Population pharmacokinetics of ticagrelor and its active metabolite in dried bloodspot data of a real-life hospitalized population

Debra van Asten[1,2], Frédéric Gaspar[1,3,4], Anne Ravix[1], Jean Terrier[5,6,7], Pauline Gosselin[5,6], Pierre Fontana[6,8] ,Youssef Daali[6,7], Jean- Luc Reny[5,6], Chantal Csajka[1,3,4*], Monia Guidi[1,4,9*]

[1]Centre for Research and Innovation in Clinical Pharmaceutical Sciences, Lausanne University Hospital and University of Lausanne, Lausanne, Switzerland. [2]Leiden Academic Centre for Drug Research (LACDR), Leiden University, Leiden, The Netherlands. [3]School of Pharmaceutical Sciences, University of Geneva, Geneva, Switzerland. [4]Institute of Pharmaceutical Sciences of Western Switzerland, University of Geneva, University of Lausanne, Geneva, Switzerland. [5]Division of General Internal Medicine, Geneva University Hospitals, Geneva, Switzerland. [6]Geneva Platelet Group, Faculty of Medicine, University of Geneva, Geneva, Switzerland. [7]Division of Clinical Pharmacology and Toxicology, Anesthesiology, Pharmacology, Intensive Care, and Emergency Medicine Department, Geneva University Hospitals, Geneva, Switzerland. [8]Division of Angiology and Haemostasis, Geneva University Hospitals, Geneva, Switzerland. [9]Service of Clinical Pharmacology, Lausanne University Hospital and University of Lausanne, Lausanne, Switzerland. (*) Equal contribution

Introduction

- Ticagrelor (a reversible P2Y12-receptor antagonist) is a well-established treatment of **acute coronary syndromes**.
- Ticagrelor is metabolized by cytochrome P450 (CYP) 3A4/5 into its **equipotent metabolite, AR-C124910XX**.
- Previous publications showed **substantial variability** in the pharmacokinetics (PK) of ticagrelor and AR-C124910XX. However, studies aiming at characterizing the drug and metabolite PK profiles are **lacking in real-world patient populations**.

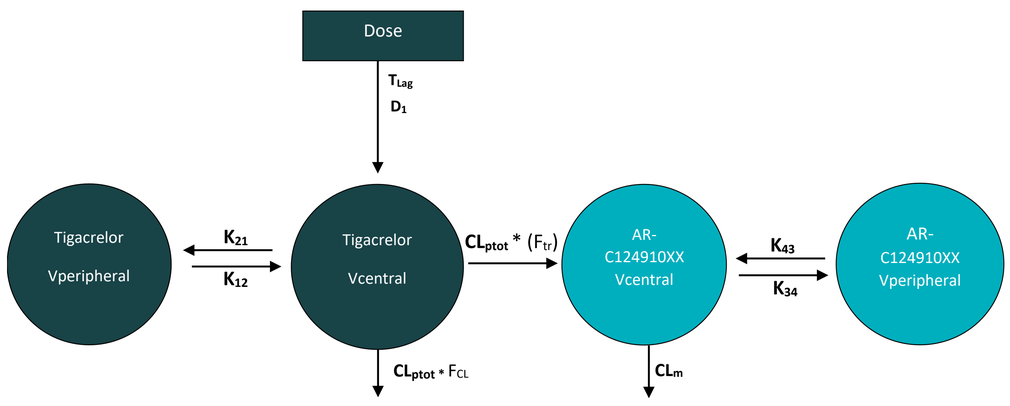
Methods & Data

- Ticagrelor and AR-C124910XX data were modelled simultaneously, via a classic stepwise population PK (popPK) approach (Monolix 2021), assuming **linear and irreversible biotransformation** between the parent drug to the metabolite.
- Rich **dried bloodspot (DBS)** data was collected from 103 hospitalized patients* who received a dose of 90 mg ticagrelor and reached steady state prior to the start of the **OptimAT study**[1].
- Tested covariates included demographic (e.g. body weight, age and gender) and genetic factors (CYP3A4/5 and P-glycoprotein (P-gp) phenotypic activity). Individual phenotypes were obtained via the **Geneva Cocktail approach** for determination of CYP and P-gp activities[2].

The aim of this study was to characterize ticagrelor and AR-C124910XX PK profiles in real-world hospitalized patients enrolled in the OptimAT study, and to identify sources of variability using a popPK-modelling approach.

Results

Figure 1. Schematic representation of the structural popPK model



Final equations:

