



Comprehensive population PK/PD modeling of Perindopril, Indapamide, and Bisoprolol in healthy volunteers: insights for fixed-dose combination therapy in hypertension

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Background

Objective: To support potential future developments of FDC including Bisoprolol, Perindopril and/or Indapamide, a PK/PD modelling analysis has been performed aiming at assessing the relevant contribution of each substance to the antihypertensive effect. The available arms in historical studies used for this purpose, ranged from mono therapy to tri-therapy settings, with one missing dual therapy (involving Bisoprolol with Indapamide).

Healthy volunteer studies used for modelling

Six interaction or bioequivalence studies involving Healthy Volunteers (HV) have been included in the population PK and population PK/PD datasets.

In the population PK analyses, with each visit considered as a distinct participant, the number of subjects included in the Perindoprilat, Indapamide and Bisoprolol models were respectively 533, 416 and 291 with 12128, 8707 and 6011 respectively after exclusion following EDA

The dataset used for the FINAL population PK/PD model included 319 participants and 4716 BP observations

Study name	Study type	Planned (actual) nb. of HV	Arms	Doses (mg)	Perindopril salt	PK sample number	BP measure number
PKH-05150-001	Interaction	60	P, B, P+B	10 and 10	arginine	24	5
PKH-05597-002	Interaction	36	P, I, P+I	8 and 2.5	tert-butylamine	22	6
PKH-05164-001§	Interaction	28 (/26)	B, T, B+T	10	na	21	7
PKH-05168-001	Bioavailability	76	PI+B, PIB	10, 2.5 and 10	arginine	24 - 20	8
PKH-05182-001*	Bioequivalence	80	P+I, PI	10 and 1.5 SR	arginine	25	9
PKH-06593-019¥	Interaction	42 (/41)	A, PI, PI+A	4 and 1.25	tert-butylamine	22	9

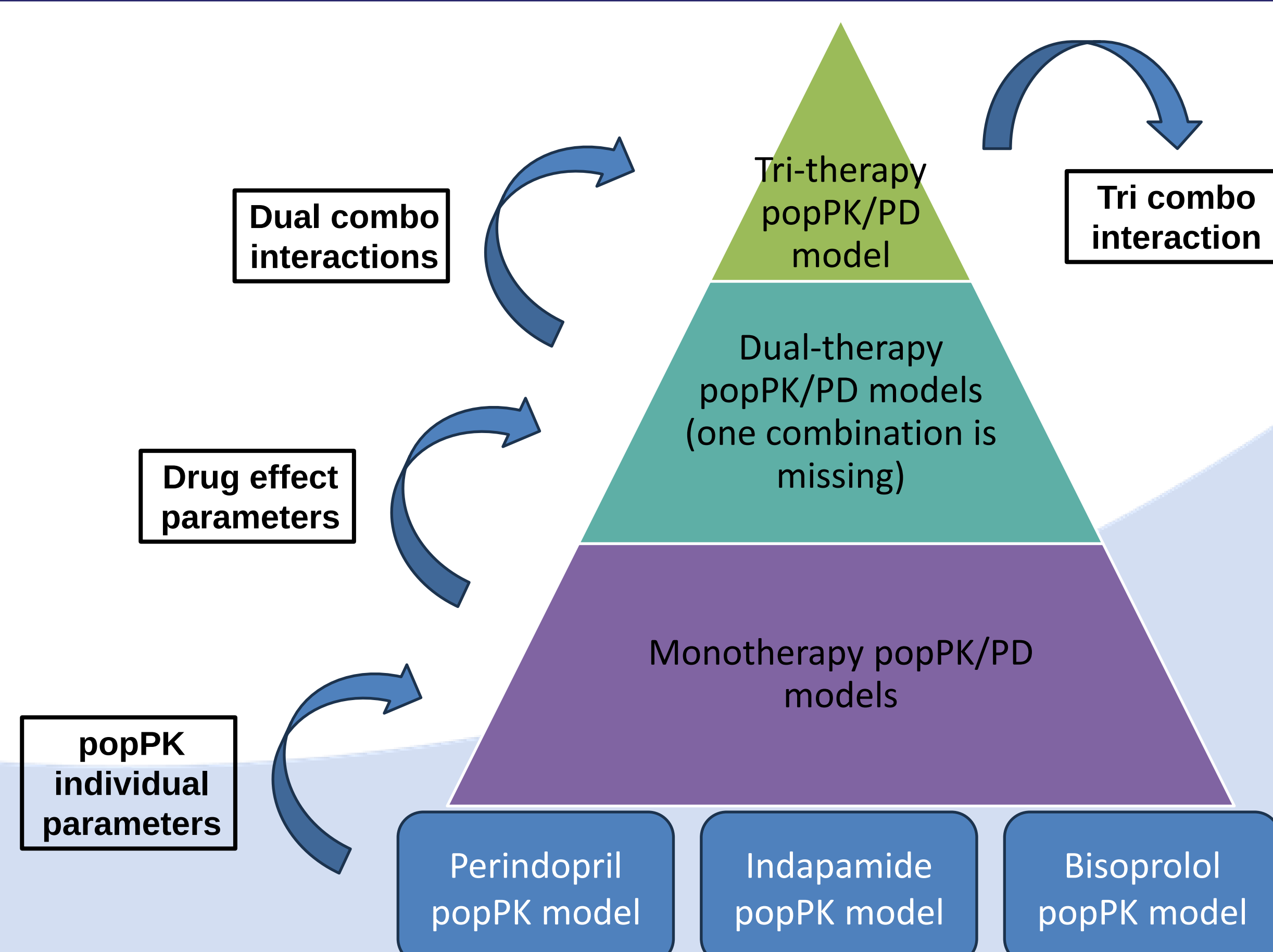
P: Perindoprilat, I: Indapamide, B: Bisoprolol, T: Trimetazidine, A: Amlodipine.

