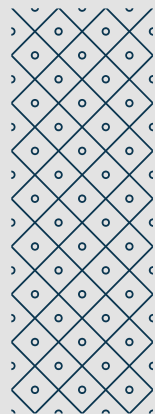




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PopPK – case studies in small molecules and rituximab

Ondřej Slanař

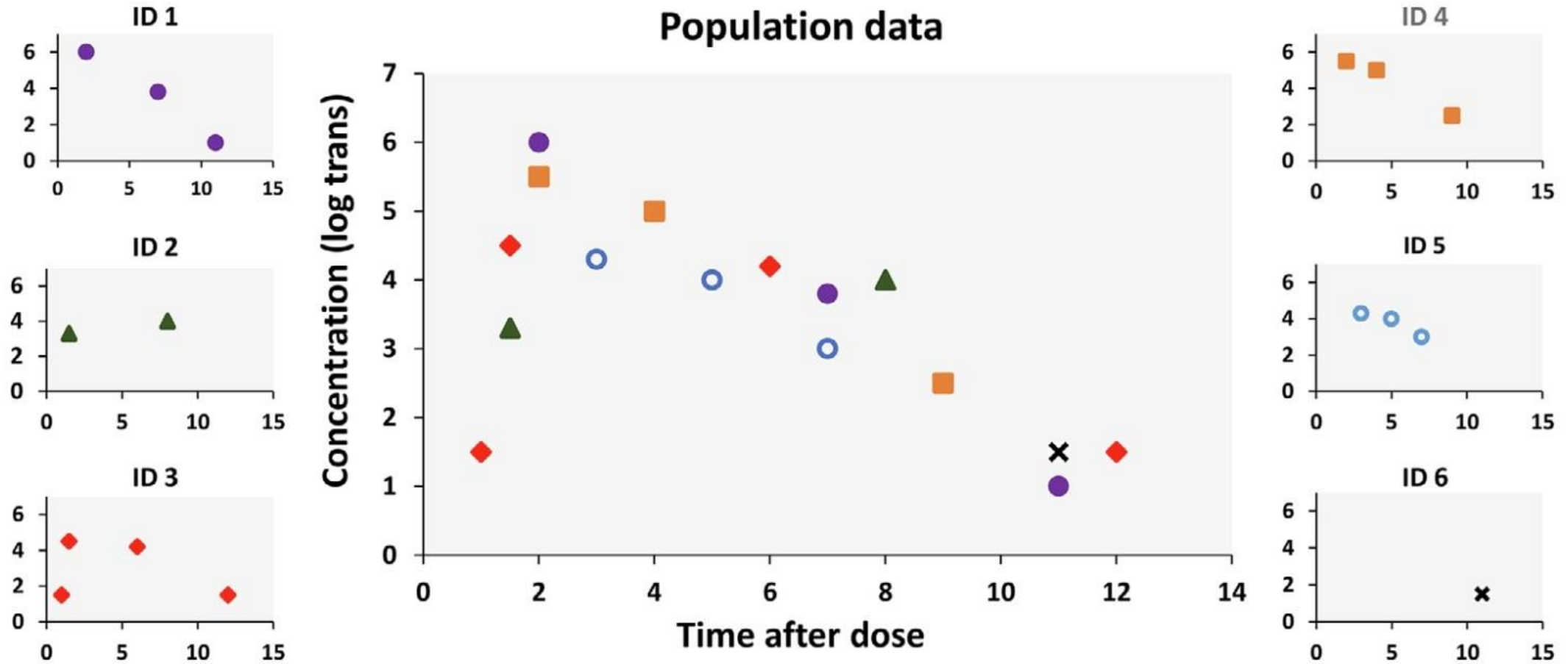


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Why Population PK Models

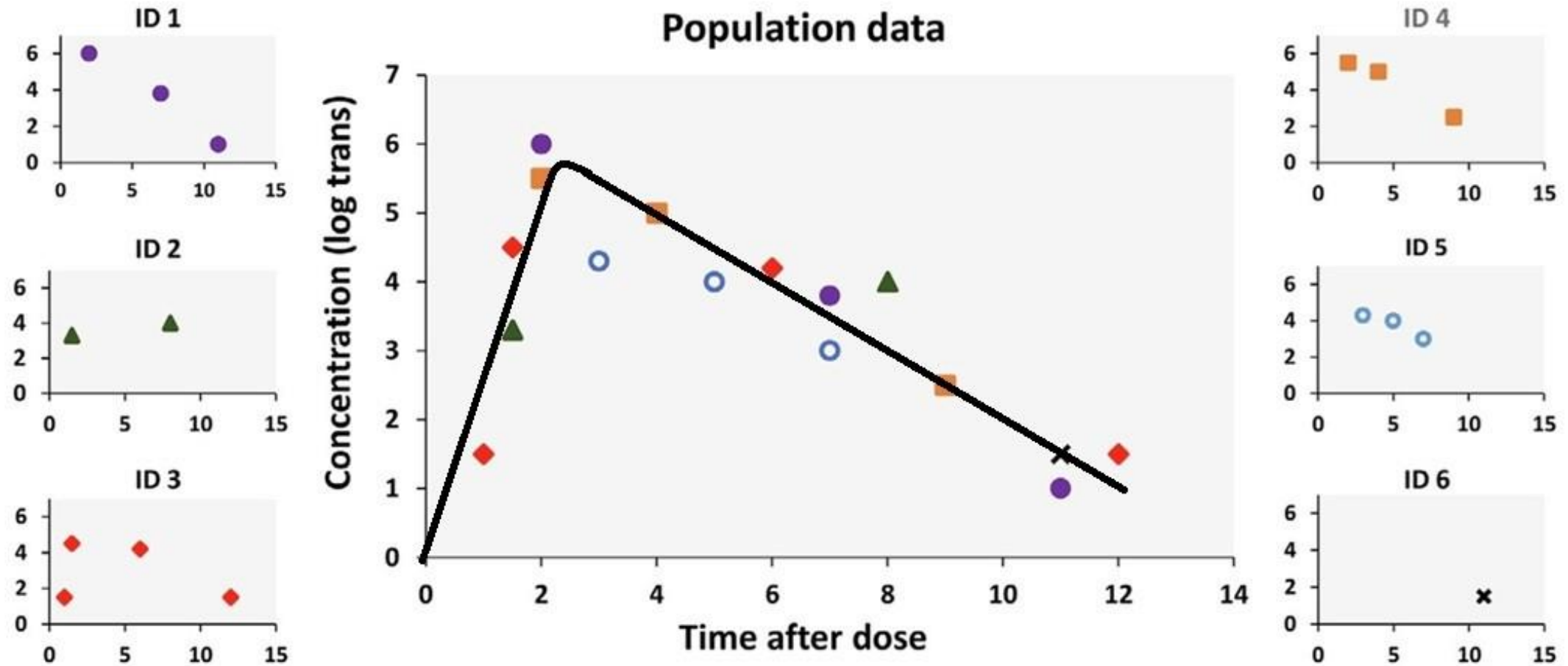
- In real-world, few measured concentrations per patient may be available
→ from which individual PK parameters are difficult to calculate
- PK variability
- Subpopulations
- Specific situations and therapeutic modalities

Population PK Modeling



Adapted from: Sassen SDT et al. doi: 10.1002/pbc.28132.

