Sessie: Do’s and Don’ts in Therapeutic Drug Monitoring

Goed Gebruik Geneesmiddelen Congres 2018;
Donderdag 19 april 2018

ZonMW GGG dossier: 836011011

What do I do?

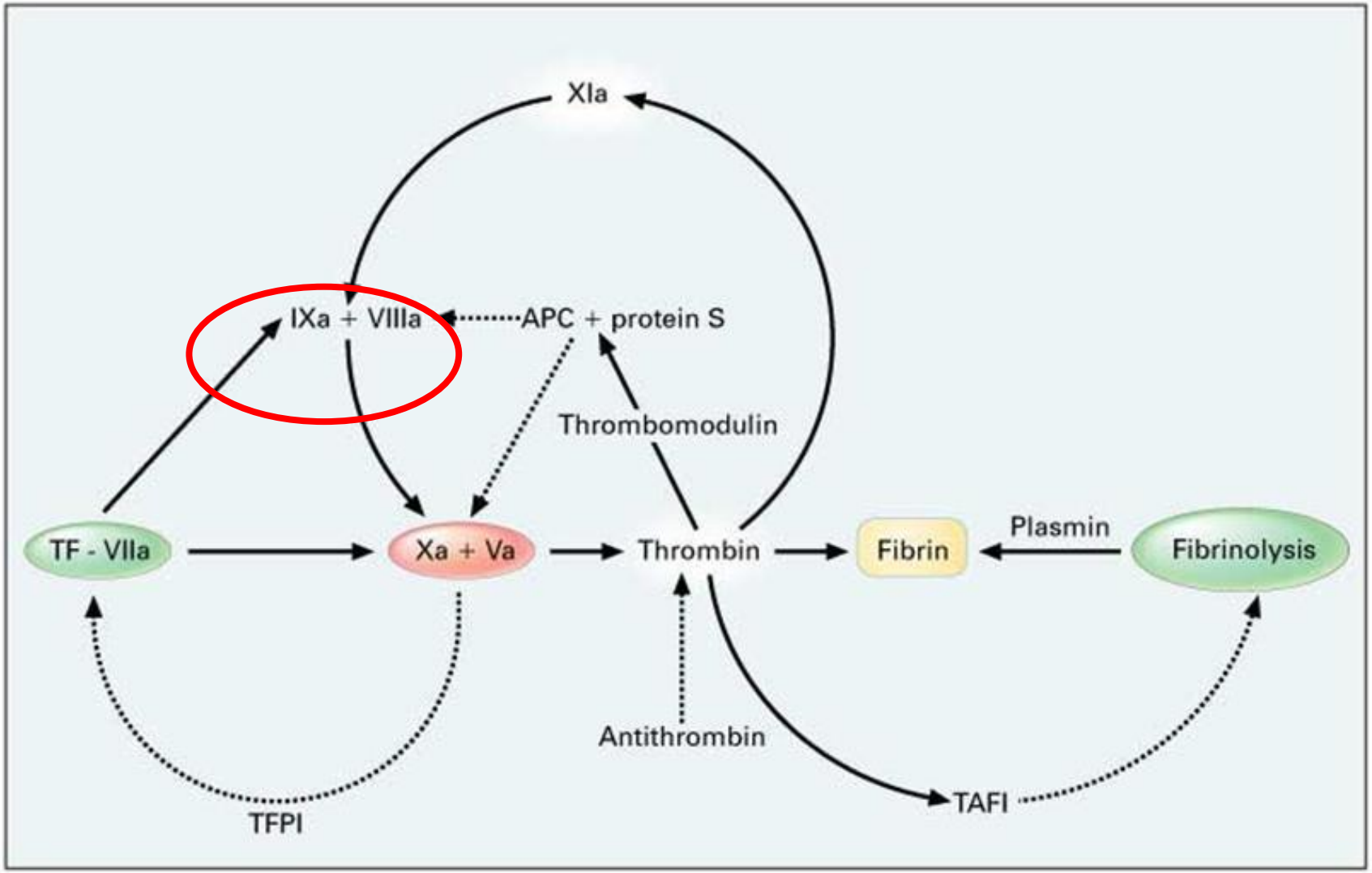
Hemophilia

- Rare X-linked bleeding disorder
- Hemophilia A (factor VIII) of hemophilia B (factor IX)
- Clinical phenotype: residual coagulation factor levels

