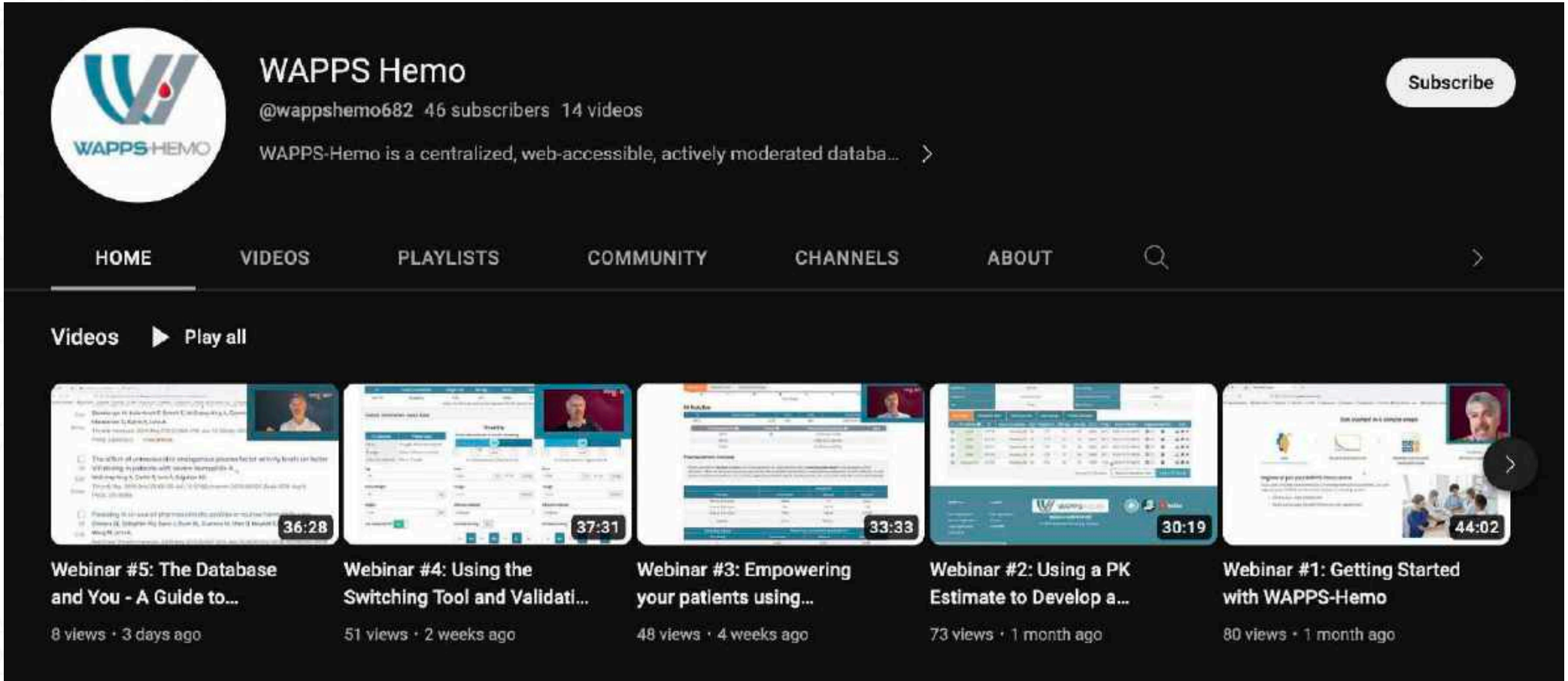


1.pre-dose
2.Early sample
3.Late sample

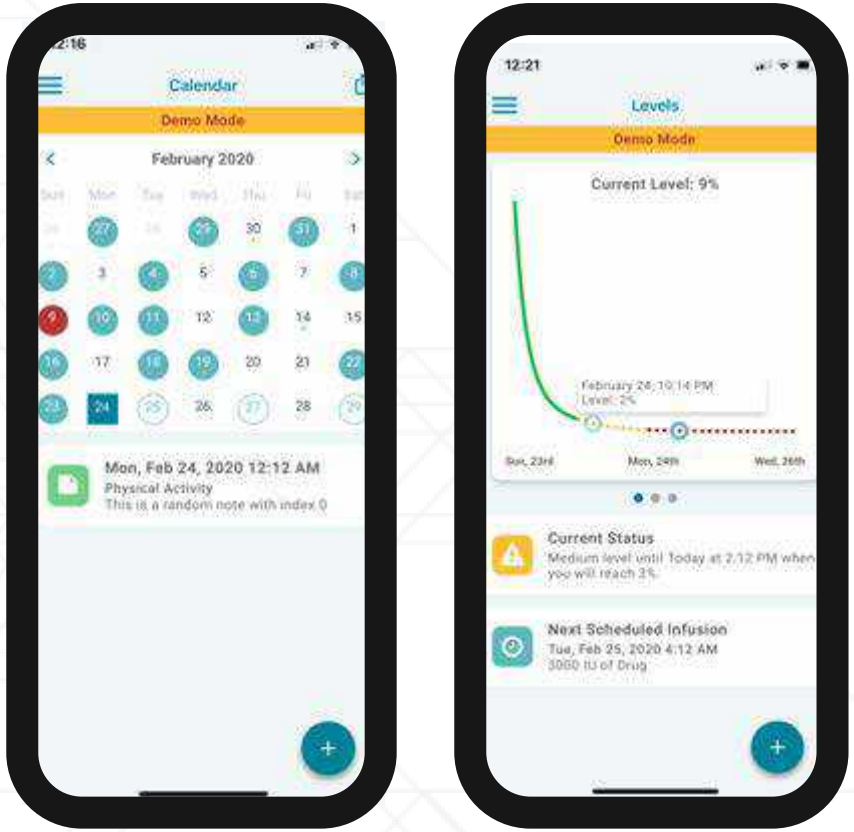
Blanchette, et al (2021). *Thrombosis and Haemostasis*. https://doi.org/10.1055/a-1376-0970