Population PK Modeling



Adapted from: Sassen SDT et al. doi: 10.1002/pbc.28132.

Monte Carlo Simulations

- Practical application of the population PK model
- Randomly generates any number of virtual patients with variability described by the population PK model
- Illustrates the distribution of PK profiles by probability of occurrence in the population
- Various dosing regimens can be simulated and calculated for:
 - Probability of achieving the desired PK/PD target
 - Probability of exceeding the toxicity threshold

Assessment of Treatment Adherence

- Studies assessing adherence by measuring drug levels usually consider a patient adherent if the level is measurable...
- "white coat adherence"
- An innovative approach to adherence assessment was proposed, based on comparing measured drug levels with predictions from a population pharmacokinetic model
- This approach was demonstrated using the example of abiraterone, where the requirement for fasting administration may contribute to a relatively high rate of non-adherence

Evaluation of adherence to abiraterone therapy in prostate cancer patients based on a population pharmacokinetic model

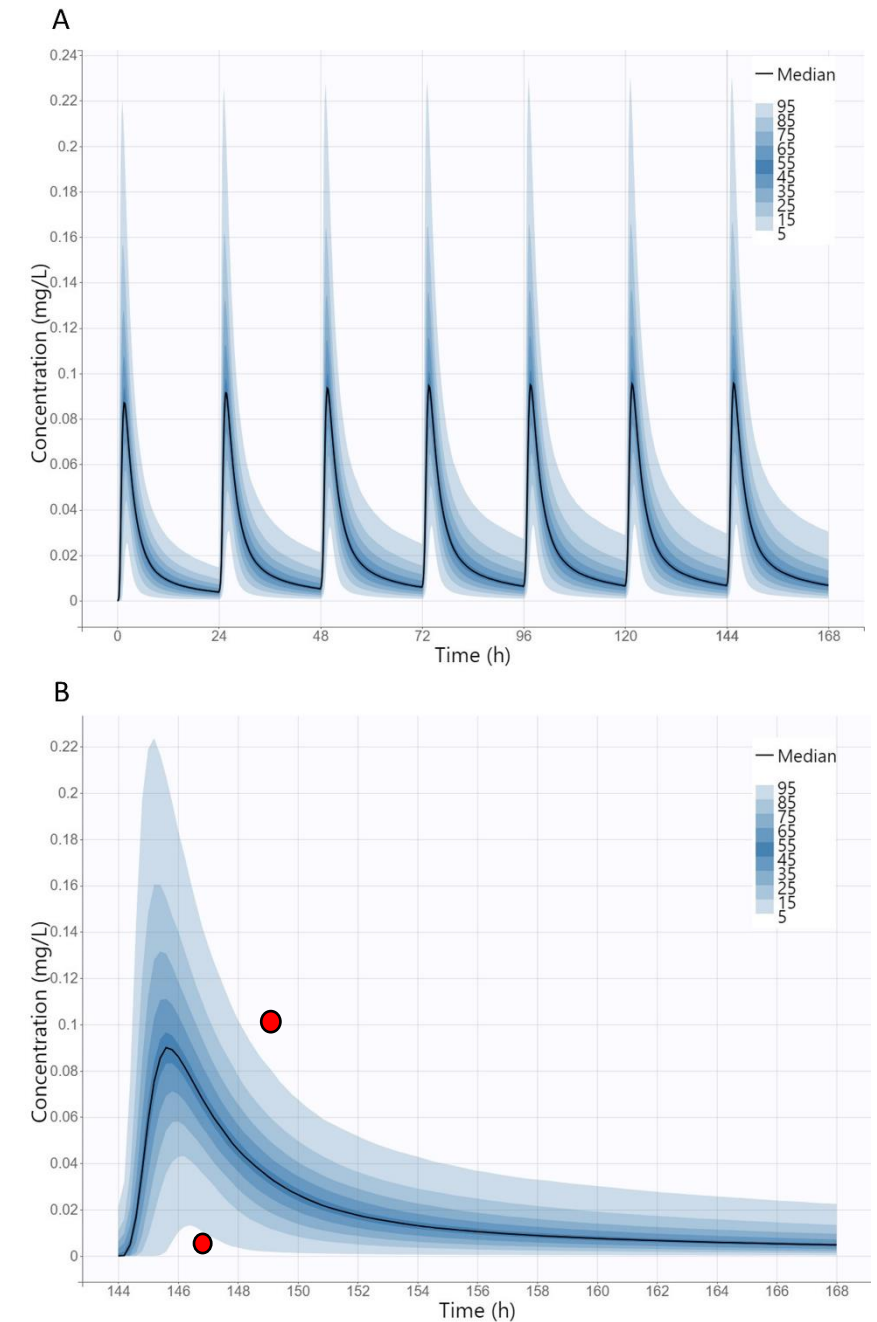
Sara Merdita ¹, Martin Šíma ¹, Jan Dvořák ², Martin Matějů ³, Igor Richter ^{4 5}, Petr Kozlík ⁶, Tomáš Křížek ⁶, Jana Královičová ¹, Jan Bosák ⁷, Luboš Petruželka ³, Ondřej Slanař ¹

- Population PK model developed from bioequivalence studie
- Concentrations at 0.33, 0.67, 1, 1.33, 1.67, 2, 2.33, 2.67, 3, 3.5, 4, 5, 6, 9, 12, 16, 24 a 48 h after administration of 1000 mg abirateronu in fasting state
- 1,469 levels from 83 subjects

Parameter	Estimate	R.S.E. (%)
Ktr_pop (h ⁻¹)	12.26	13.3
Mtt_pop (h)	0.74	5.51
Ka_pop (h ⁻¹)	1.92	12.5
CL/F_pop (L/h)	1644.93	5.68
Vc/F_pop (L)	4420.64	8.06
Q/F_pop (L/h)	1083.03	8.58
Vp/F_pop (L)	16403.25	7.50

Abiraterone - adherence

- 36 outpatients (prostate cancer)
- Comparison of measured levels with simulation
- A patient was considered non-adherent if the level was
 - **above 95th percentil** (95% probability of not taking fasting)
 - **12 patients (33%)** - 2 subsequently admitted taking after food
 - **below 5th percentil** (95% probability of not taking regularly)
 - **1 patient (3%)**



Linezolid

- Population PK analysis of levels from 22 patients (hemato-oncology ICU)
- 1, 2, 4, 6, 8 h ; 1st + 4th day of treatment
- Age, body weight, height, body surface area, serum creatinine, creatinine clearance, serum bilirubin, aspartate aminotransferase, alanine transaminase, alkaline phosphatase, gamma-glutamyl transferase, and international normalized ratio were assessed as **continuous covariates**
- sex and neutropenia were tested as **categorical covariates**
- Potential differences in linezolid pharmacokinetics between the 1st and 4th day of therapy were examined as a regressor (i.e., **time-varying covariate**)