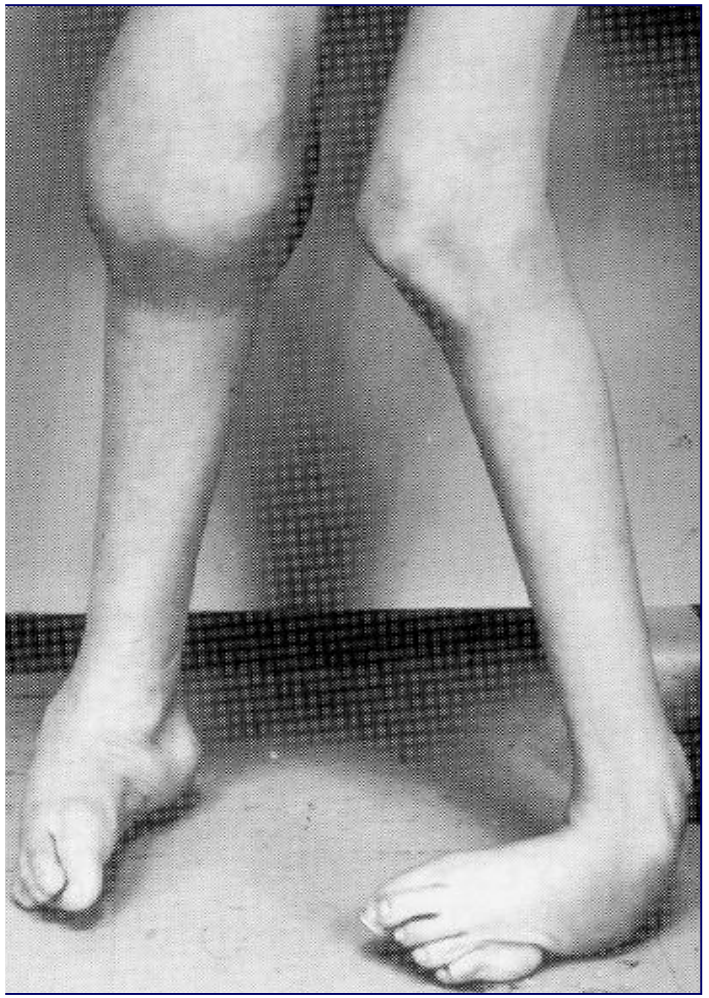
  severe: factor VIII/ factor IX <1%

  moderate: factor VIII/ factor IX 1-5%

  mild: factor VIII/ factor IX >5%
- Defect secondary hemostasis

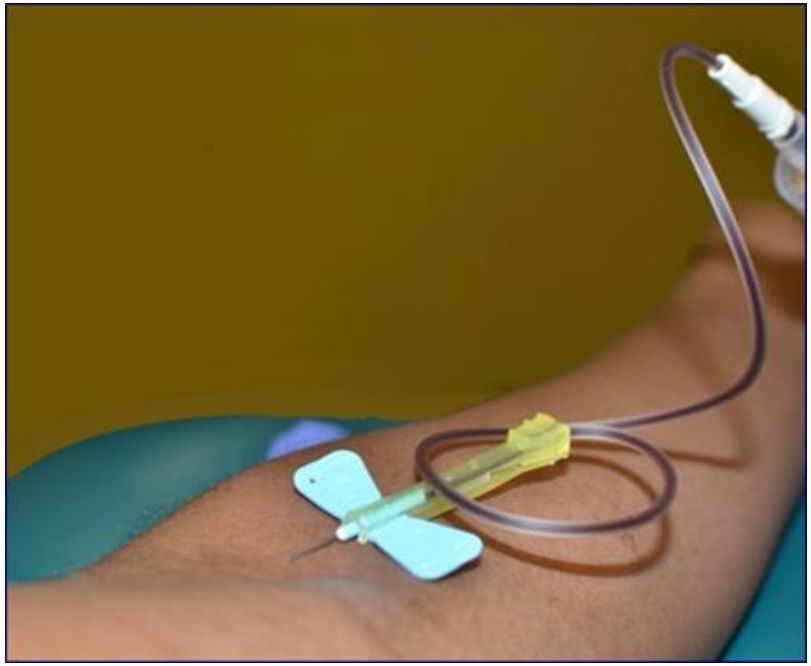

XIa
IXa + VIIIa
APC + protein S
Thrombomodulin
TF - VIIa
Xa + Va
Thrombin
Fibrin
Plasmin
Fibrinolysis
Antithrombin
TAFI
TFPI

Hemophilia arthropathy



Current treatment

- Prophylaxis versus “on demand”
- Clotting factor concentrate dosing based on bodyweight