$$F_{tr} = 1 - F_{CLp}$$

$$k_{tr}[/h] = \frac{(CL_{totp} * F_{tr})}{V_{pc}}$$

$$k_p\,[/h] = \frac{(CL_{totp} * F_{CL})}{V_{pc}}$$

$$CL_m[L/h] = TVCL_m * \left(\frac{Age_i}{63.2}\right)^{-1.11}$$

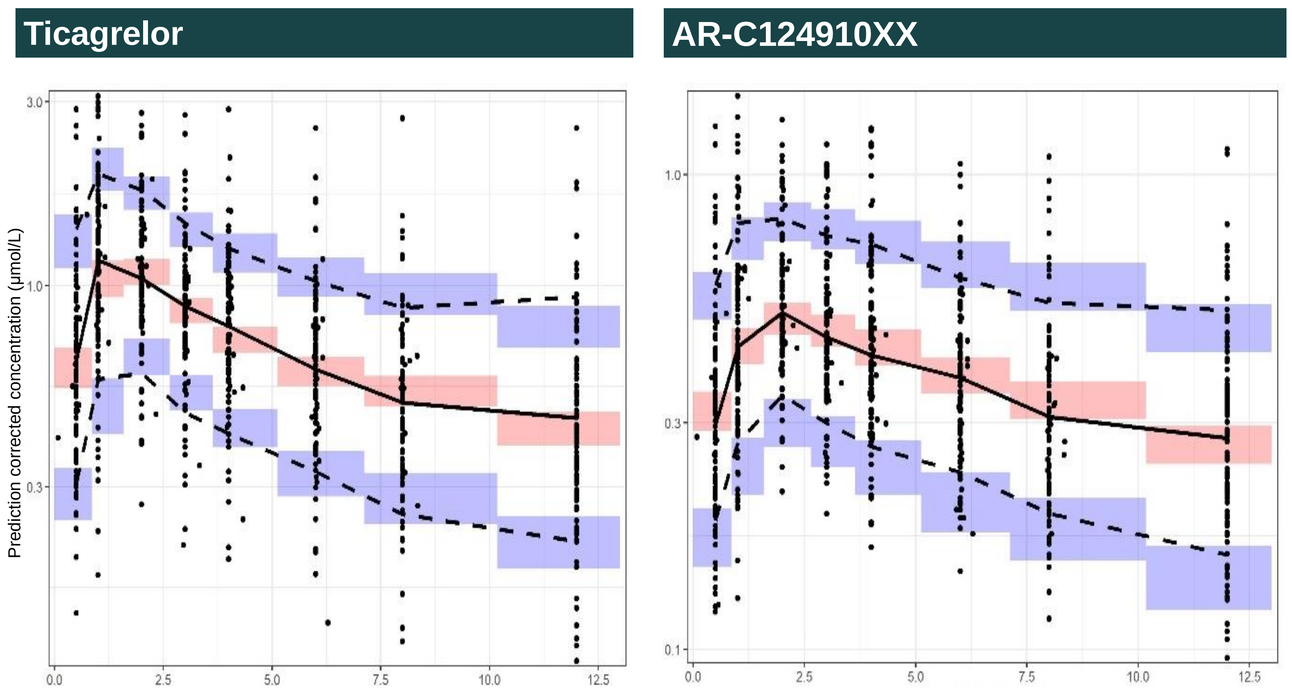
F_{tr}: fraction of CL_{totp} due to the metabolism of ticagrelor into AR-C124910XX
F_{CLp} ; fraction of CL_{totp} due to remaining elimination pathways
k_{tr}; metabolic transfer rate from ticagrelor to AR-C124910XX
CL_{totp}: total clearance of the ticagrelor (bio transfer and elimination)
V_{pc}: central volume of distribution of ticagrelor
k_p : elimination rate constant of ticagrelor
CL_m: Clearance of the metabolite
$TVCL_m$: Typical CL_m value

Table 1. Parameter estimates of the final popPK model

Label	Estimate (RSE%) Population parameters (θ)	Estimate (RSE%) Inter-individual variability (CV(%))
Parent		
D_1 (h)	1.07 (7.3)	65 (11.1)
T_{Lag} (h)	0.34 (7.4)	66 (9.3)
CL_{ptot} (L/h)	18.9 (4.4)	45 (7.4)
V_{pc} (L)	118 (6.5)	57 (9.7)
V_{pp} (L)	326 (11.0)	125 (9.0)
Q_p (L/h)	59.8 (5.1)	-
F_{CLp}	0.36 (1.5)	-
Metabolite		
CL_m (L/h)	21.6 (3.7)	36 (7.7)
Age on CL_m	-1.11 (18.4)	-
V_{mc} (L)	1	-
V_{mp} (L)	41.6 (13.9)	119 (13)
Q_m (L/h)	29.2 (2.7)	-
Correlations		
V_{pc} and CL_p	0.73	11.4
Residual variability (CV(%))		
Parent: Proportional	13.1 (3.3)	
Metabolite: proportional	10.0 (3.1)	

RSE = relative standard error, D_1 = Duration zero-order absorption, T_{Lag} = lag time, V_{pp} and Q_p = Peripheral volume of distribution and inter-compartmental CL ticagrelor, V_{mc}, V_{mp} and Q_m = central volume of distribution, peripheral volume of distribution and inter-compartmental CL of AR-C124910XX.

Figure 2. Prediction corrected visual predictive check (pcVPC) of the final popPK model



The thick and dashed black lines represent the median and 80% intervals of the observed data. The black dots represent the prediction corrected observations in the dataset. The pink and purple areas represent the 95% CI around the median and 80% prediction intervals of the predicted data.

Main findings

- A 2-compartmental model structure with **zero-order absorption and a lag-time** accurately characterized OptimAT data.
- An inverse covariate relationship between CL_m **and age** was included in the model. An increase of 10-years in age produces a 15% relative decrease (3.2 L/h) in CL of the metabolite.
- No significant associations could be identified between PK model parameters and other available covariates, **including CYP3A4/5 and P-gp phenotypic activity**.

Conclusion

- **This study confirmed the substantial variability in the PK profile of ticagrelor and its metabolite in DBS samples.**
- **Further research is needed to confirm the influence and study the clinical significance of the large IIV and the relationship between CL of the metabolite and age.**

1. Antithrombotics' Therapeutic Optimization in Hospitalized Patients Using Physiologically- and Population-based Pharmacokinetic Modeling.
2. Bosilkovska, M., et al., Geneva cocktail for cytochrome p450 and P-glycoprotein activity assessment using dried blood spots. Clin Pharmacol Ther, 2014. 96(3): p. 349-59.