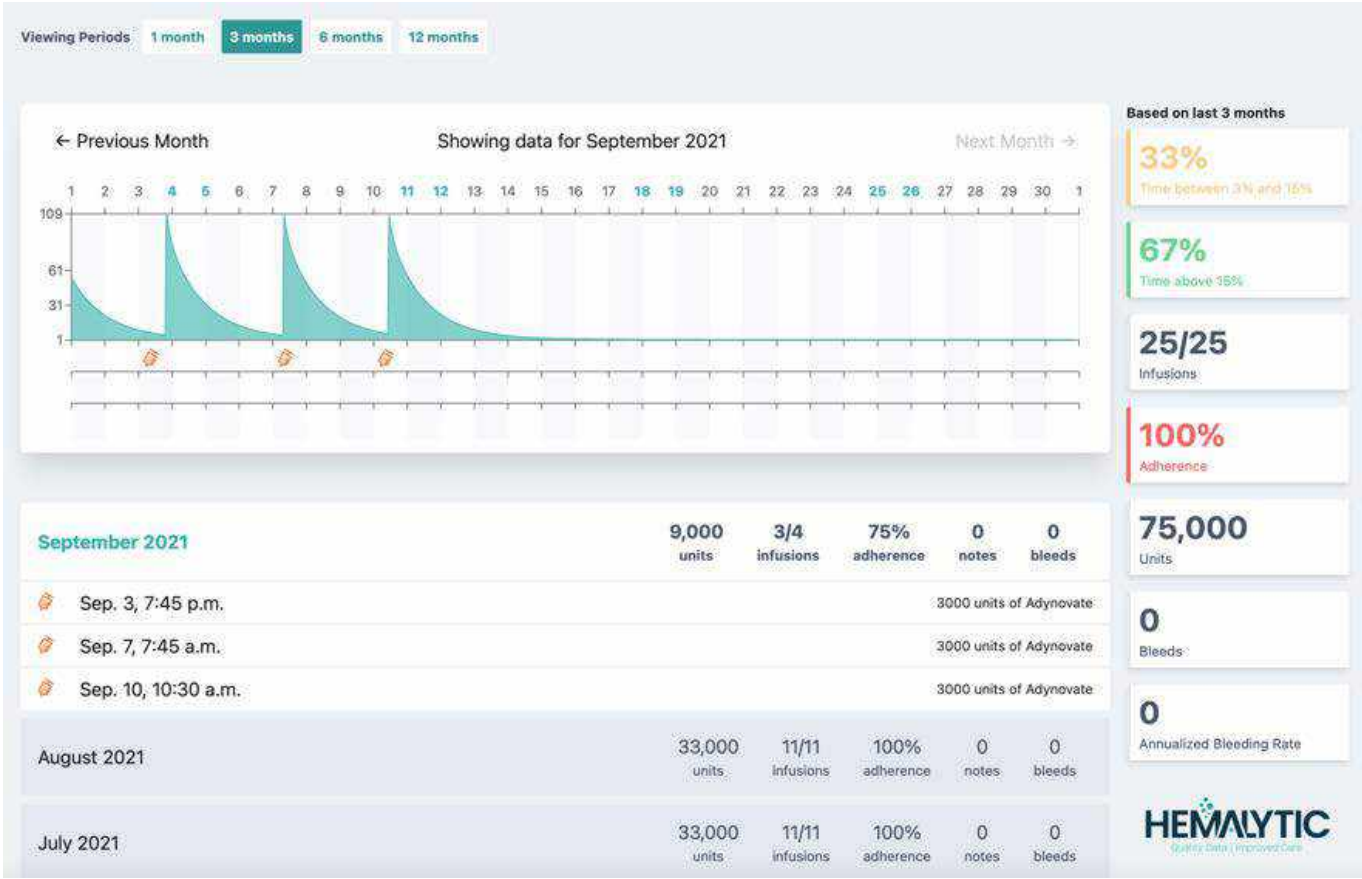
Educational webinar series

- WAPPS-Hemo YouTube channel: https://www.youtube.com/@wappshemo682/featured



”Rewards” and “usable outputs”





Viewing Periods | 1 month | 3 months | 6 months | 12 months

June 2022	15,000 units	15/15 infusions	100% adherence	0 notes	0 bleeds
May 2022	16,500 units	17/16 infusions	100% adherence	0 notes	0 bleeds
April 2022	15,000 units	15/15 infusions	100% adherence	0 notes	0 bleeds
March 2022	15,500 units	16/15 infusions	100% adherence	0 notes	0 bleeds
February 2022	14,000 units	14/14 infusions	100% adherence	0 notes	0 bleeds
January 2022	16,000 units	16/16 infusions	100% adherence	0 notes	0 bleeds
December 2021	15,000 units	15/15 infusions	100% adherence	0 notes	0 bleeds
November 2021	16,000 units	16/15 infusions	100% adherence	0 notes	0 bleeds
October 2021	15,000 units	15/15 infusions	100% adherence	0 notes	0 bleeds

Based on last 12 months

39%
Time between 3% and 15%

41%
Time above 15%

159/176
Infusions

90%
Adherence

158,000
Units

0
Bleeds

0
Annualized Bleeding Rate

HEMALYTIC

Educational learning for the talk

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   B) focusing on switching patients to EHL factor VIII

Note: Main focus on prophylaxis based on factor concentrates

Rurioctocog alfa pegol PK-guided prophylaxis in hemophilia A: results from the phase 3 PROPEL study

Robert Klamroth,[1] Jerzy Windyga,[2] Vlad Radulescu,[3] Peter W. Collins,[4] Oleksandra Stasyshyn,[5] Hishamshah Mohd Ibrahim,[6] Werner Engl,[7] Srilatha D. Tangada,[8] William Savage,[8] and Bruce Ewenstein[8]

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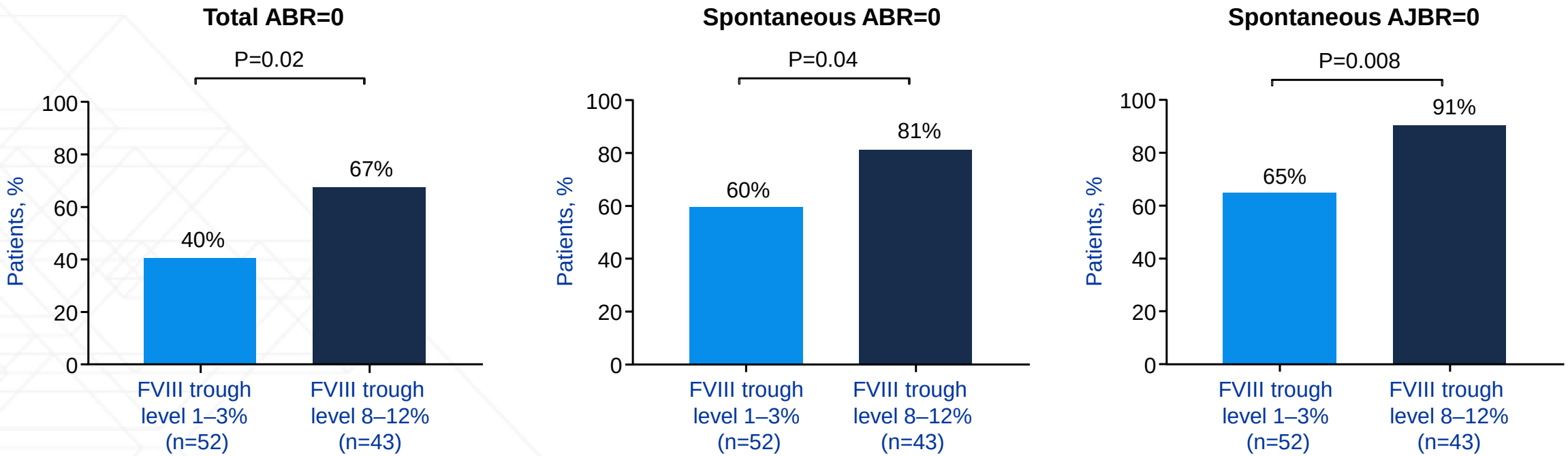

	FVIII trough level 1–3% (n=52)	FVIII trough level 8–12% (n=43)
Total ABR, mean (SD)	2.8 (3.0)	1.2 (2.4)
Spontaneous ABR, mean (SD)	1.7 (2.5)	0.6 (1.5)
Spontaneous AJBR, mean (SD)	1.2 (2.0)	0.4 (1.4)

ABR, annualized bleeding rate; AJBR, annualized joint bleeding rate; FVIII, factor VIII.
P<0.05 between the 1–3% and 8–12% trough arms is considered statistically significant.

P values are by χ^2 test

Klamroth, R. *Blood*, *137*(13), 1818–1827.