Linezolid

$$\begin{aligned}\text{Log (CL)} = & \log (\text{CL}_{\text{pop}}) + \beta_{\text{CL_Age}} \times \text{Age} \\ & + \beta_{\text{CL_CL_4th day}} [\text{if 4th day}] + \eta_{\text{CL}};\end{aligned}$$

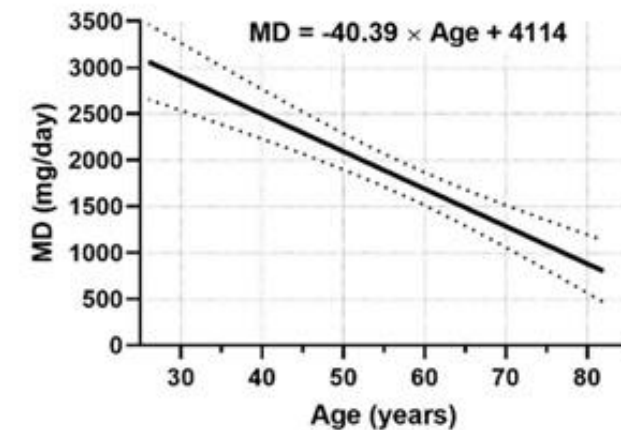
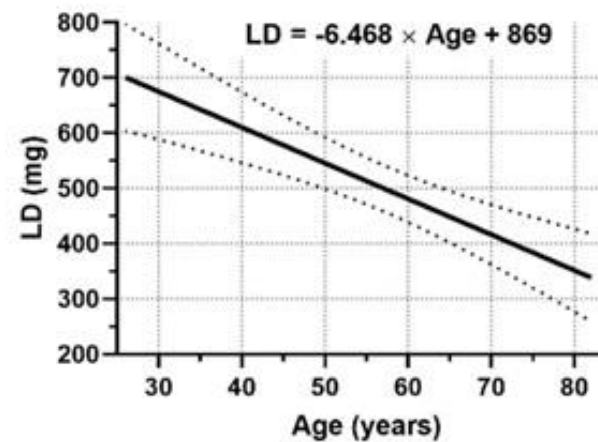
$$\text{Log (Vd)} = \log (\text{Vd}_{\text{pop}}) + \beta_{\text{Vd_Age}} \times \text{Age} + \eta_{\text{Vd}};$$

> Clin Transl Sci. 2025 Sep;18(9):e70346. doi: 10.1111/cts.70346.

Population Pharmacokinetic Model-Based Optimization of Linezolid Dosing in Hematooncological Patients With Suspected or Proven Gram-Positive Sepsis

Alžběta Zavřelová¹, Sara Merdita², Pavel Žák¹, Jakub Radocha¹, Benjamin Víšek¹,
Miriam Lánská¹, Jana Maláková³, Pavel Michálek⁴, Ondřej Slanář², Martin Šíma²

- $\text{Vd (L)} = 99,44 \times e^{-0,013 \times \text{age}}$
- $\text{CL (L/h)} = 46,93 \times e^{-0,023 \times \text{age}}$



Estimated attainment of PK targets

For MIC = 2 mg/L	$\geq 85\% T > MIC \wedge AUC_{24} < 300 \text{ mg.h/L}$
SmPC: 600 mg q 12 h	54% (↓32%; ↑14%)
Off label 600 mg q 8 h	63% (↓3%; ↑34%)
LD + MD nomogram	74% (↓0%; ↑26%)

Real attainment of PK targets

- Since 12/2024, the dosing algorithm has been part of standard procedures
- 40 patients till 11/2025 dosed according to the nomogram

For MIC = 2 mg/L	$\geq 85\% T > MIC \wedge AUC_{24} < 300 \text{ mg.h/L}$
SmPC: 600 mg q 12 h	54% (↓32%; ↑14%)
Off label 600 mg q 8 h	63% (↓3%; ↑34%)
LD + MD nomogram	74% (↓0%; ↑26%)
Real LD + MD nomogram	80% (↓0%; ↑20%)

Propofol

- Target-controlled infusion (TCI) of general anaesthetics is up-to date and well-established method of administering general anaesthesia
- anaesthesia depth monitoring (pEEG...)



- Eleveld model currently most suitable for cardiac anaesthesia
- the only model based on data obtained from cardiac surgery patients (n=30, 1996)
- does it predict for deep hypothermia with circulatory arrest?

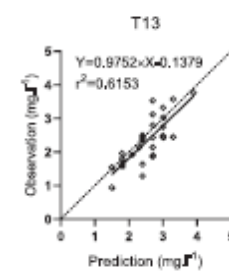
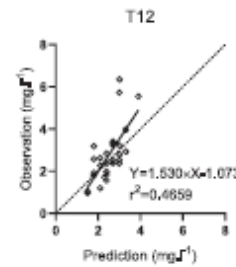
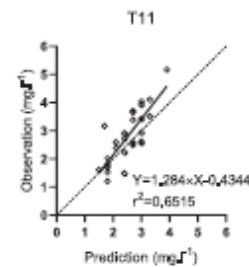
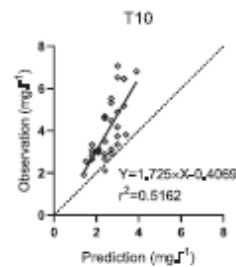
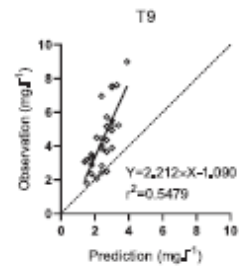
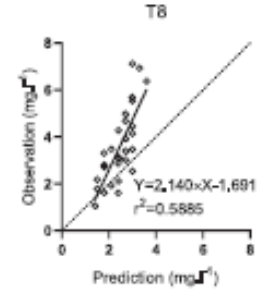
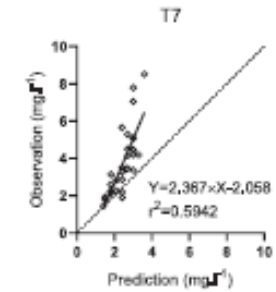
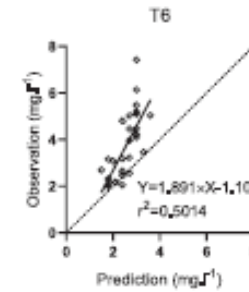
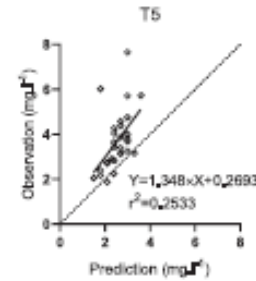
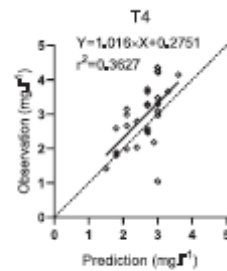
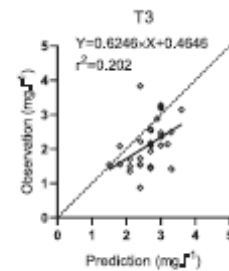
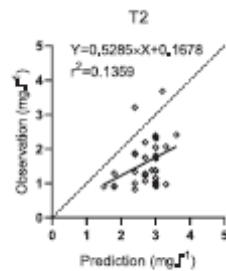
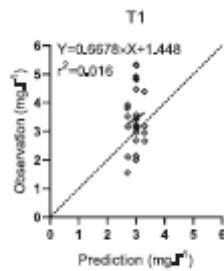
Propofol