Rationale dosing

**1 unit of infused FVIII per kilogram ↑FVIII level with 2%*

FVIII Dose = 0.5 (actual-desired %) x bodyweight in kg

Equation is based on FVIII recovery of 2*

(Wt x i) / d = k

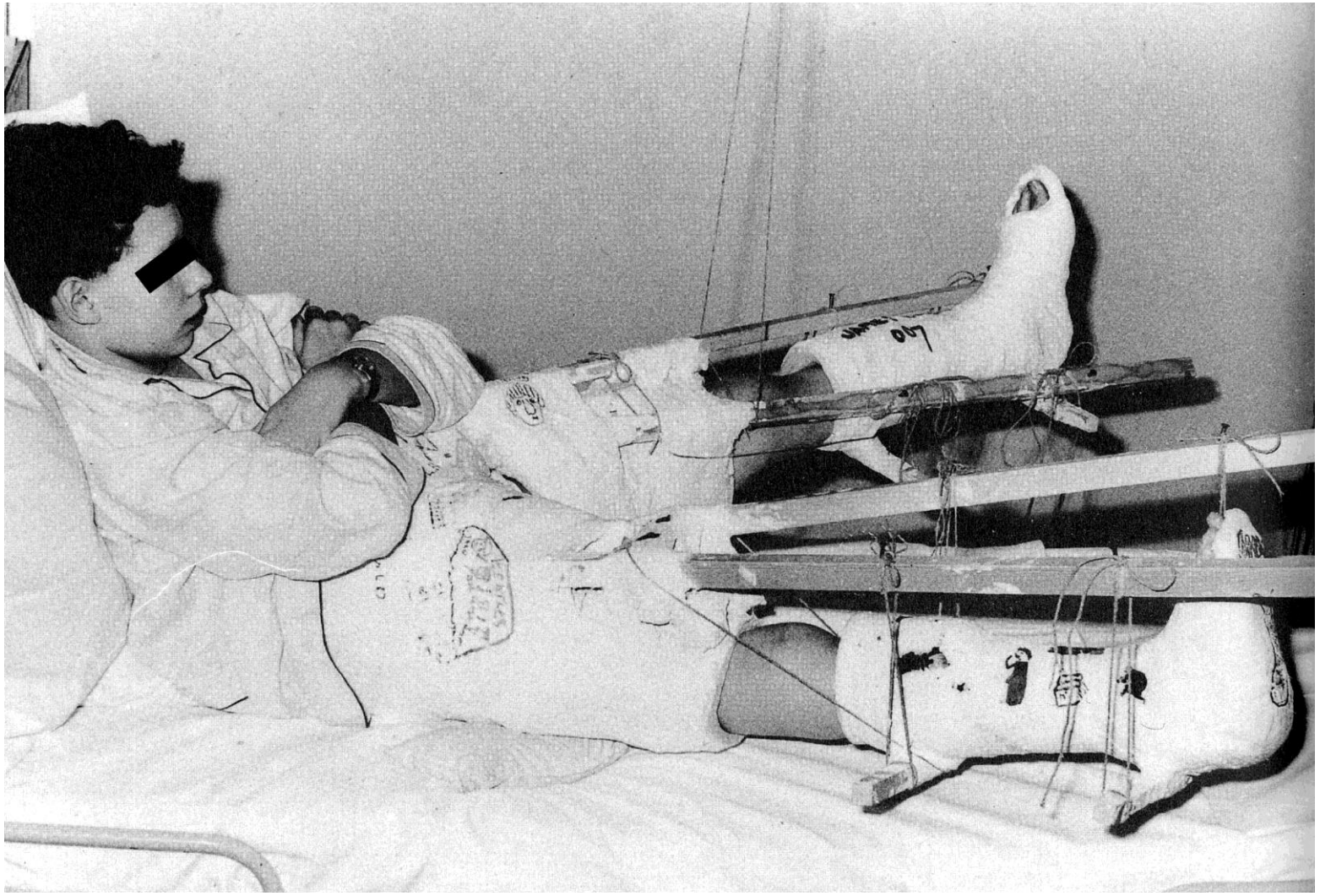
Wt = weight

I = observed FVIII increase,

D = administered dose

*Validated by Ingram et al. 1981

Treatment hemophilia in 1970's



Hemophilia treatment in 2018

Large interindividual variation

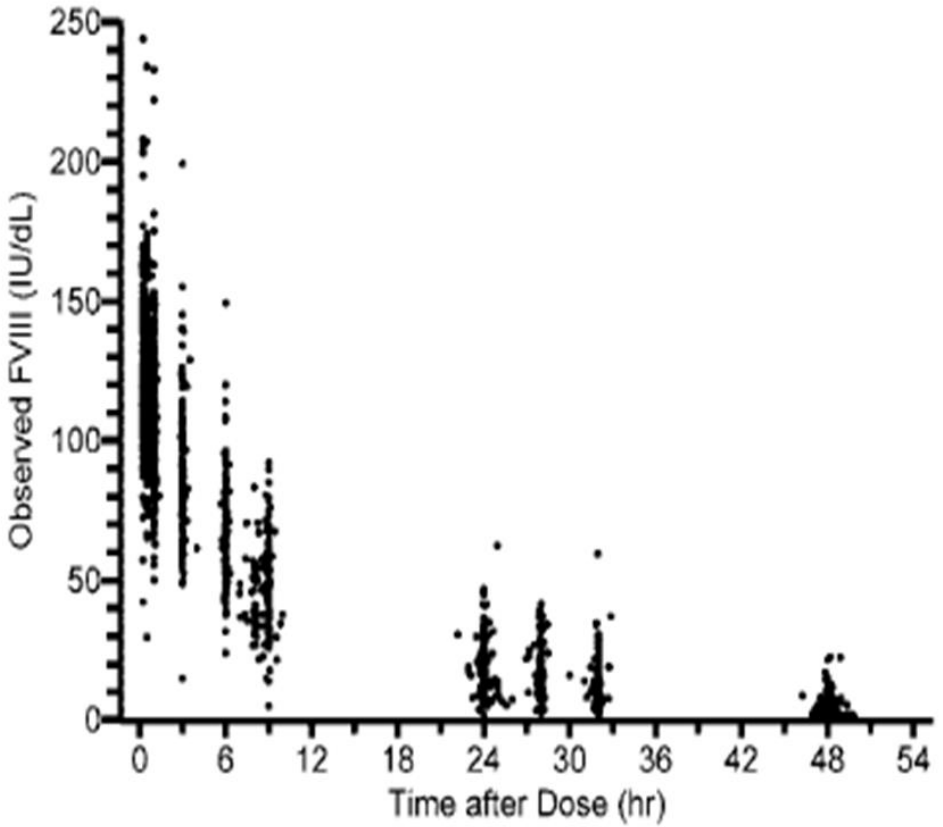


Figure 1. Observed FVIII levels (n = 2035) plotted against time after the infusion.

Bjorkman, Blood 2012

Carlsson et al. (1997)

Haemophilia (1997), 3, 96–101

Improved cost-effectiveness by pharmacokinetic dosing of factor VIII in prophylactic treatment of haemophilia A

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Hospital Pharmacy, Departments for Coagulation Disorders and Paediatrics, Malmö University Hospital, Sweden

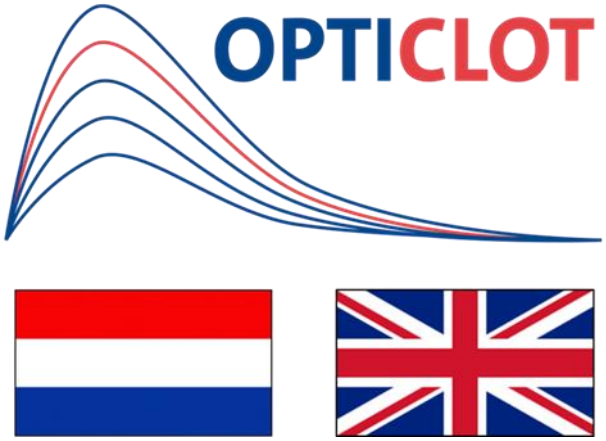
30% reduction FVIII consumption;
Higher trough levels,
No increase bleeding events

Summary. The aim of the study was to investigate the feasibility of optimizing prophylactic dosing of factor VIII by the use of individual pharmacokinetic data. Twenty-one patients were enrolled in a randomized cross-over study on standard dosage regimens vs. dosing according to pharmacokinetic principles. The study period was 2×6 months. Using single-dose pharmacokinetic data for each patient, plasma factor VIII procoagulant activity (FVIII:C) curves following various doses and intervals were computer-simulated. From these calculations, a suitable dosage was chosen. FVIII:C was also repeatedly measured during study periods. Trough levels of FVIII:C, numbers of spontaneous joint bleedings and amounts of factor concentrate used during the two study periods were compared for each patient.

There was a close correlation between predicted and measured values of FVIII:C. As the half-lives of FVIII:C in the patien beneficial netic dat periods. Mean trough level of exogenous FVIII:C was raised from 0.89 (SD 0.73) U dL^{-1} during standard dosage to 2.2 (1.5) U dL^{-1} during pharmacokinetic dosage. Concomitantly, mean 6-month consumption of factor VIII was decreased from 124 000 (SD 30 000) units to 84 000 (31 000) units. Numbers of reported bleedings were generally similar during both periods.