Impact of Adopting Population Pharmacokinetics for Tailoring Prophylaxis in Haemophilia A Patients: A Historically Controlled Observational Study

Michaela Stemberger[1,2] Felix Kallenbach[2] Elisabeth Schmit[2] Alanna McEneny-King[3] Federico Germini[4,5] Cindy H. T. Yeung[4] Andrea N. Edginton[3] Sylvia von Mackensen[6] Karin Kurnik[7] Alfonso Iorio[4,8]

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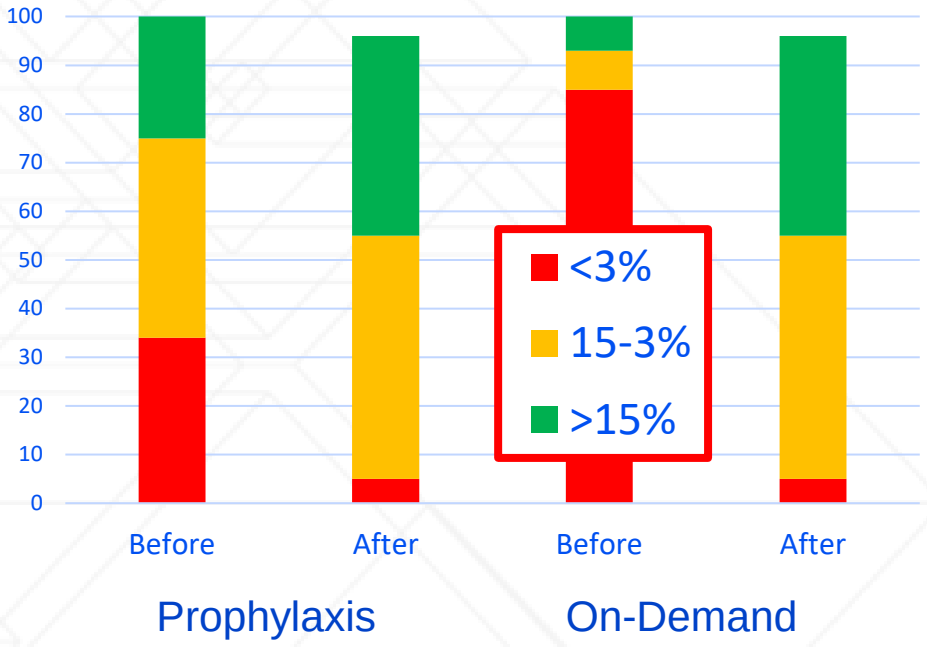
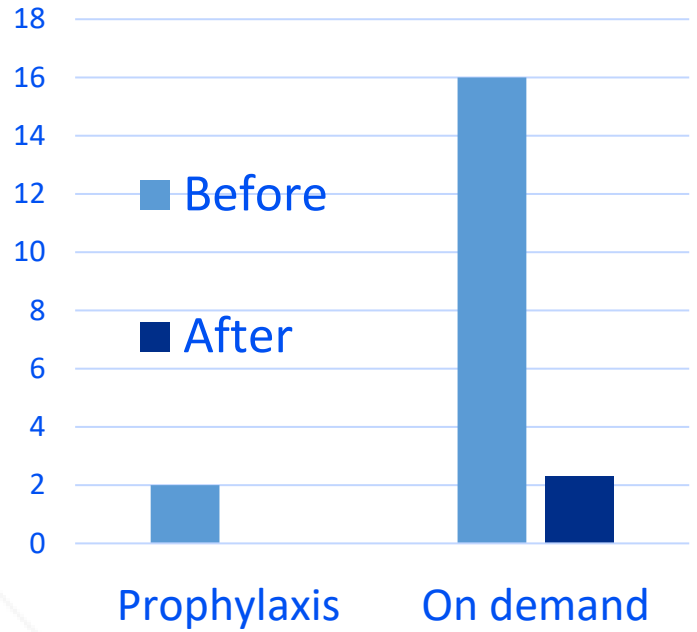
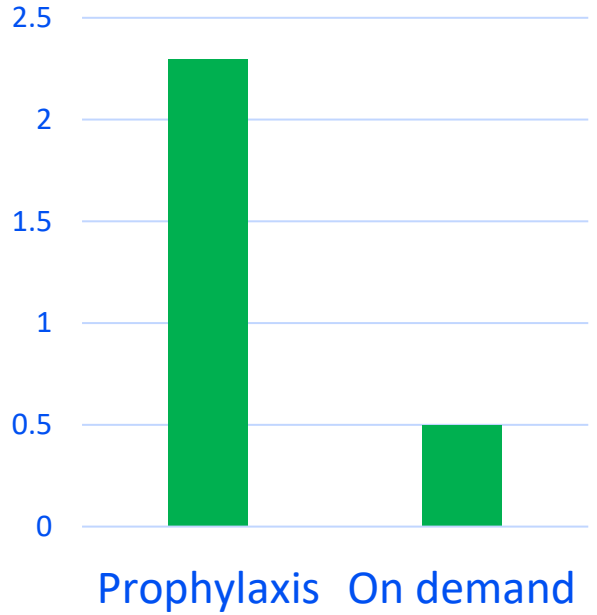
Time spent in range (AUC)



ABR



Hema-A-QoL



Stemberger M,. *Thromb Haemost* 2019; **119**: 368–76.

Received: 14 September 2021 | Revised: 5 April 2022 | Accepted: 23 April 2022

DOI: 10.1111/hae.14584

Haemophilia WFH WILEY

ORIGINAL ARTICLE

Clinical haemophilia

Pharmacokinetic profile of children with haemophilia A receiving low-dose FVIII prophylaxis in Indonesia: A single centre experience

Fitri Primacakti | Teny T. Sari | Djajadiman Gatot | Hikari A. Sjakti | Novie A. Chozie

Conclusion: Our study identified inter-individual differences in the PK parameters using LDP of FVIII twice weekly. The inter-individual results in different dosing intervals advise the timing of LDP. Estimating individual PK parameters enables the identification of the optimal prophylaxis frequency to prevent bleedings.

For dosage and administration, please refer to the package insert.

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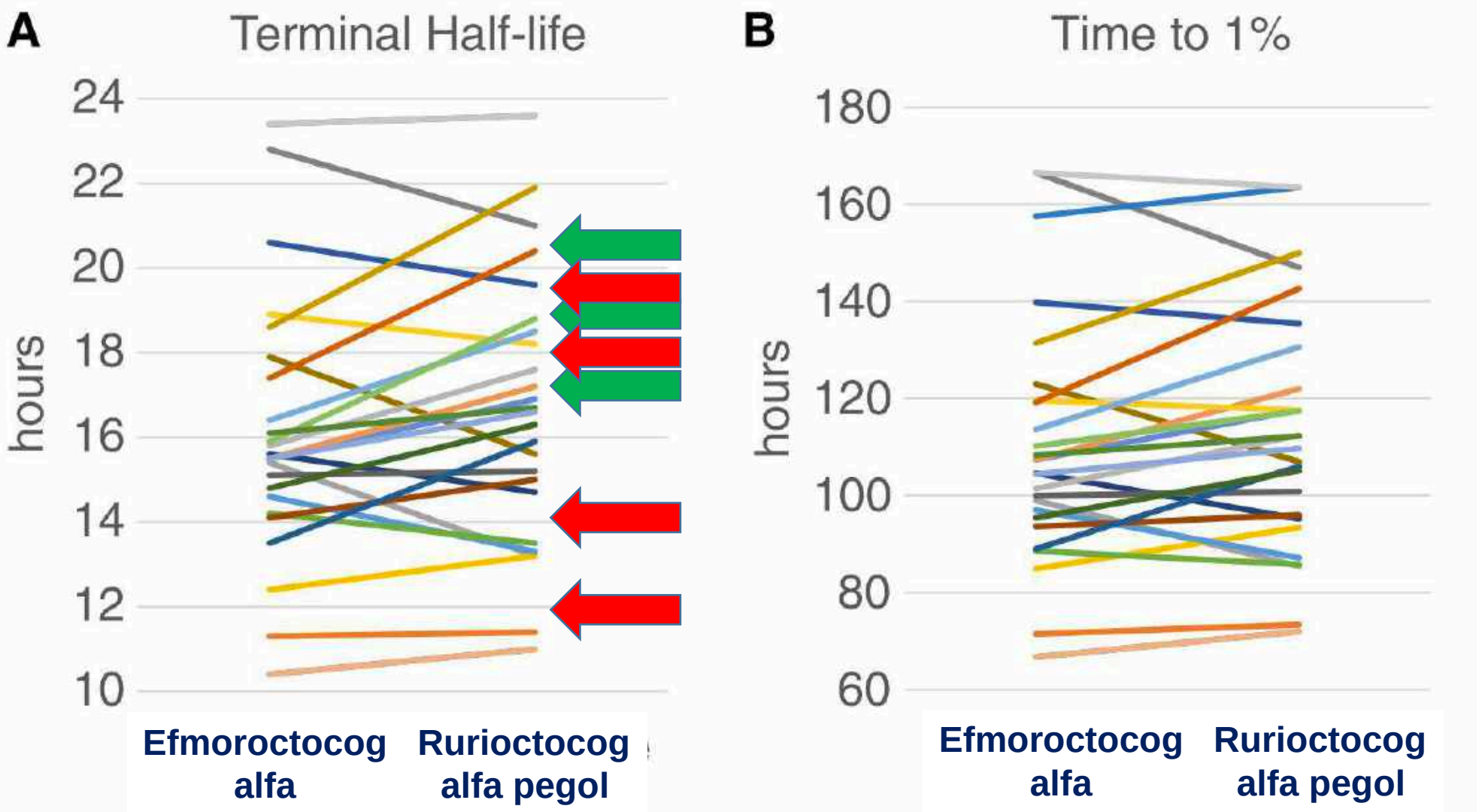
Interindividual variability



Carcao MD et al. Comparative pharmacokinetics of two extended half-life FVIII concentrates (Eloctate and Adynovate) in adolescents with hemophilia A: Is there a difference? J Thromb Haemost. 2019 Jul 2;17(7):1085–96.