- elective pulmonary endarterectomy
- 30 patients with chronic thromboembolic pulmonary hypertension
- connecting the patient to cardiopulmonary bypass (CPB)
- cooling to a core temperature of 16–20°C
- 20-minute circulatory arrest + opening right pulmonary artery branches + thrombectomy
- 15-min reperfusion
- 20-minute circulatory arrest + opening left pulmonary artery branches + thrombectomy
- during each circulatory arrest period, blood drains back into the CPB reservoir
- rewarming

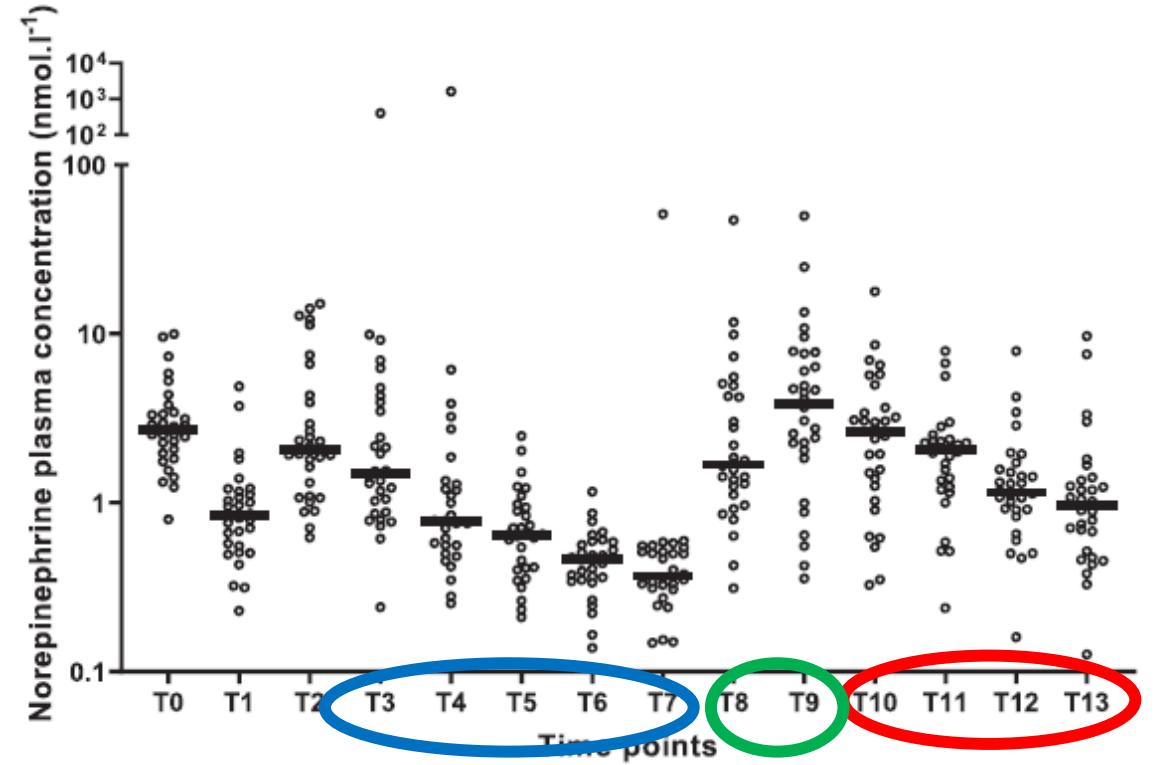
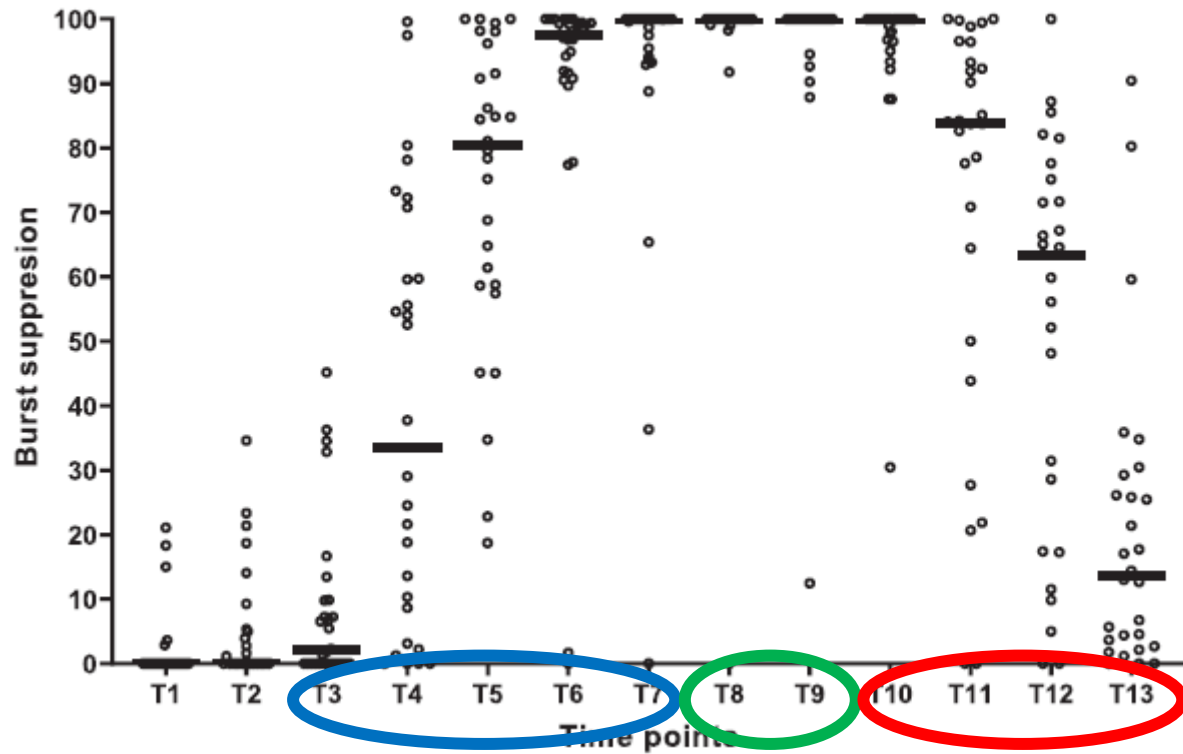
Propofol