The study demonstrates the usefulness of individual pharmacokinetics as a tool for cost-effective utilization of factor VIII in the prophylactic treatment of haemophilia A.

Keywords: cost-effectiveness, dosage, factor VIII, haemophilia A, pharmacokinetics, prophylaxis.



“Patient tailOred PharmacokineTIc-guided dosing of CLOTting factor concentrates and DDAVP in bleeding disorders

Multicenter (inter)national studies

amc

Erasmus MC
Universitair Medisch Centrum Rotterdam

UMC St Radboud

LUMC
Leids Universitair Medisch Centrum

OPTICLOT

umcg

UMC
Universitair Medisch Centrum
Utrecht

ZonMw

NVHP

“OPTI-CLOT” studies

Aim

- To implement patient-tailored treatment by pharmacokinetic (PK)-guided dosing of clotting factor concentrates and DDAVP in patients with bleeding disorders

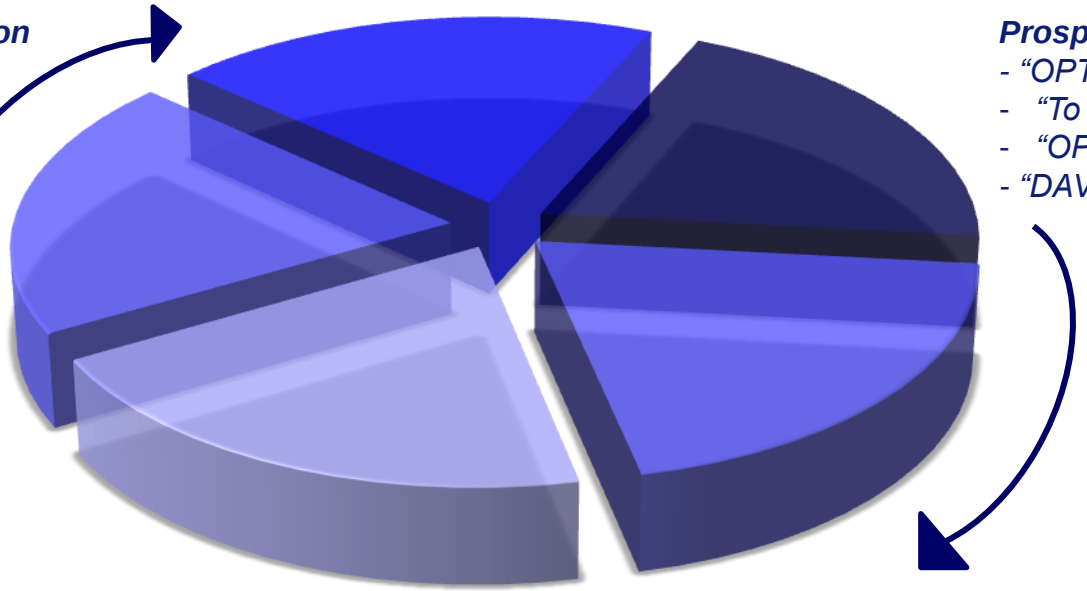
Goals

- Individualization of therapy
- (Risk of) bleeding ↓, consumption clotting factor concentrates ↓
- Possibly cost-effective; clotting factor concentrates: >€130 million/year
- Perioperative setting: 15% of annual yearly doses of concentrates

“OPTI-CLOT” studies

Construction of population PK models

Retrospective data collection
- *Hemophilia A*
- *Hemophilia B*
- *Von Willebrand Disease*



Prospective validation
- *“OPTI-CLOT” trial*
- *“To WiN” study*
- *“OPTI-CLOT B” trial (future)*
- *“DAVID” studies*

Personalized treatment

Implementation
- *“OPTI-CLOT: TARGET” studies*

“OPTI-CLOT” studies

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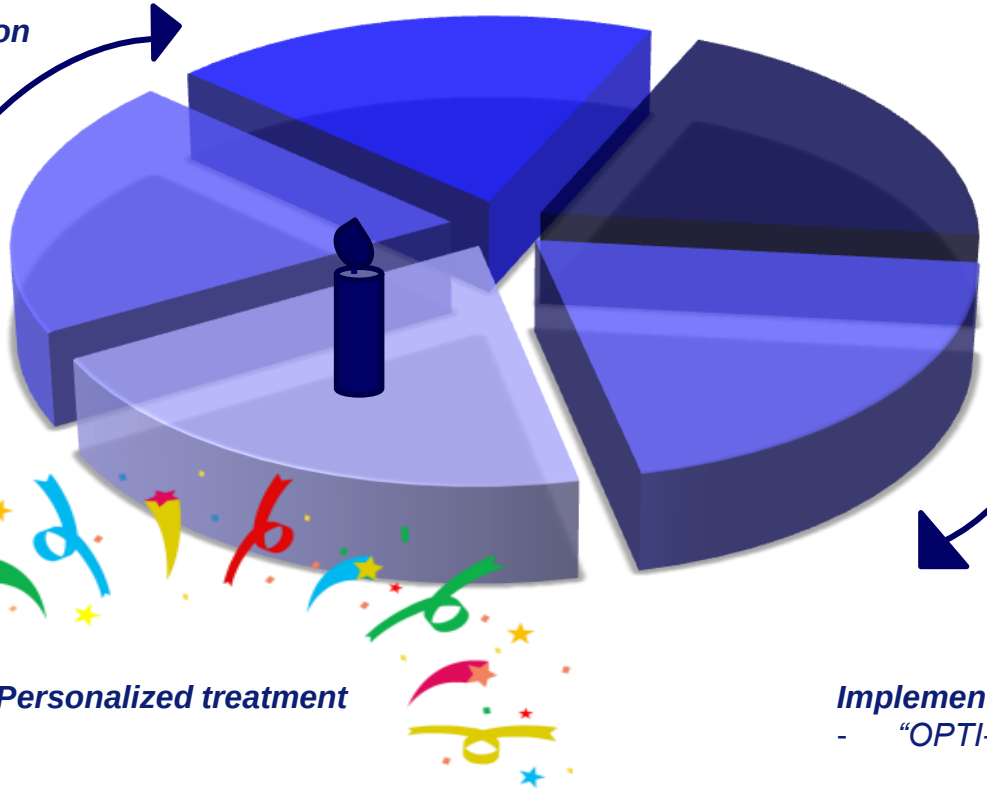