§: only the Bisoprolol arm has been included in the current analysis.

¥: only the PI arm has been included in the current analysis (S05590 data).

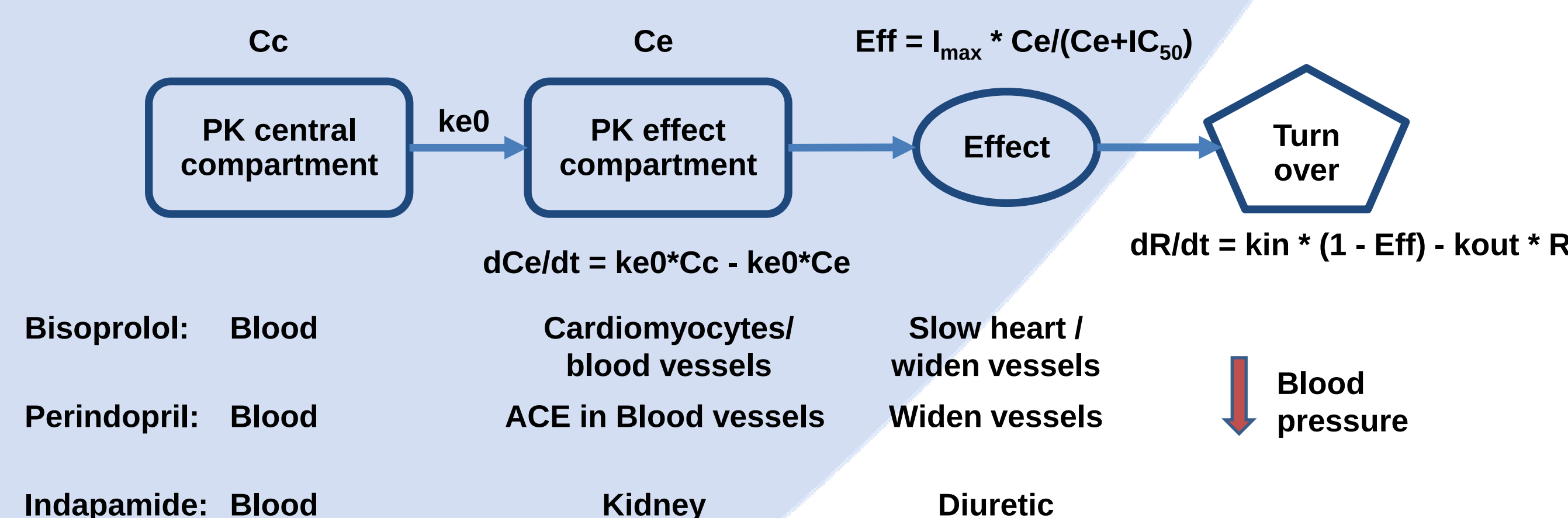
*: with Indapamide SR formulation

Modeling strategy



$$effect(C_x, C_y, C_z) = [effect(C_x, C_y) + effect(C_x, C_z) + effect(C_y, C_z)]/2 - \alpha_{xyz} * [effect(C_x, C_y) * effect(C_x, C_z) * effect(C_y, C_z)]$$

$$effect(C_x, C_y) = effect(C_x) + effect(C_y) - \alpha_{xy} * [effect(C_x) * effect(C_y)]$$