- (T0) before induction of general anaesthesia
 - 15 min after induction (T1)
 - after initiation of cardiopulmonary bypass (T2)
 - then at 5 °C intervals during cooling from 35 °C (T3) to 20 °C (T6)
 - reaching the target temperature, T7
 - Reperfusion between the two periods of DHCA (T8)
 - before the start of rewarming (T9)
 - at 20 °C during rewarming (T10)
 - and subsequently at 5 °C intervals until the initial temperature of 35 °C was reached (T13)
- Age, height, body weight, ideal body weight, adjusted body weight, lean body mass, body surface area, body mass index, serum creatinine, estimated glomerular filtration rate, haemoglobin and DHCA were tested as continuous covariates
 - sex as a categorical covariate
 - Temperature was tested as a time-varying continuous covariate
 - a time-varying categorical covariate describing the rewarming phase (0 =cooling/steady state, 1 =active rewarming) was tested to account for potential hysteresis between hypothermia and rewarming at the same temperature

Propofol



Propofol



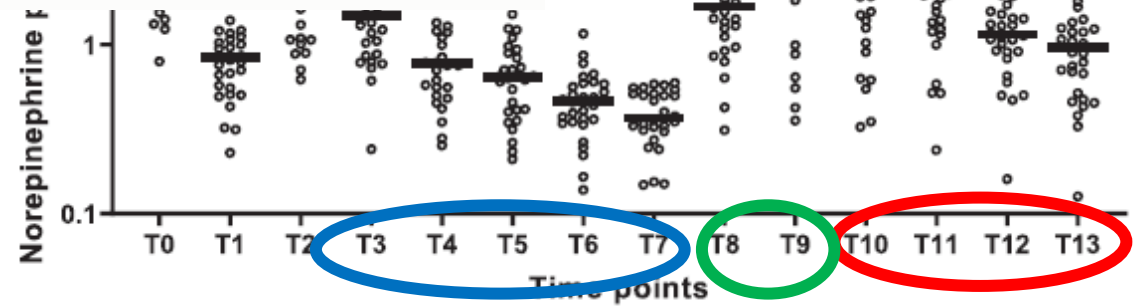
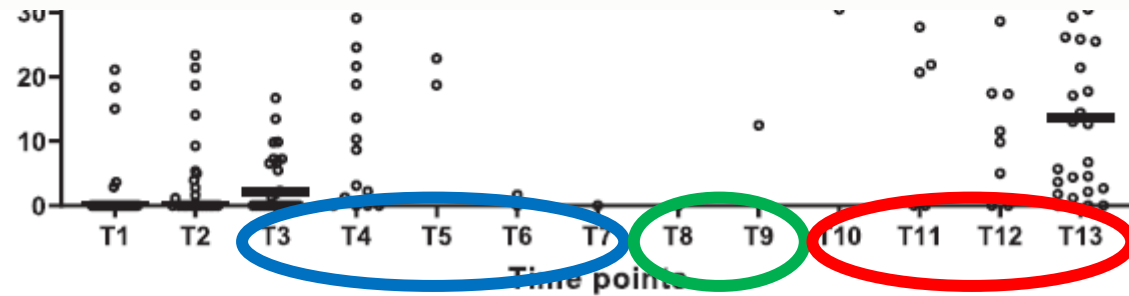
Propofol



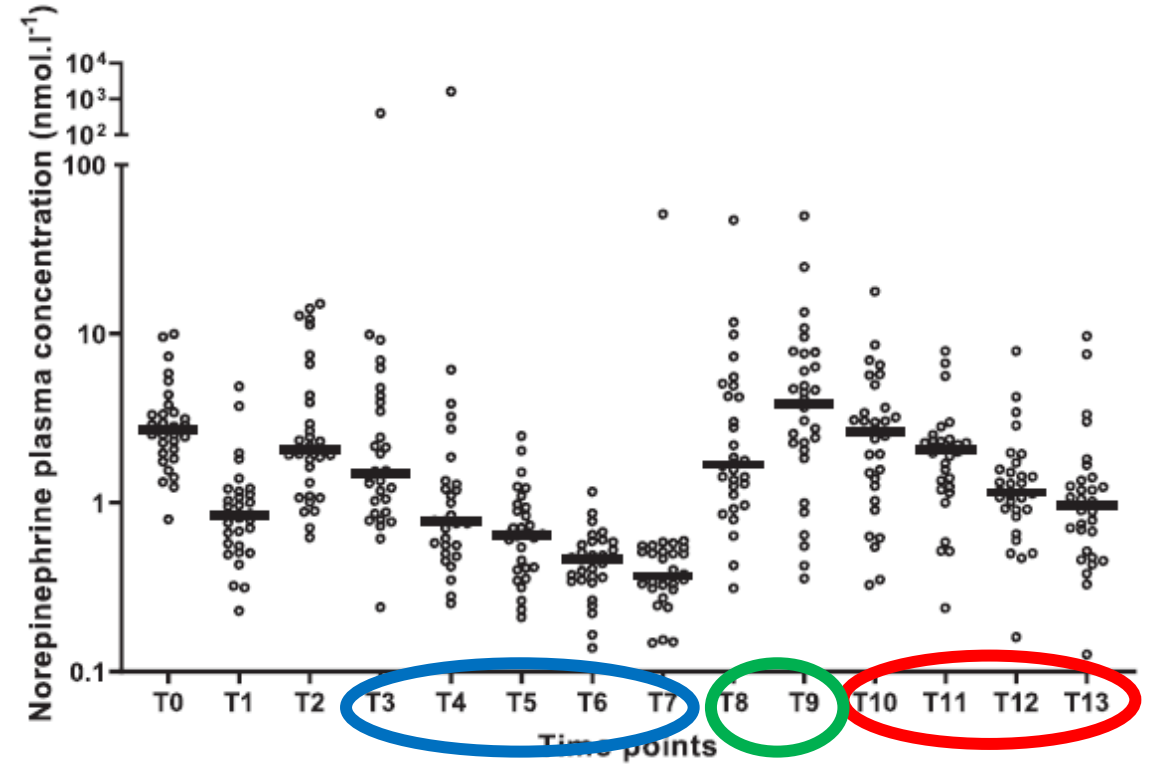
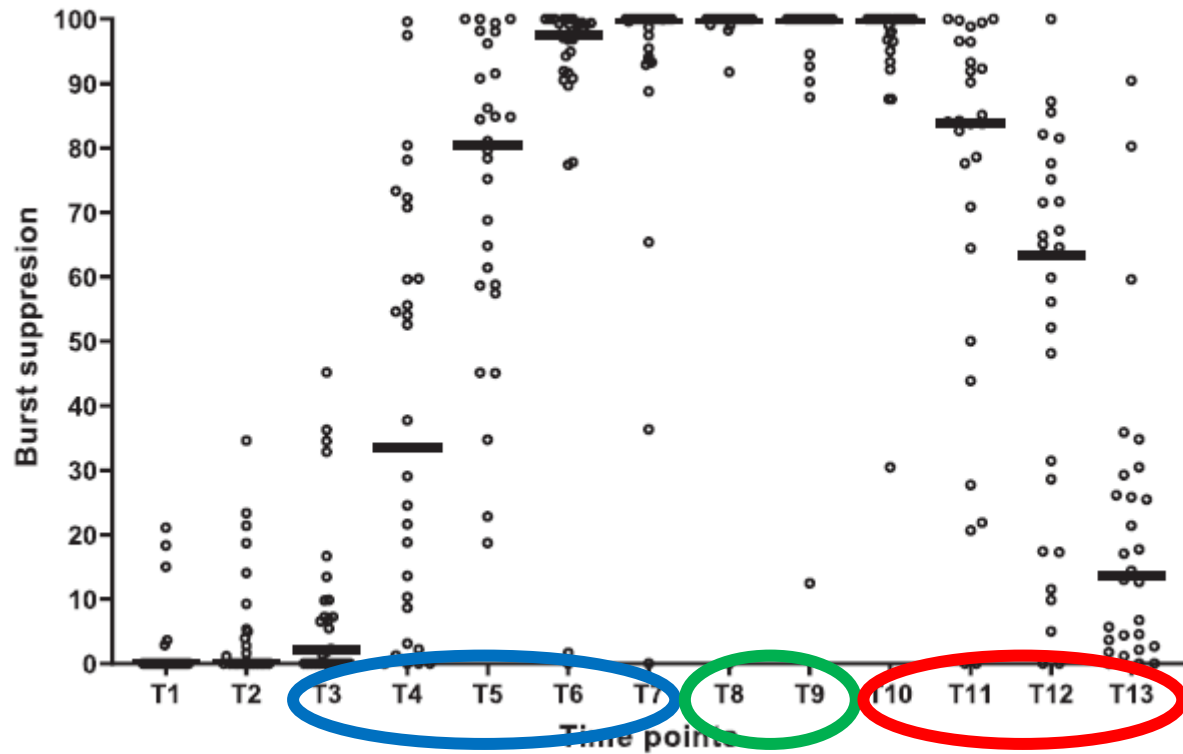
BSR 100% — isoelectric (flat)