Thrombosis Research 184 (2019) 31–37

Contents lists available at ScienceDirect

Thrombosis Research

journal homepage: www.elsevier.com/locate/thromres

Full Length Article

A comparison of methods for prediction of pharmacokinetics across factor concentrate switching in hemophilia patients

Jacky K. Yu (PharmD)[a], Alfonso Iorio (MD, PhD)[b], Pierre Chelle (PhD)[a], Andrea N. Edginton (PhD)[a,*]

[a] School of Pharmacy, University of Waterloo, Waterloo, Ontario, Canada
[b] McMaster-Bayer Endowed Research Chair for Clinical Epidemiology of Congenital Bleeding Disorde
Evidence and Impact, McMaster University, Ontario, Canada

HemaSphere

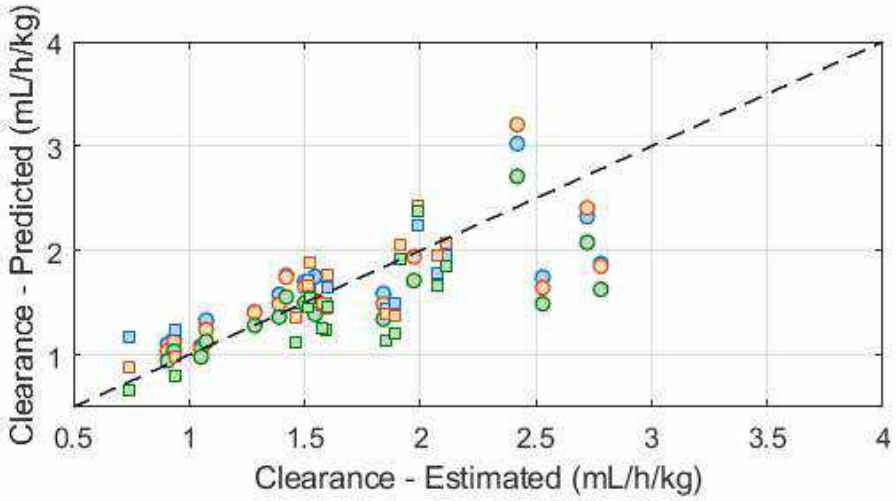
EHA EUROPEAN HEMATOLOGY ASSOCIATION

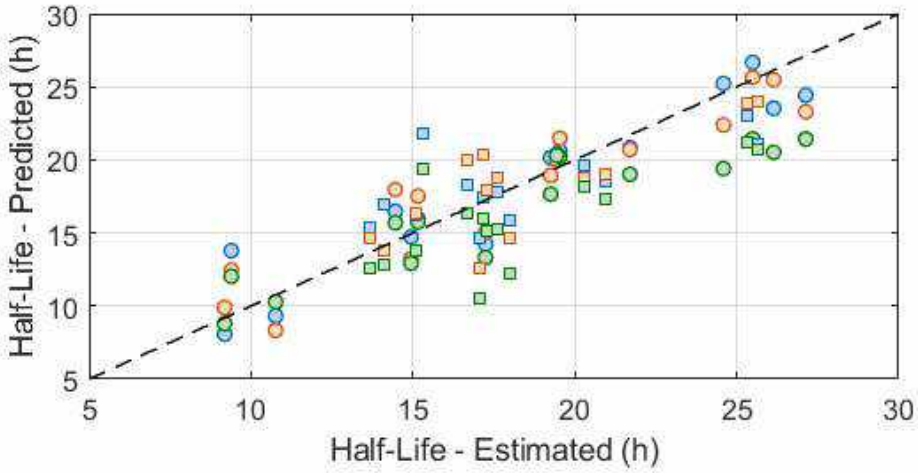
Article
Open Access

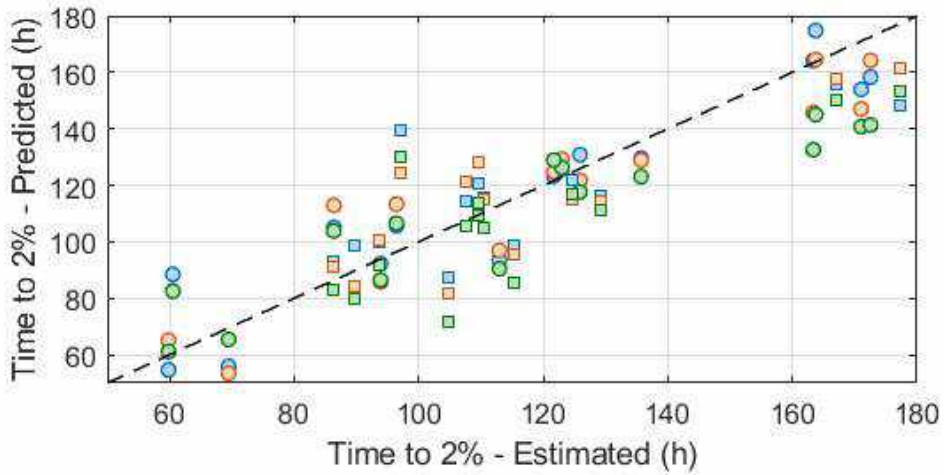
Predicting Individual Changes in Terminal Half-Life After Switching to Extended Half-Life Concentrates in Patients With Severe Hemophilia

Olav Versloot[1], Emma Iserman[2], Pierre Chelle[3], Federico Germini[2,4], Andrea N. Edginton[3], Roger E. G. Schutgens[1], Alfonso Iorio[2], Kathelijn Fischer[1]; on behalf of the prophylaxis working group of the International Prophylaxis Study Group*