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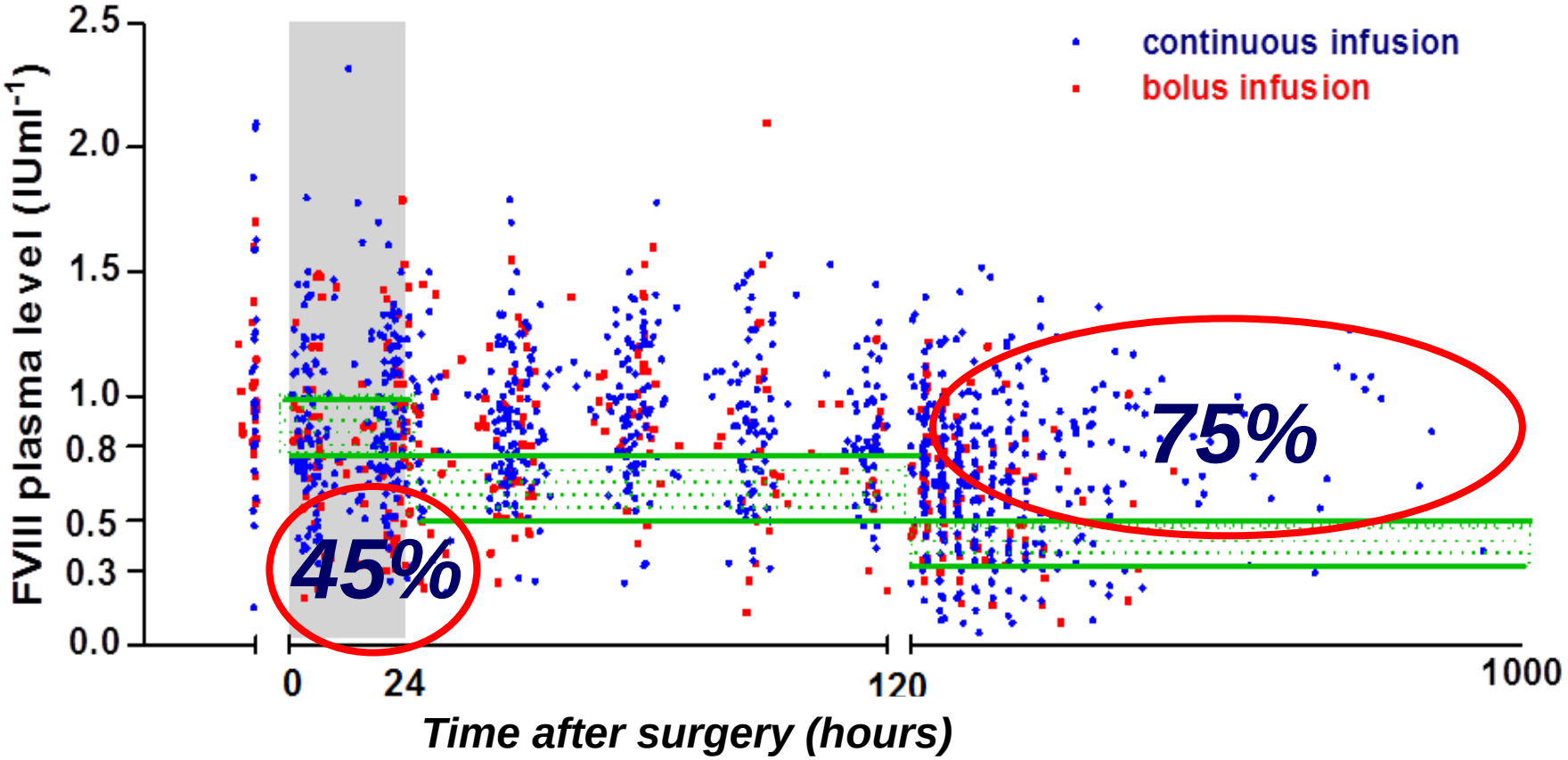
Perioperative FVIII population PK model



Hazendonk et al. JTH 2016

Perioperative FVIII population PK model

Hazendonk et al. Haematologica 2016: 101 (10):1159-69

Population parameters

$$CL = 150 \cdot \left(\frac{BW\ (kg)}{68}\right)^{0.75} \cdot \left(\frac{AGE\ (y)}{40}\right)^{-0.17} \cdot \left(1.26^{blood\ group}\right) \cdot \left(0.93^{severity\ surgery}\right)\ ml/h$$

$$V1 = 2810 \cdot \left(\frac{BW\ (kg)}{68}\right) \cdot \left(\frac{AGE\ (y)}{40}\right)^{-0.09}\ ml$$

$$Q = 160 \cdot \left(\frac{BW\ (kg)}{68}\right)^{0.75}\ ml/h$$

$$V2 = 1900 \cdot \left(\frac{BW\ (kg)}{68}\right)\ ml$$

Inter-individual variability

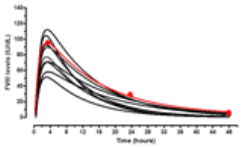
CL:	37 %
V1:	27 %

Residual variability

Additive error	− center1,2:	0.015	IU/ml
	−center 3,4,5:	0.05	IU/ml
Proportional error	− center 1,2:	18	%
	−center 3,4,5):	23	%