Electrocerebral silence

No detectable activity



Propofol



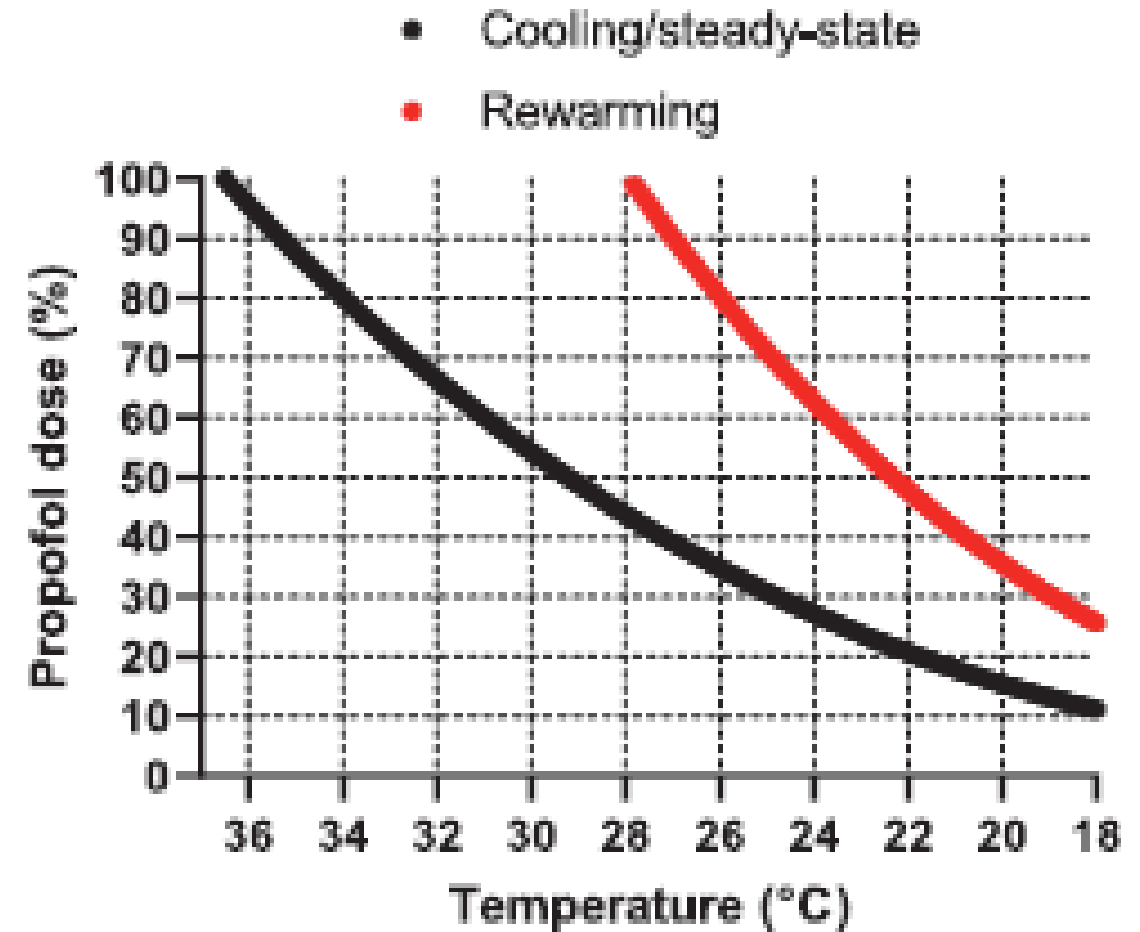
Propofol

Deep hypothermia reduces the predictive accuracy of the Eleveld propofol model: Population pharmacokinetic modelling in cardiac surgery

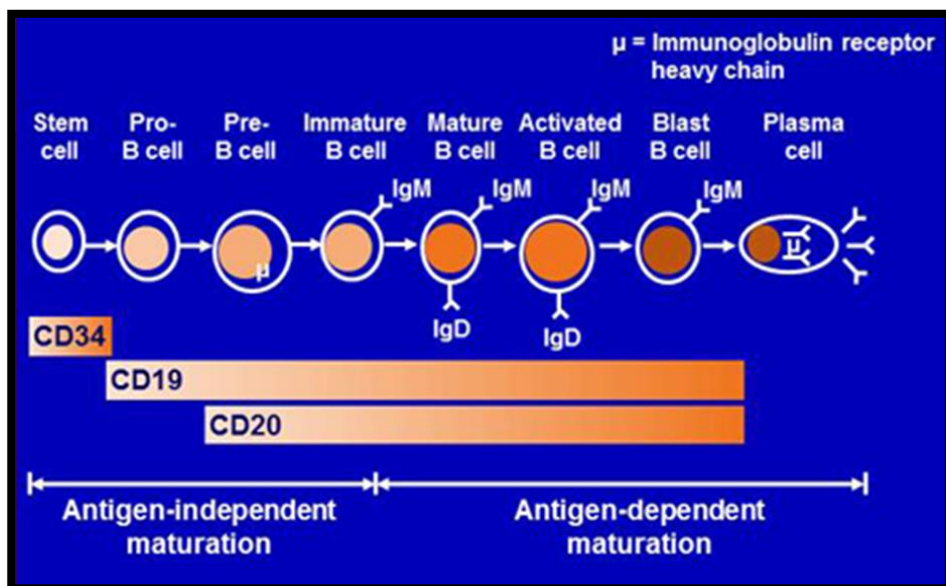
Tereza Bartošová^a, Martin Šíma^{b,*,1}, Tomáš Prskavec^c, Pavel Jansa^d, Pavel Michálek^a, Michal Lipš^e, Tomáš Brožek^a, Petr Kopecký^a, Petr Kozlík^e, Tomáš Krízek^e, Ondřej Slanář^f, Jan Kunštyř^g