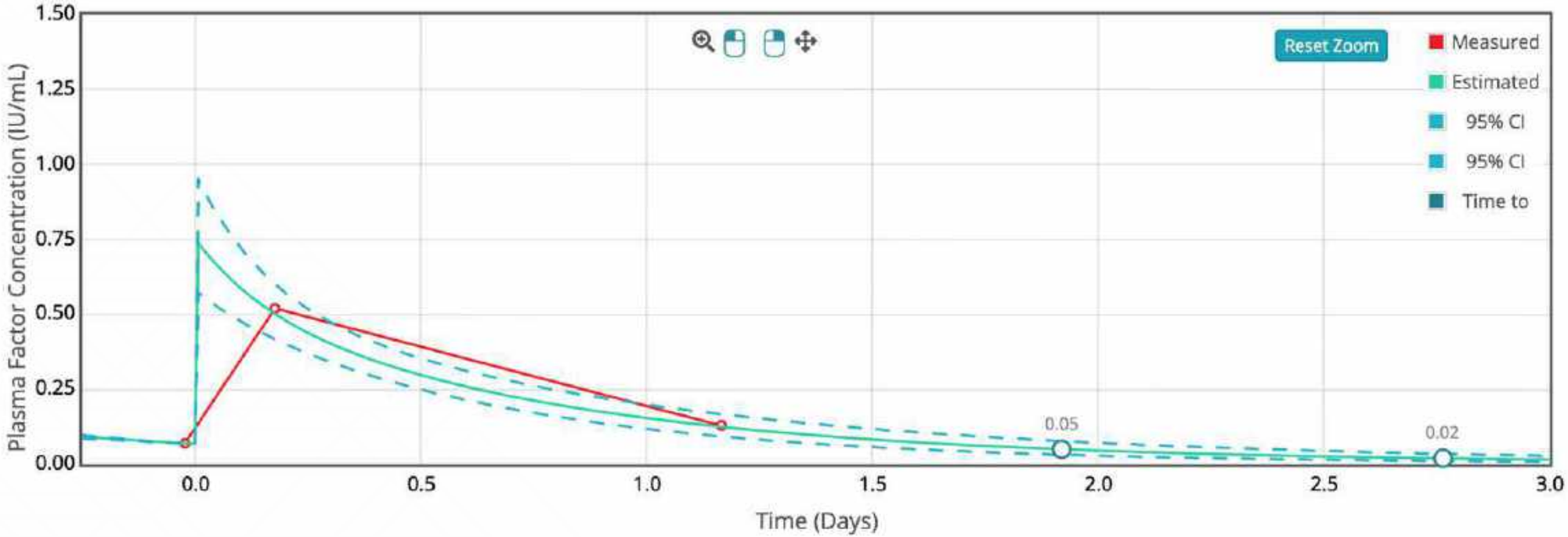
Observations vs Predictions (1)







PK Estimate | Validation Point | Updated PK Estimate



PK Study Data

ID	Factor Concentrate	Tot IU	IU/kg	End of infusion
	Kovaltry	2000	31.7	2022-01-01 08:00

Time Elapsed (hh:mm)	Pre-dose	Plasma Factor Concentration	Notes
-00:35	✓	0.070 IU/mL (7.0%)	
+04:12		0.520 IU/mL (52.0%)	
+27:56		0.130 IU/mL (13.0%)	

The WAPPS-Hemo calculator switching support function: first scenario – keep the same treatment plan

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Treatment Plan	Kovaltry			Jivi		
	Mo	We	Fr	Mo	We	Fr
Dose, IU	2000	2000	2000	2000	2000	2000
Infusion Interval, Days	2.0	2.0	3.0	2.0	2.0	3.0
Peak, IU/mL (95% CI)	0.7 (0.565-0.908)	0.73 (0.609-0.918)	0.73 (0.617-0.918)	0.92 (0.787-1.164)	0.98 (0.868-1.192)	0.99 (0.890-1.193)
Trough, IU/mL (95% CI)	0.043 (0.012-0.095)	0.045 (0.013-0.103)	0.016 (0.002-0.051)	0.106 (0.034-0.211)	0.114 (0.035-0.233)	0.043 (0.007-0.129)
Weekly Dosage, IU	6000			6000		
Time above 0.01 IU/mL	100%			100%		
Time above 0.03 IU/mL	90%			100%		
Time above 0.15 IU/mL	43%			72%		
	Save			Save		

For dosage and administration of Damoctocog alfa pegol, please refer to the package insert.

The WAPPS-Hemo calculator switching support function: second scenario – less frequent infusions

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Treatment Plan	Kovaltry		Jivi	
	Mo	Th	Mo	Th
Dose, IU	2000	2000	2000	2000
Infusion Interval, Days	3.0	4.0	3.0	4.0
Peak, IU/mL (95% CI)	0.69 (0.540-0.906)	0.7 (0.559-0.908)	0.89 (0.720-1.159)	0.91 (0.762-1.164)
Trough, IU/mL (95% CI)	0.015 (0.002-0.045)	**< 0.01** (0.001-0.026)	0.039 (0.006-0.105)	0.017 (0.001-0.063)
Weekly Dosage, IU	4000		4000	
Time above 0.01 IU/mL	94%		100%	
Time above 0.03 IU/mL	65%		89%	
Time above 0.15 IU/mL	27%		47%	
	Save		Save	

The WAPPS-Hemo calculator switching support function: third scenario – dose calculation to achieve target trough

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Switch simulation input data

Treatment Plan	Kovaltry	Jivi
Dose, IU (95% CI)	4724 (1108-32065)	1431 (396-9660)
Infusion Interval, Days	3.0	3.0
Peak, IU/mL (95% CI)	1.64 (0.315-14.546)	0.65 (0.160-5.622)
Trough, IU/mL	0.03	0.03
Weekly Dosage, IU	11023	3339
Time above 0.01 IU/mL	100%	100%
Time above 0.03 IU/mL	100%	100%
Time above 0.15 IU/mL	55%	45%
	Save	Save

Variations in PK parameters *(AUC and clearance)* observed in patients switching from Kovaltry to Jivi: Canadian switching experience

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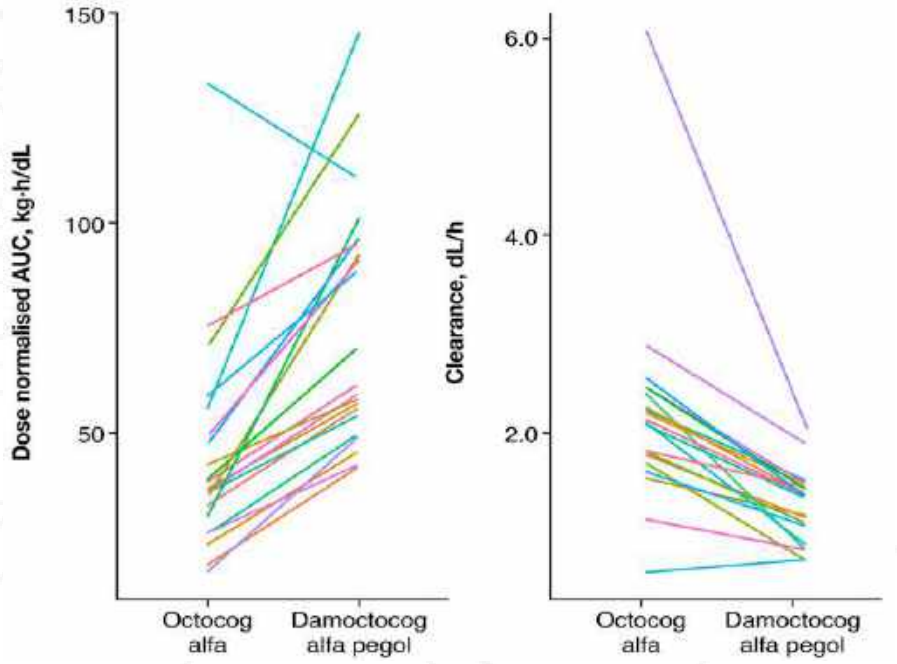
Single-centre, intra-patient comparison of Jivi PK with Kovaltry, using data routinely collected by the Hamilton-Niagara Regional Hemophilia Treatment Centre

Evaluate the changes in PK parameters in patients switching from Kovaltry to Jivi in real-world practice

