

Introduction and objectives

- Antithrombotics are among the most high-risk medications associated with bleeding and ischemia due to over-or underdosing
- There is no reliable tool to predict the right dosage for a given patient
- This issue could be solved using adjustment methods based on pharmacokinetic (PK) modeling, such as population PK modeling (**popPK**) or physiologically based PK (**PBPK**)
- Therapeutic individualization based on **popPK** is well established in clinical practice but has limitations
- Recent advances in **PBPK** models may be an alternative for therapeutic individualization but there is a lack of evidence

Aim of the work:

- To develop and to validate a **popPK** model for **Ticagrelor** and its active metabolite (**AM**) (**part I**)
- To compare **popPK** and **PBPK** results in individual drug exposure predictions (**part II**)

Methods

Part I: popPK analysis

- A «top-down» **popPK** model was built and validated using full PK profiles collected in healthy volunteers (table 1) in NONMEM 7.4.3
- Several covariates were tested on Ticagrelor PK parameters (including CYP3A4/5 phenotype)
- The final model was used to predict drug exposure (**AUC_{0-24,popPK, pred}**)

Part II: PBPK prediction and comparison

- A **PBPK** model based on physiologic characteristics was used in SIMCYP 18. Individual physiological, demographic and genetic characteristics (CYP3A4/5 phenotype) were integrated in the model to predict individual drug exposure (**AUC_{0-24,PBPK, pred}**)
- Predicted and observed systemic exposures were then compared in each subject by mean-fold error (MFE=AUC_{0-24pred}/AUC_{0-24obs}) to assess the predictability of both approaches



Two validation criteria were applied: MFE 0.5 to 2.0, a criterion commonly used in PBPK modelling, and MFE 0.8 to 1.25, largely used for bioequivalence studies

Results

Table 1: Population Description

Healthy volunteers' characteristics (n=20)	median [IQR] or n (%)
Men	19 (100)
Age (years)	27 [19-45]
Body weight (kg)	76 [64 – 94]
Height (cm)	181 [169 - 189]
CYP3A4/5 ratio ¹	23 [1 – 52]

¹CYP3A phenotype was assessed using metabolic ratio of midazolam (OH-midazolam/midazolam) 1 hour after intake of a single 100 µg dose

Among the variables tested on PK parameters, only CYP3A4 had a significant influence on clearance (p=0.012), which was 10% lower in poor (CYP3A4/5 ratio 11 [1-22]) and 30% higher in rapid (CYP3A4/5 ratio 39 [35-52]) compared to extensive metabolizers

Table 2 (part I): PK parameters of the final **popPK** model with bootstrap results.

Parameter	Estimate (RSE %)	Bootstrap results (n=2000)	
		Median	CI 95%
CL _{Tica} (L/h)	49 (5)	48	38 – 59
θ _{CYP3A4/5}	1.2 (13)	1.2	1.1 – 1.3
V ₂ (L)	25 (21)	24	19 – 28
K ₁₂ (h ⁻¹)	0.4 (24)	0.3	0.1 – 0.6
D ₁ (h ⁻¹)	0.8 (13)	0.8	0.7 – 1.0
Q (L/h)	56 (40)	52	43 – 61
V ₄ (L)	270 (11)	268	232 – 304
K ₂₃ (h ⁻¹)	1.0 (9)	1.0	0.8 – 1.2
CL _{AM} (L/h)	30 (39)	29	15 – 38
BSV CL _{Tica} (%)	19 (25)	19	17 – 20
BSV V ₂ (%)	15 (34)	14	10 – 18
BSV K ₂₃ (%)	32 (17)	31	21 – 42

Final Ticagrelor model: CL/F(L/h)= CL_{Tica} × (CYP3A4/5 ratio / CYP3A4/5 ratio_{med})*θ_{CYP3A4/5}