Parameter	Final model		Bootstrap analysis
	Estimate	RSE (%)	Median (95% CI)
Fixed effects			
$Vd1 = Vd1_{pop}$			
$CL = CL_{pop} \cdot (TEMP/36.5)^{\beta_{pop}} \cdot (1 + \gamma_{pop} \cdot REWARM)$; $REWARM \in \{0, 1\}$			
$Vd2 = Vd2_{pop}$			
$Q = Q_{pop}$			
$Vd1_{pop}$ (l)	40.67	5.11	40.76 (40.09–41.16)
CL_{pop} (l · h ⁻¹)	97.23	9.29	100.5 (99.0–101.2)
$Vd2_{pop}$ (l)	273.0	n/a	n/a
Q_{pop} (l · h ⁻¹)	66.6	n/a	n/a
β_{pop}	3.11	7.50	3.19 (3.15–3.22)
γ_{pop}	1.31	34.8	1.27 (1.25–1.29)
Between subject variability (%)			
$Vd1$	26.0	43.1	22.5 (22.0–23.0)
CL	22.0	24.0	20.5 (20.0–21.0)
Error model parameter			
Proportional	0.33	4.30	0.33 (0.33–0.33)

$Vd1$ – central volume of distribution; CL – clearance; $Vd2$ – peripheral volume of distribution; Q – intercompartmental clearance; β_{pop} – effect of temperature on CL ; $TEMP$ – temperature (°C); γ_{pop} – effect of rewarming on CL ; $REWARM$ – rewarming $\in \{0, 1\}$; pop – typical value of parameter; CI – confidence interval; RSE – relative standard error; n/a – not applicable.



Rituximab anti-CD20 antibody



- **Haematologic indications:**

- *NHL*
- *CLL*

- **Immunosuppressant:**

- *rheumatoid arthritis*
- *pemphigus*
- *granulomatosis with polyangiitis*
- *microscopic polyangiitis*
- *minimal change nephrotic syndrome*
- *focal-segmental glomerulosclerosis*
- *lupus nephritis*
- ...

Different glomerular diseases:

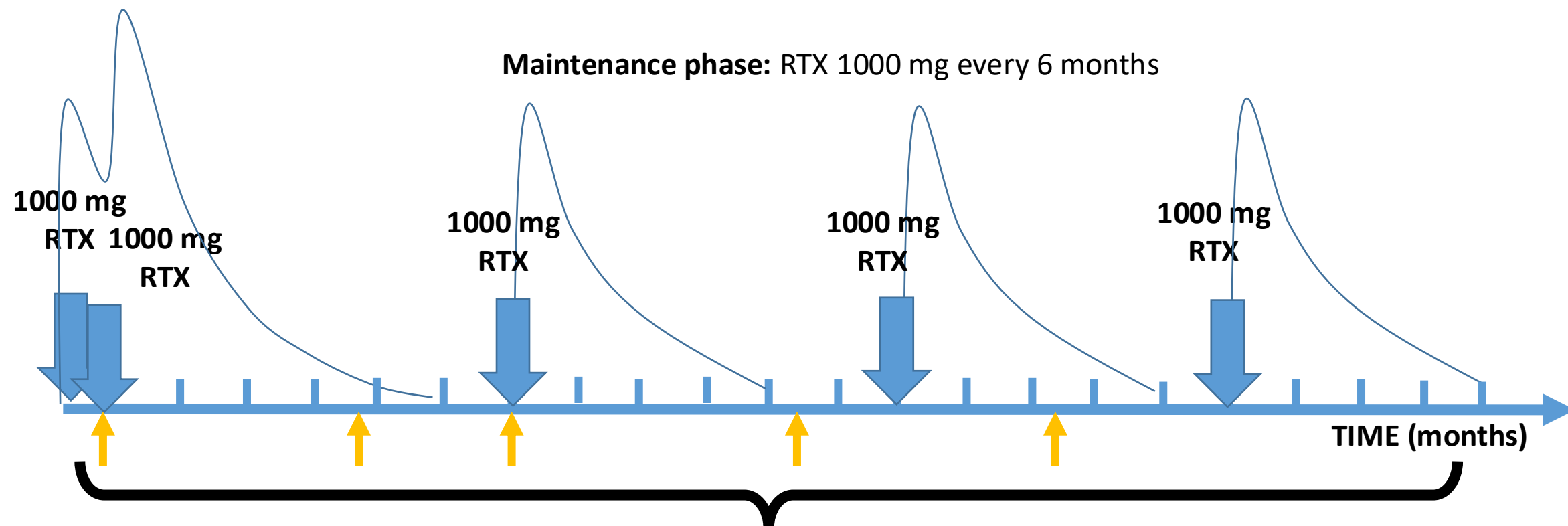
- different range of proteinuria
- different pathogenesis and inflammation characteristics

Probably different RTX pharmacokinetics?
Definitely different response rate to RTX treatment....

Study protocol (MAY 2020 – JUN 2023)

Induction phase:

RTX 2x 1000 mg 14 days apart



RTX levels and anti-RTX ADA levels were examined on every out-patient control (sampling intervals were largely irregular and varied between patients)

Demography

Population PK analysis of 445 RTX levels from 185 patients with glomerulonephritis

Demographic parameter	The whole population (N = 185)
Age (years)	55 (38-68)
Body weight (kg)	81 (70-94)
Height (cm)	173 (165-180)
BMI (kg/m ²)	28.81 (23.83-31.24)
BSA (m ²)	1.96 (1.80-2.13)
Sex (M/F)	103/82
Anti-RTX antibodies	25 (13.5 %)
Leukocyte count (10 ⁹ /L)	8.3 (6.9-9.5)
PCR (g/mmol)	0.05 (0.01-0.2)
Baseline IgG levels (g/L)	7.51 (5.71-9.64)
Initial CD19+ relative count	9.10 (6.00-12.80)
Duration of RTX therapy (days)	413 (116-826)
Prior RTX therapy*	25 (13.5%)

2 groups with different PK which mirrored also overall response rate.