OPTI-CLOT trial: Flowchart

PK profile



Randomization

PK-guided dosing (n=30) → **Surgery** → Follow up: 14 days postoperative

Standard dosing (n=30) → **Surgery** → Follow up: 14 days postoperative

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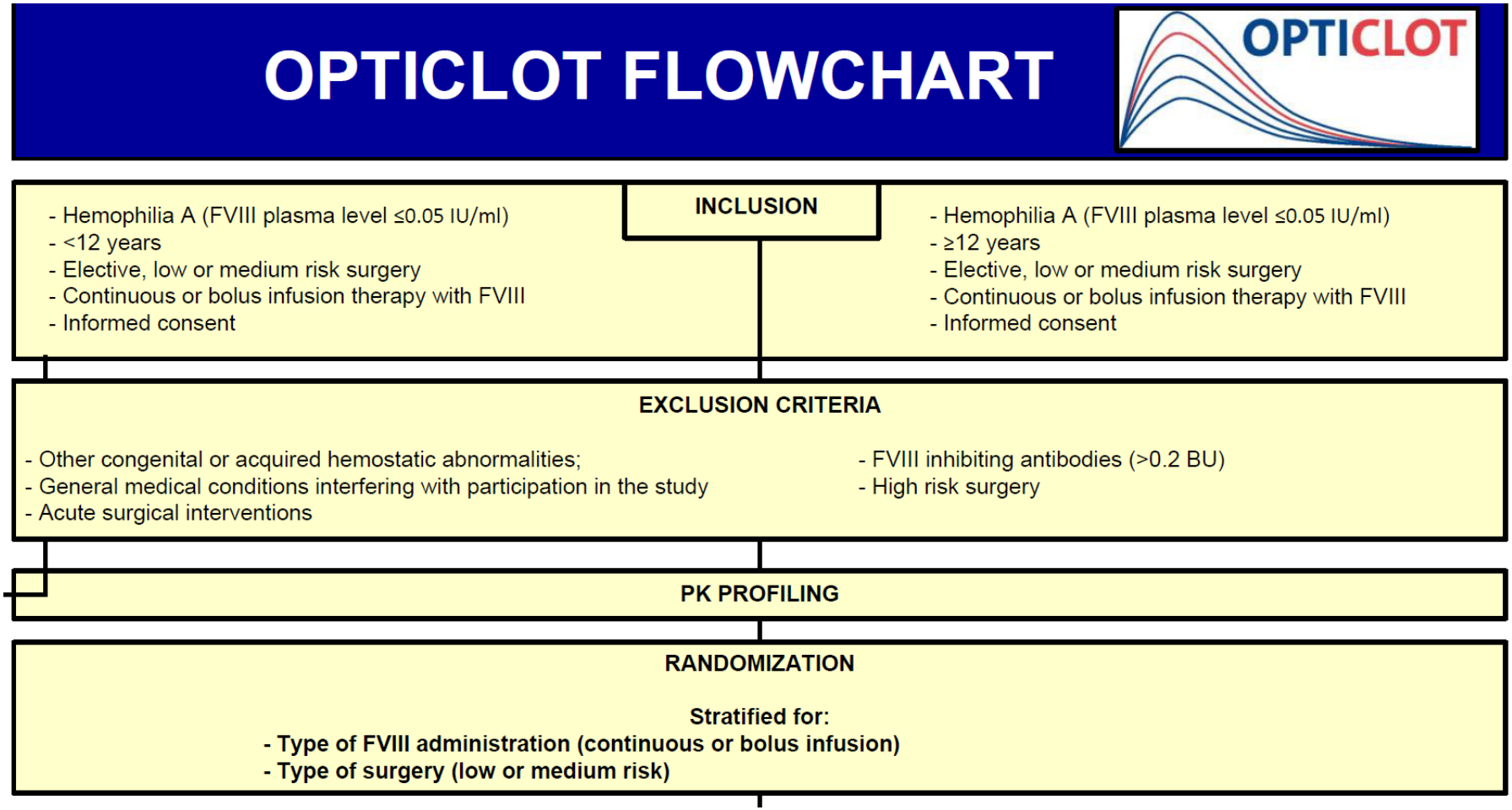
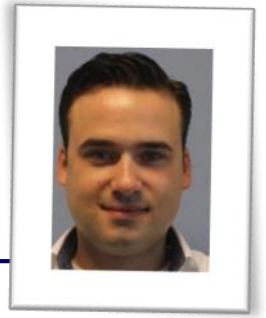
Stratification: severity of surgery and bolus vs continu infusion

Hazendonk et al. 2015, TH

OPTI-CLOT trial flow chart (1)



OPTI-CLOT trial flow chart (2)