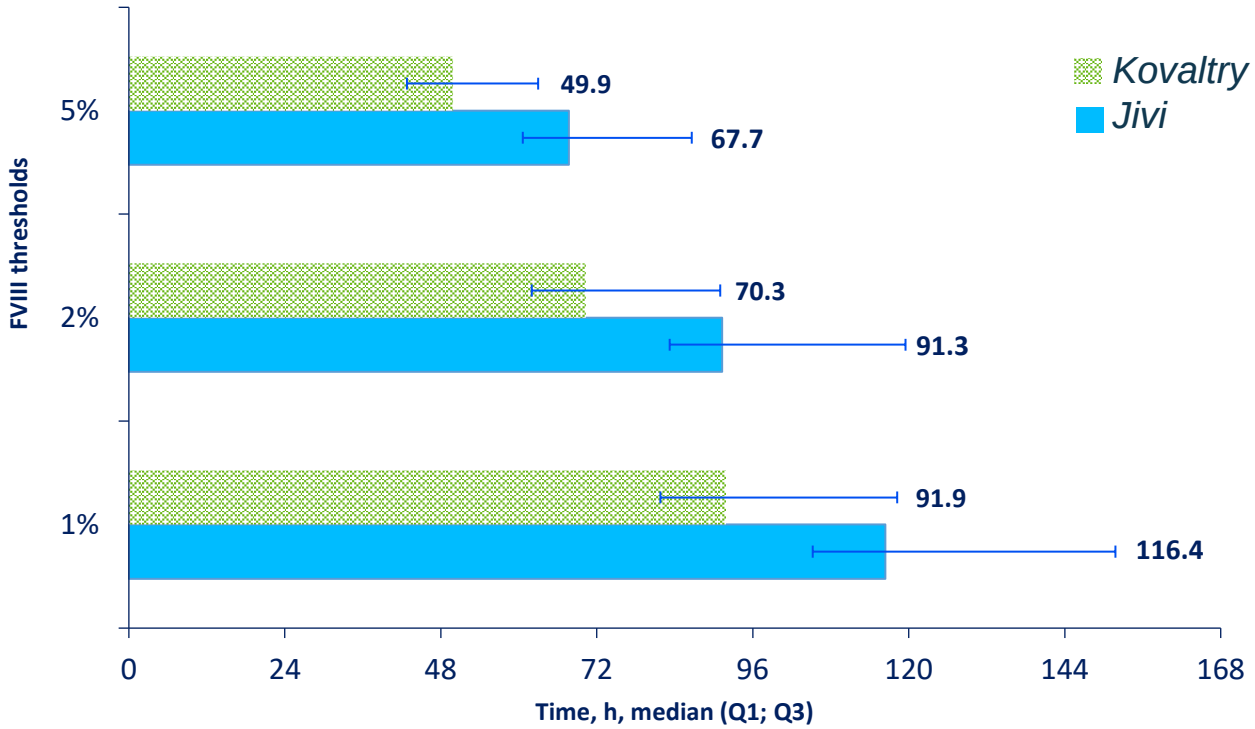
- ✓ Aged ≥12 years
- ✓ Severe or moderately severe Hem A (FVIII:C ≤2%)
- ✓ Kovaltry prophylaxis for ≥9 months

Fig. 1. Dose normalised AUC and clearance by patient (n=22)



	Octocog alfa	Damoctocog alfa pegol	Octocog alfa	Damoctocog alfa pegol
Median (Q1; Q3)	37.6 (30.8; 53.9)	66.0 (54.8; 94.3)	2.1 (1.8; 2.4)	1.3 (1.1; 1.4)

Fig. 2 . Time to FVIII thresholds



EHL, extended-half-life; PK, Pharmacokinetics; HemA, Hemophilia A. Kovaltry: ocotocog alfa); Jivi: Damoctocog alfa pegol
Iorio A. et al. Poster PO041 presented at EAHAD 2022

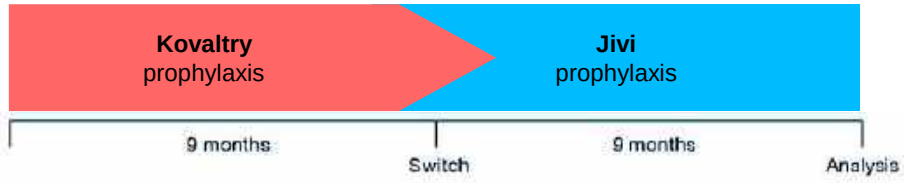
31

Changes in clinical outcomes in already well-maintained patients: Canadian switching experience

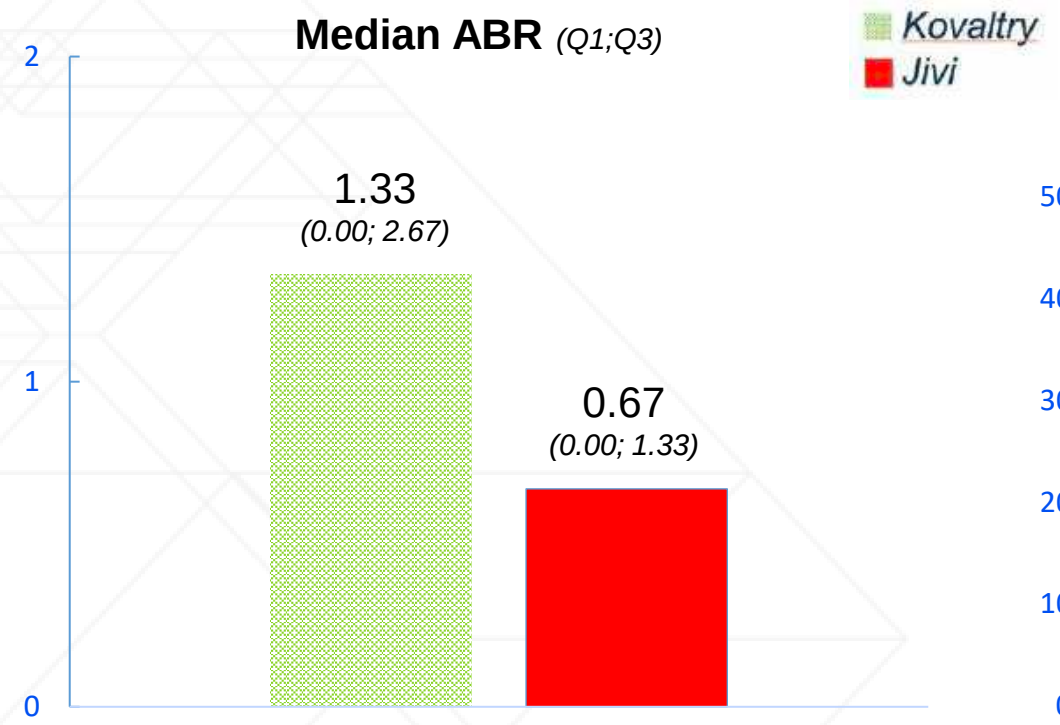
Single-centre, intra-patient comparison of Jivi clinical outcomes with Kovaltry, using data routinely collected by the Hamilton-Niagara Regional Hemophilia Treatment Centre

Evaluate the changes in effectiveness, utilization and patient satisfaction in patients switching from Kovaltry to Jivi in real-world practice

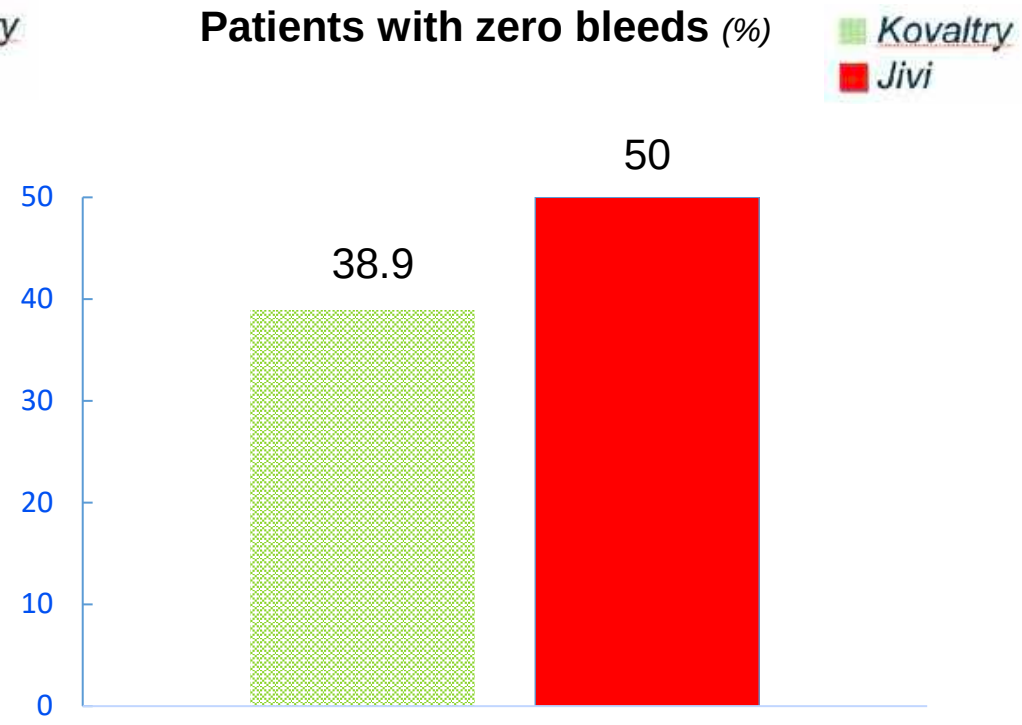
Study duration was **18 months per patient**