Diagnoses		
AAV	77 (41.6 %)	Standard response
MCD	23 (12.4 %)	
MN	41 (22.2 %)	Difficult to treat
FSGS	15 (8.1 %)	
LN	18 (9.7 %)	
others	11 (5.9 %)	

* finished more than a year before first dose of study course of treatment

A novel dosing approach for rituximab in glomerular diseases based on a population pharmacokinetic analysis

Jan Miroslav Hartinger¹, Martin Šíma², Zdenka Hrušková³, Alena Pilková², Vojtěch Krátký³, Romana Ryšavá³, Eva Jančová³, Daniel Bobek², Jiří Douša², Ivana Francová⁴, Vladimír Tesař³, Ondřej Slanář⁵

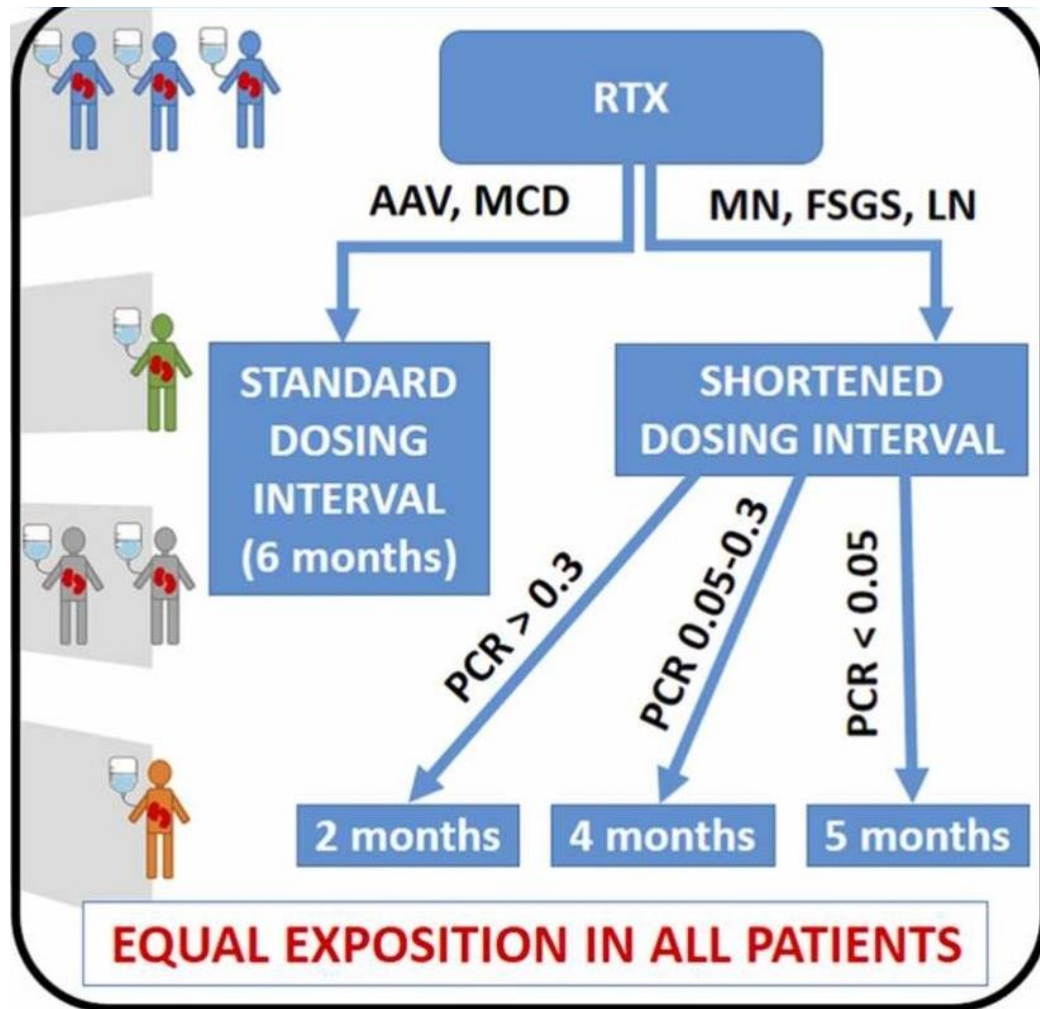
- $V_d (L) = 7,22 \times e^{0,0083 \times BW}$
- $CL (L/h) = 0,14 \times e^{0,0089 \times BW} \times e^{0,74 \times PCR} \times 1,42 \text{ (if DTTDg)} \times 1,15 \text{ (if ADA)} \times 0,84 \text{ (if } \geq 2 \text{ years)}$
 - *BW: body weight*
 - *PCR: protein-to-creatinine ratio*
 - *DTTDg: membranous nephropaty, lupus nephritis, focal segmental glomerulosclerosis*
 - *SRDg: ANCA-associated vasculitis, "minimal change disease" nephritis*
 - *ADA: presence of anti-RTX antibodies*

Results:

*covariates
influencing
RTX
pharmaco-
kinetics*

- **Volume of distribution:**
 - positive correlation with body weight
- **Clearance**
 - positive correlation with body weight
 - negative correlation with length of treatment
 - **positive correlation with urinary protein/creatinine ratio**
 - **higher CL in patients with ADA**
 - **increased CL in patients with MN, LN, FSGS (DTTDg)**
 - covariate independent on PCR

Diagnosis	Vd [L]	CL [L/day]	T _{1/2} [days]
ALL (N=185)	14.33 (13.14-15.66)	0.40 (0.29-0.54)	25.39 (18.91-33.32)
SRDg (N=100)	14.14 (12.89-15.72)	0.31 (0.26-0.38)	31.27 (26.06-37.18)
DTTDg (N=85)	14.65 (13.62-15.66)	0.54 (0.43-0.66)	18.72 (15.58-22.92)
AAV (N = 77)	14.29 (13.06-16.23)	0.31 (0.26-0.39)	31.68 (25.86-38.31)
MCD (N = 23)	13.12 (12.25-14.88)	0.30 (0.26-0.37)	30.44 (27.39-35.14)
MN (N=41)	14.98 (14.08-15.94)	0.60 (0.47-0.78)	17.54 (13.91-21.76)
FSGS (N=15)	14.87 (14.19-16.71)	0.56 (0.42-0.66)	18.52 (16.15-23.66)
LN (N=18)	13.53 (12.32-14.59)	0.43 (0.40-0.53)	19.18 (17.69-24.00)
Other (N=11)	14.49 (13.74-15.19)	0.47 (0.39-0.56)	20.45 (18.76-24.35)



ADA

- SRDg: 13/145 (9 %)
- DTTDg: 41/155 (26 %)

- AAV: 9/110 (8 %)
- MCD 4/35 (11 %)
- MN: 19/72 (26 %)
- FSGS 9/29 (31 %)
- SLE 5/31 (16 %)
- other 7/23 (30 %)

Clinical relevance?

- Likely more ADRs
- Do not always affect efficacy
- Shorten T1/2

Concluding Remarks

- Important to respect the limits of the model
-
- Pop PK
 - important tool to improve dosing schedules,
 - enables improvement of treatment,
 - reduction of adverse effects, and
 - more efficient utilization of healthcare resources
- Integration of advanced modeling methods represents the future of personalized pharmacotherapy



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Thank you



zeNTIVA



**KRAJSKÁ
NEMOCNICE
TOMÁŠE BATI**



Krajská nemocnice Liberec, a.s.



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