Figure 1 (part I) : **PopPK** model best describing the Ticagrelor and AM data

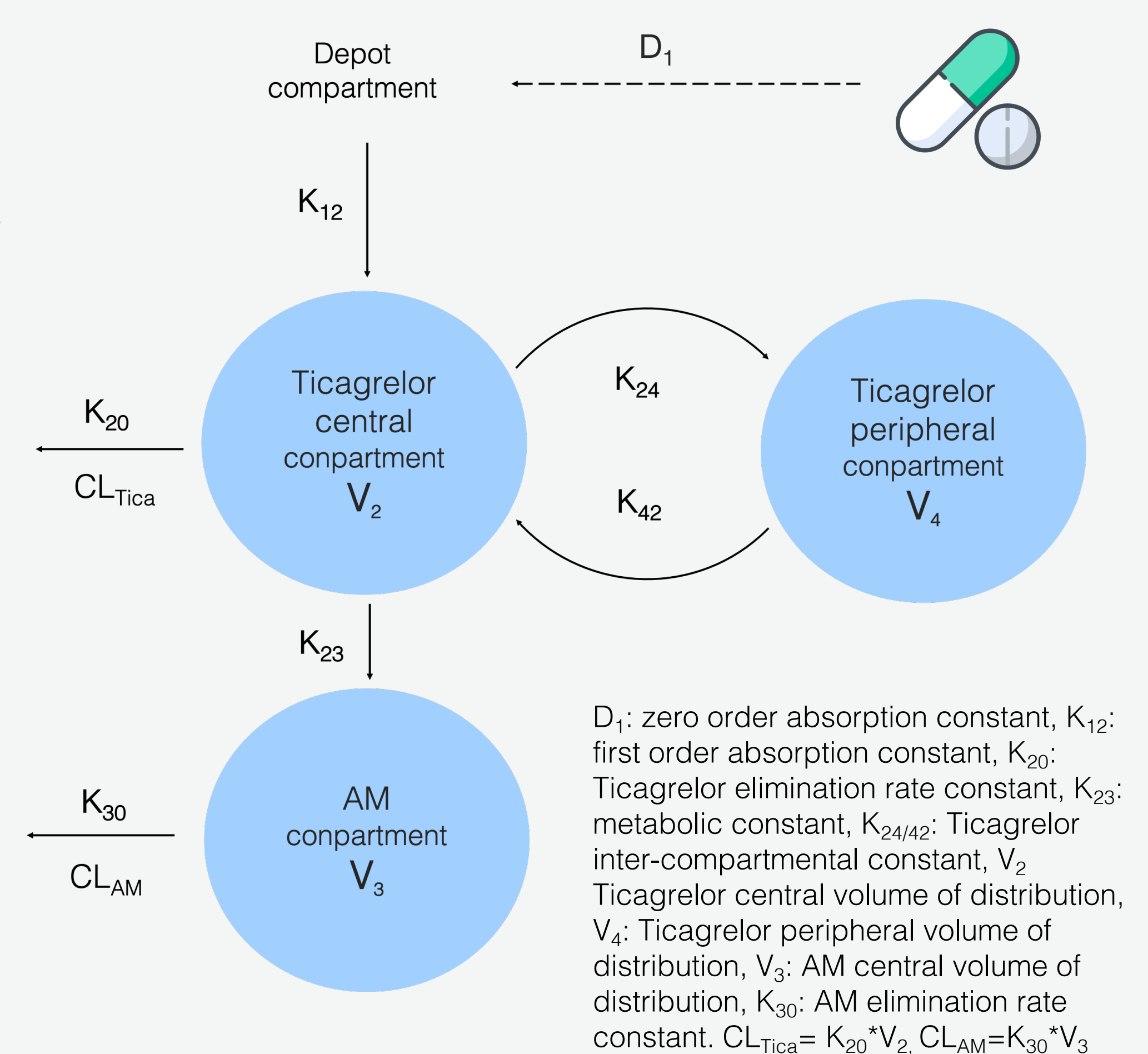
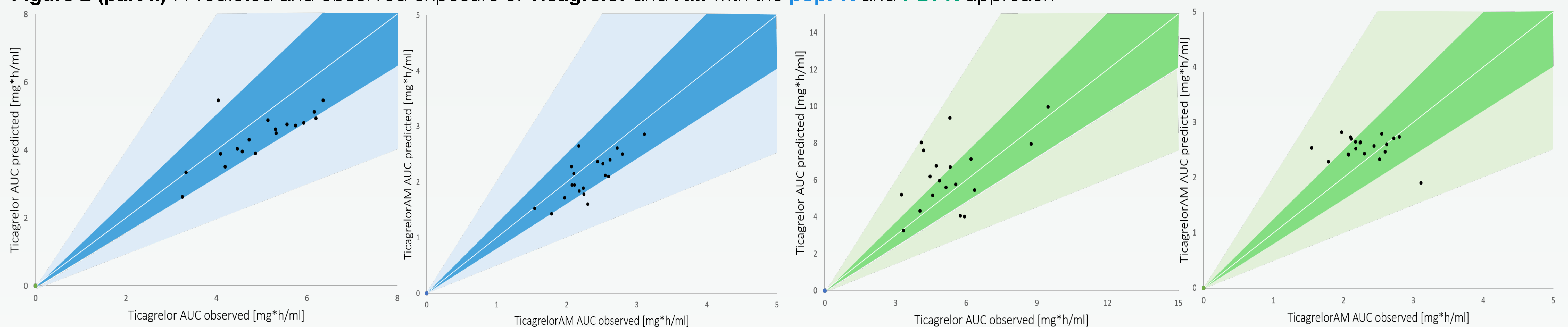


Figure 2 (part II) : Predicted and observed exposure of **Ticagrelor** and **AM** with the **popPK** and **PBPK** approach



The two validation criteria are presented in the graph, the dark part presents the MFE 0.5 to 2.0 interval and the light part MFE 0.8 to 1.25; the white line represents the ratio 1:1

PopPK approach

Ticagrelor and its AM AUC_{obs} were adequately predicted in all subjects using the large criterion (100%), and in 80% with the stricter criterion.

PBPK approach

All predictions for Ticagrelor and AM are in the defined large criterion range. 58% and 68% are within the stricter criterion for Ticagrelor and AM respectively. Precision was greater for the AM.

Conclusion

- Developed and validated **popPK** and **PBPK** models have been successfully used to predict individual Ticagrelor and AM exposure
- As a first step towards therapy individualisation based on **PBPK**: these preliminary data demonstrate that **PBPK** modeling could offer future perspectives in personalized medicine.
- To be clinically relevant in daily practice, it will be however necessary to develop a robust **PBPK** model integrating influencing covariates. For such purpose, a dual **PopPK** and **PBPK** development may be the right way to follow.
- These results need to be confirmed in real-life settings using data collected in hospitalized patients