Median ABR *(Q1;Q3)*



Patients with zero bleeds *(%)*



Kovaltry: ocotocog alfa; Jivi: Damoctocog alfa pegol
Adapted from Matino D. et al. Poster PB1142 presented at ISTH 2022

32

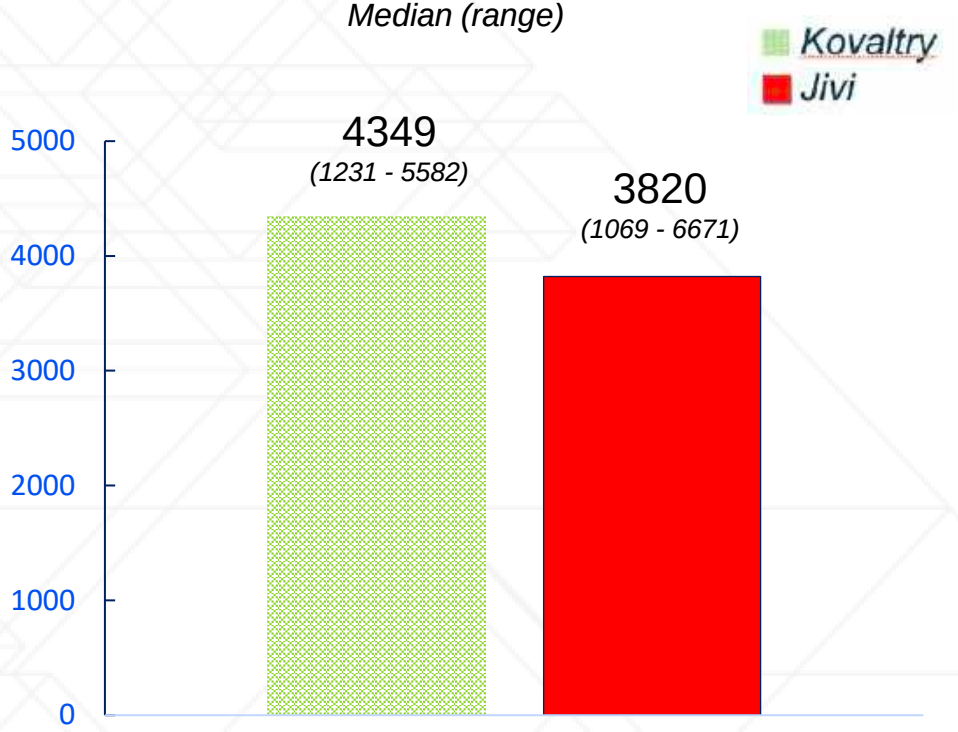
Changes in utilization in already well-maintained patients: Canadian switching experience

Single-centre, intra-patient comparison of Jivi clinical outcomes with Kovaltry, using data routinely collected by the Hamilton-Niagara Regional Hemophilia Treatment Centre

Evaluate the changes in effectiveness, utilization and patient satisfaction in patients switching from Kovaltry to Jivi in real-world practice

Annualized utilization

Median (range)



Recorded infusions per week, n/week

	Kovaltry	*Jivi*
Median *(range)*	**2.7** *(1.0 - 3.6)*	**2.2** *(1.0 - 3.3)*

Dose per infusion, IU/kg

	Kovaltry	*Jivi*
Median *(range)*	**31.5** *(17.5 - 43.2)*	**30.5** *(17.0 – 40.9)*

Kovaltry: ocotocog alfa; Jivi: Damoctocog alfa pegol
Adapted from Matino D. et al. Poster PB1142 presented at ISTH 2022

*For dosage and administration of Damoctocog alfa pegol, please refer to the package insert.

Educational learning for the talk

1) A) Provide the foundational elements for the role and value of individualized population PK profiling

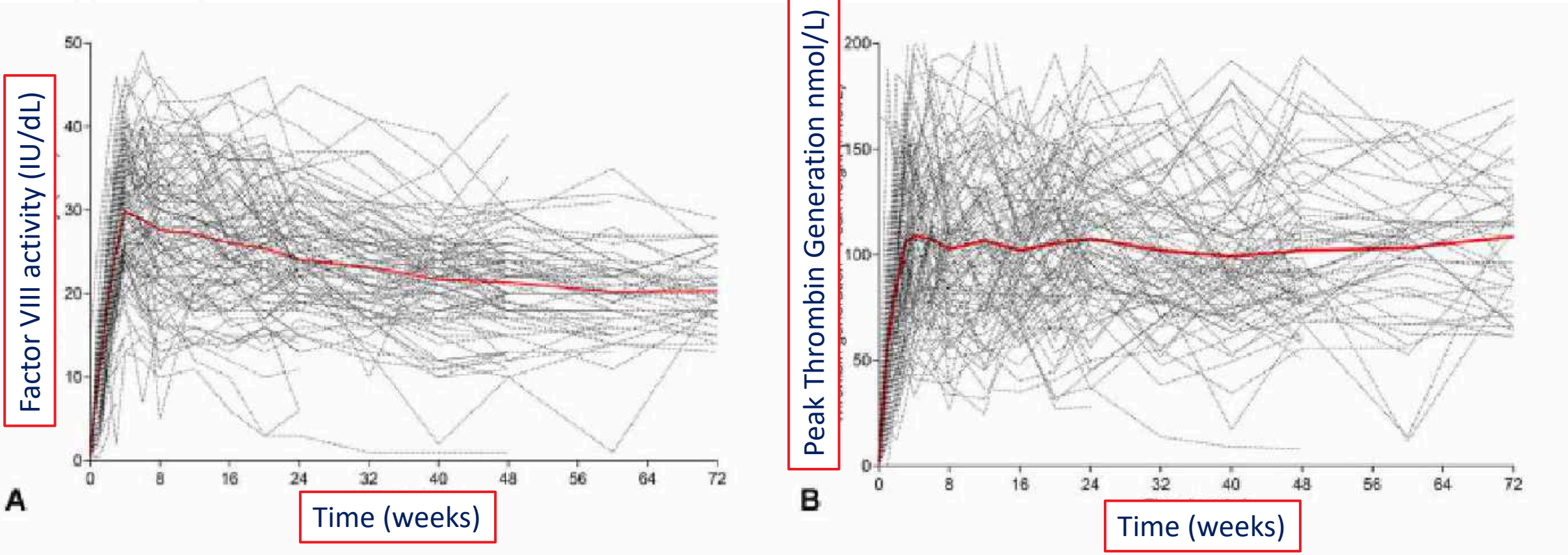
   B) Discuss the practicalities of performing population PK profiling with WAPPS-Hemo

2) A) Present evidence supporting the clinical results you can expect to see by adopting WAPPS-Hemo based hemophilia treatment