INTERVENTION ARM

Dosing according to PK-model

N=30

STANDARD TREATMENT ARM

Dosing according to FVIII plasma levels and body weight

N=30

SURGERY

DOSAGE ADAPTIONS According to iterative PK profiling

DUTCH HEMOPHILIA CONSENSUS

Target levels of FVIII

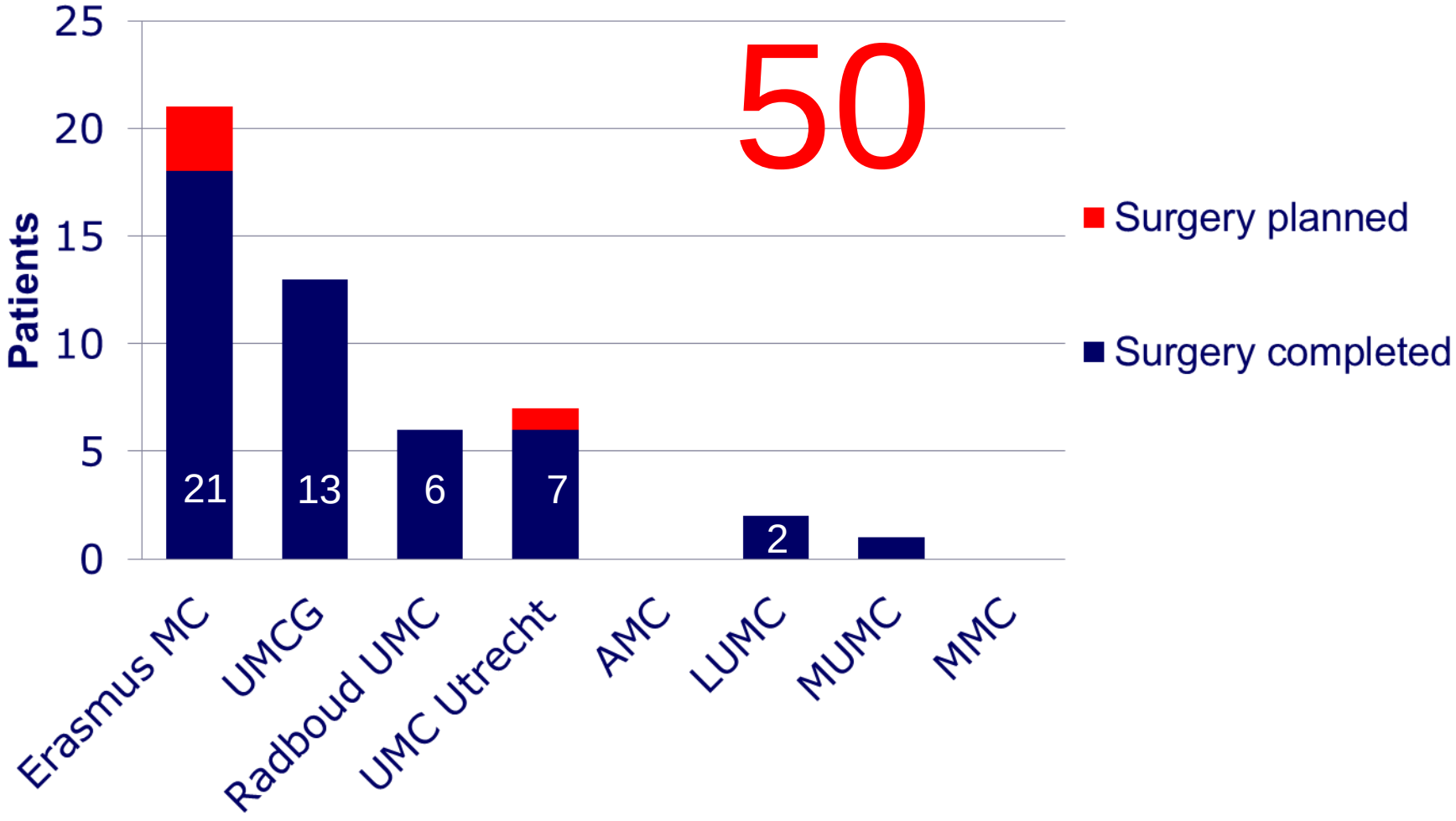
Day 1: 0.8-1.0 IU/ml
Day 2-5: 0.5-0.8 IU/ml
Day>6: 0.3-0.5 IU/ml

DOSAGE ADAPTIONS According to Dutch Hemophilia Consensus

PRIMARY ENDPOINT
1. Total amount of infused FVIII (IU)

SECONDARY ENDPOINTS
1. Achieved FVIII levels after FVIII infusion
2. Perioperative blood loss
2. Length of hospitalization
3. Economic evaluation

OPTI-CLOT trial



“Bloody serious”

“Do’s”

Why?

- Important step towards personalized treatment in bleeding disorders
- Impact: Potential cost reduction with ↑ quality of care
- Developments: Novel extended half-life products

How?

- Team up with an expert clinical pharmacologist
- Logistics PK management
- Educate “team”: “what is important in PK-guided dosing?”
    - Patients, professionals, nurses, PhD students
    - Be precise: exact dose, timing dosing and blood sampling
- Think about implementation (Grob et al.)

“Do not”

- Do not forget to be explicit, do not assume knowledge
- “Keep your eye on the ball”. Be aware of clinical (bleeding) symptoms
- Unknown variables: which troughs, peaks to achieve?

Ultimate aim pharmacokinetic- pharmacodynamic (PK-PD) models

Implementation

Discrete Choice Experiment (DCE) Analysis

Quantification of barriers and faciliatators for PK-guided prophylactic dosing in patients, parents and professionals

Example

DCE questionnaire:

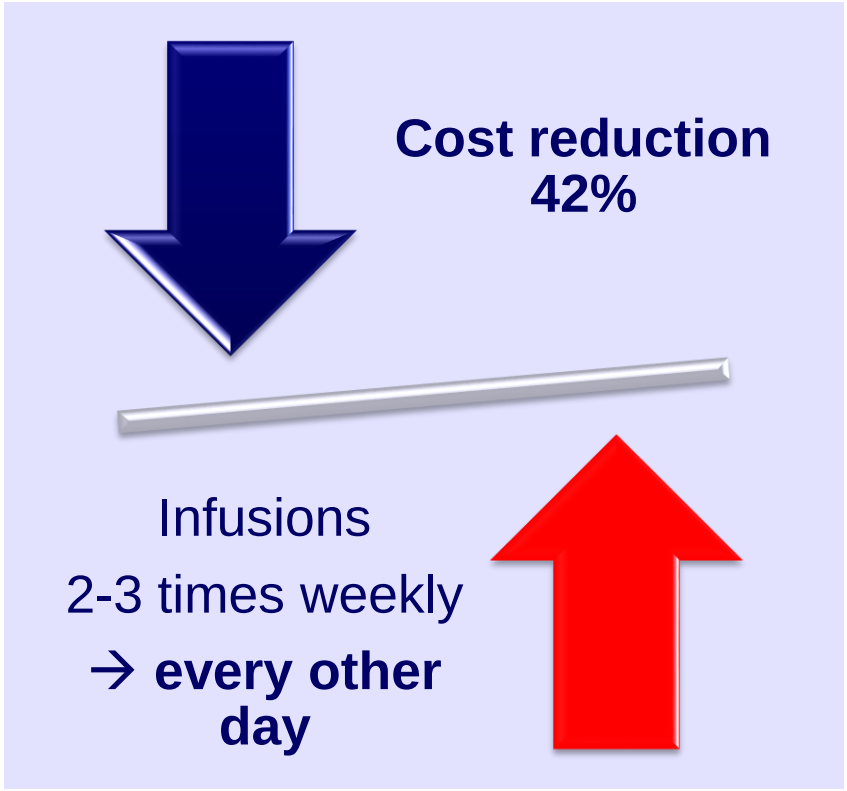
Attributes

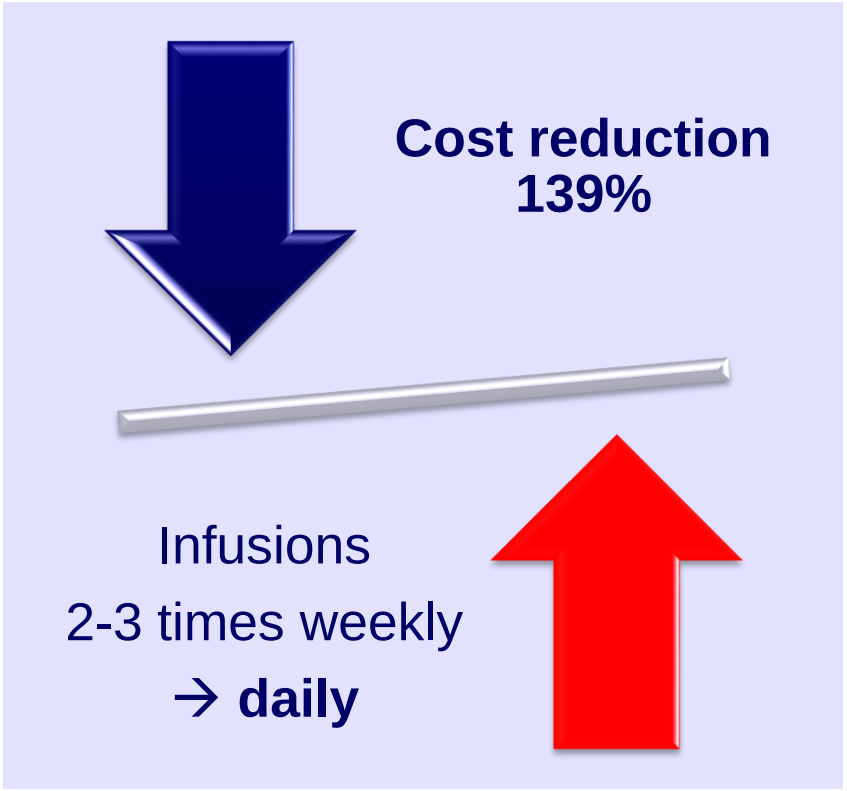
Attribute levels

	New treatment 1	New treatment 2
Construction of PK-profile 	PK-profile Determination Factor VIII level at 1 time points (24 hours after single administration of Factor VIII) 	PK-profile Determination Factor VIII levels at 3 time points (4, 24, 48 hours after single administration of Factor VIII) 
Frequency of intravenous prophylactic infusions after PK-profiling 	*Dosage adjusted to PK-profile,* with infusions every day Su X Mo X Tu X We X Th X Fr X Sa X	*Dosage adjusted to PK-profile,* with infusions every other day Su X Mo Tu X We Th X Fr Sa X
Frequency of PK-profiling in the futu	Once	Every two years
[illegible]	Current frequency of bleeding 	Reduced frequency of bleeding 
Cost for society 	Cost reduction of 0% 	Cost reduction of 15% 
Which alternative would you choose?	☐	☐

Barrier: Daily infusions

Patients/parents require…





Discrete Choice Experiment

- Do not aim for daily dosing
- Frequent bleeding: Motivator for PK-guided dosing
- Discuss costs of treatment, reduction by PK-guided dosing

Patients

Felix Factor

Field trip to Zandvoort

Project Members

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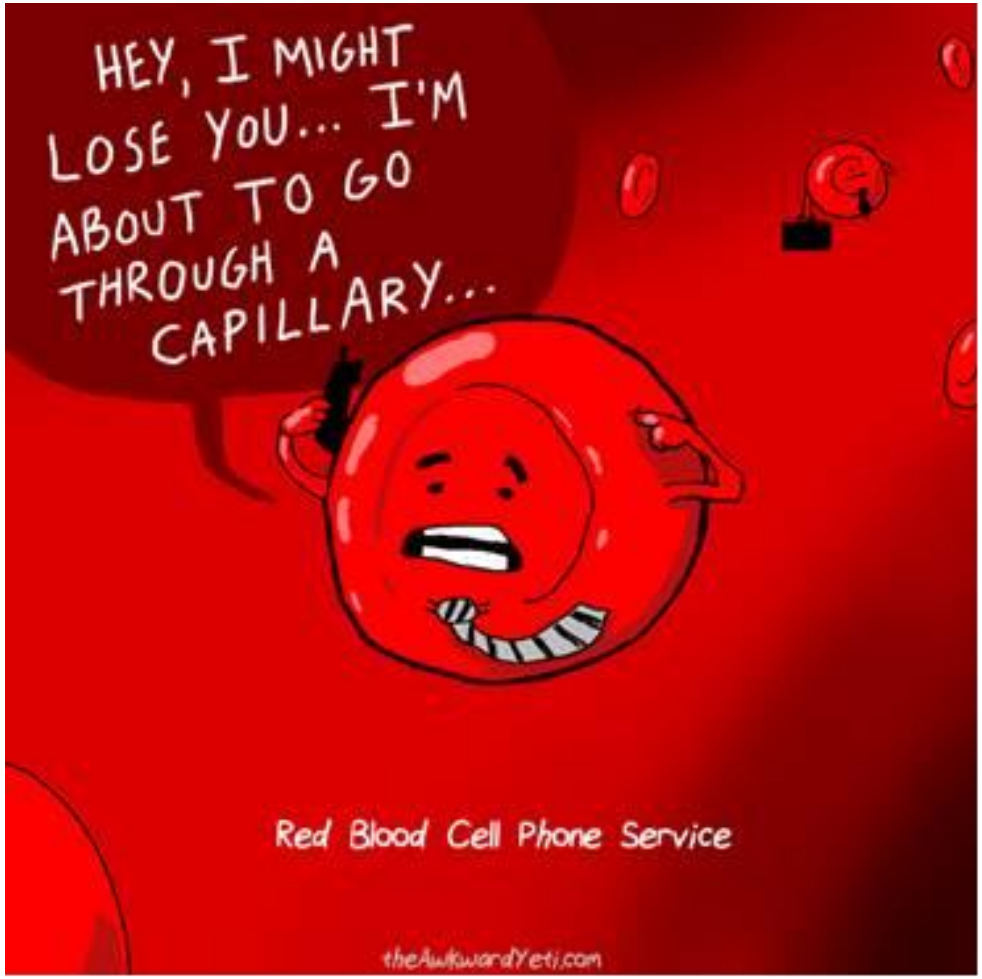
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