   B) focusing on switching patients to EHL factor VIII

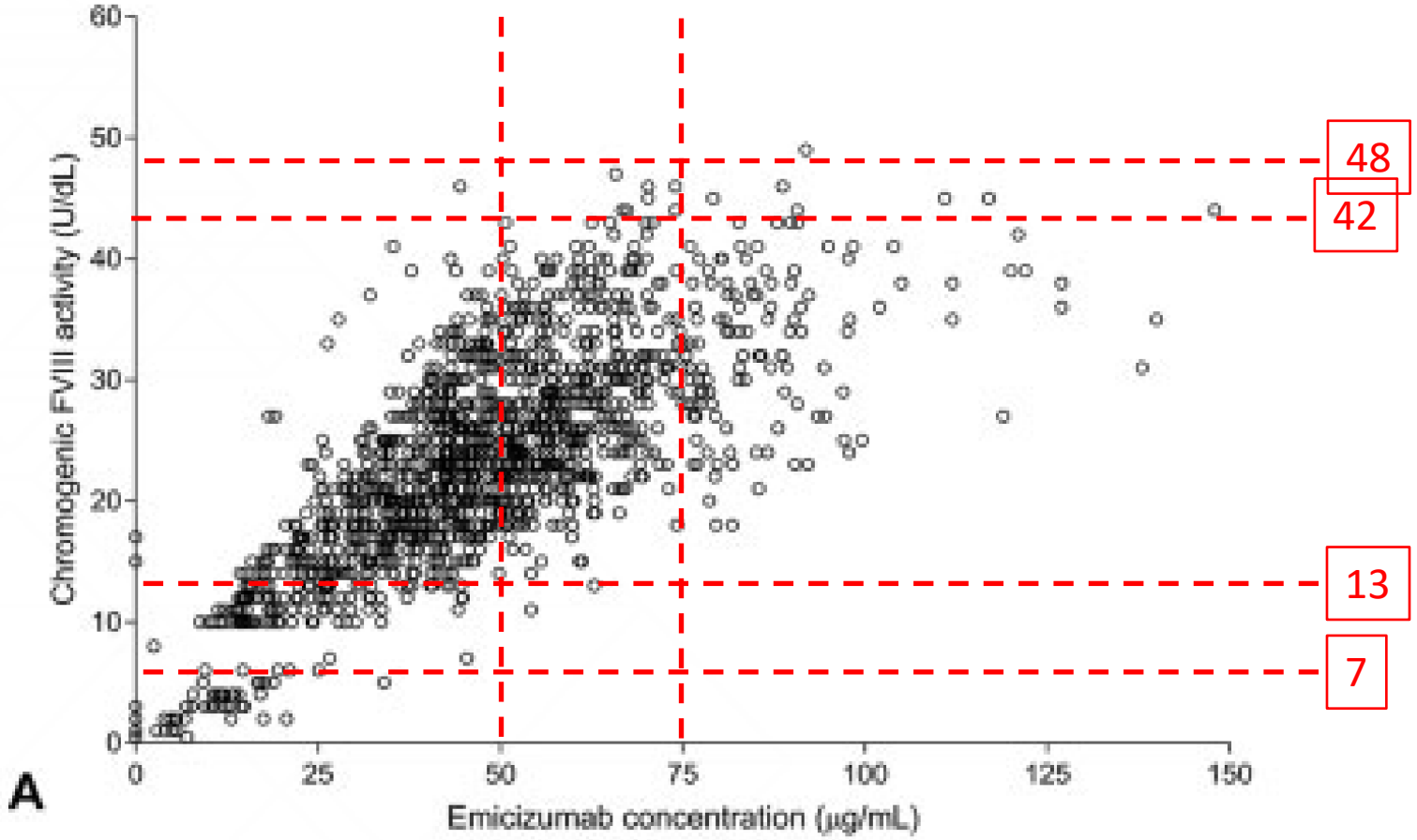
Note: Main focus on prophylaxis based on factor concentrates

Individual response variability



Schmitt, C., *Thrombosis and Haemostasis*, 2021, *121*(03), 351–360.

Dose-response predictability



Schmitt, C., *Thrombosis and Haemostasis*, 2021, *121*(03), 351–360.

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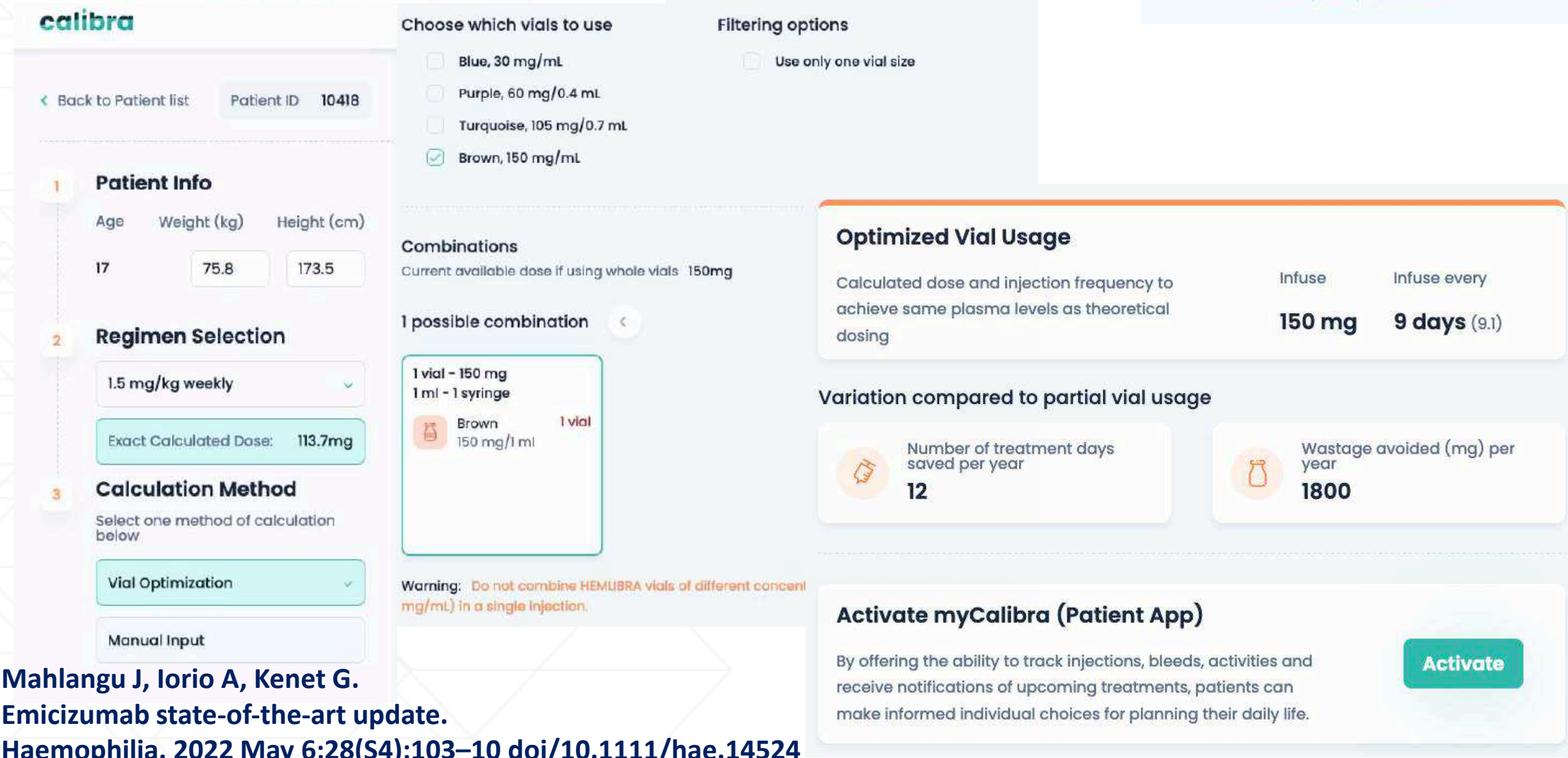

Mahlangu J, Iorio A, Kenet G. Emicizumab state-of-the-art update. Haemophilia. 2022 May 6;28(S4):103–10 doi/10.1111/hae.14524

Conclusions

- Population PK **effectively models** the variability in the population and **makes it simple and feasible** to estimate individual profiles

- Adoptions of PK tailored profiling **is associated with patient important outcomes**, even when using low dose prophylaxis

- **Canadian data** show how **population PK applications** use optimizes **the value of EHLs.**

Thank you