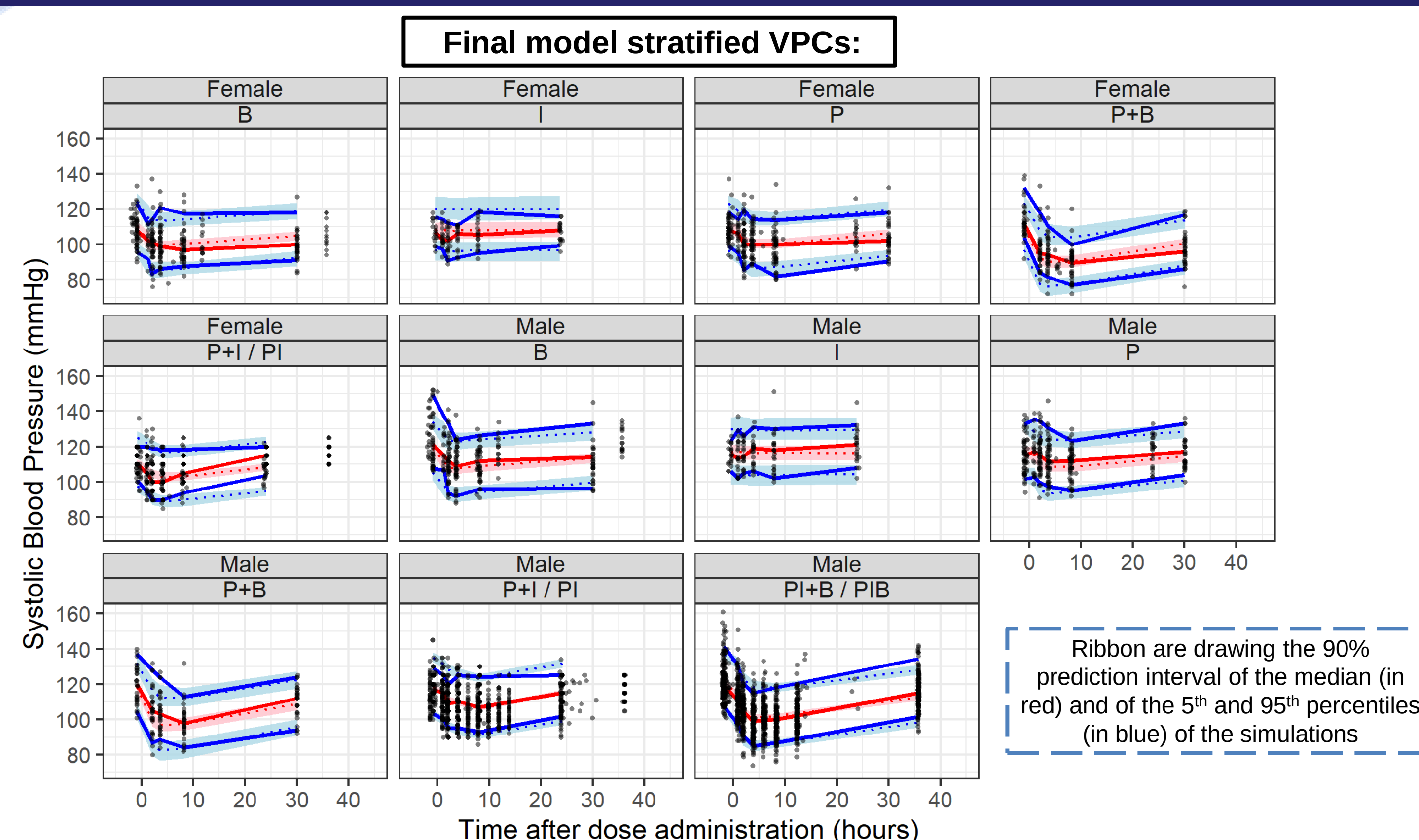
PK/PD models starting point:

Indirect turnover models with inhibition of the production k_{in} , baseline response R_0 , degradation rate k_{out} , maximal fraction of inhibition I_{max} , and half-maximal inhibitory concentration IC_{50}

The studies drugs have different mode of actions and targets, the interaction are not competitive. Bliss with interaction models were used.

Results

- The final PK models provided robust description of the PK profiles for each drug (very rich sampling schedules enabling accurate parameter estimation).
- The PK/PD relationship with Systolic Blood Pressure (SBP) was best described with the starting point model which was kept
- The covariate analysis identified significant relationships such as gender, weight, and ethnicity affecting SBP baseline levels. Gender-specific differences and body-weight association with SBP baseline were consistent with literature^[6].
- The estimated interaction parameter value ($\alpha_{PI} = 22.7$) for the Perindoprilat/Indapamide showed a less than additive effect
- The estimated interaction parameter value ($\alpha_{PB} = 2.6$) for the Perindoprilat/Bisoprolol combo showed a slightly less than additive effect.
- With three drugs the interaction parameter α_{PIB} was found to be non-different from zero, indicating an additive effect of this combo.



Conclusion

This comprehensive PK/PD modeling study provided valuable insights for the PK and PD of Perindopril, Indapamide, and Bisoprolol in HV and their interaction. Modelling analysis highlighted the strong antihypertensive property of Bisoprolol and Perindopril in HV and single administration setting. A clear additive effect was observed for the tri-therapy combination. The developed models are robust and can be used for further simulations and predictions of drug effects in HV. Overall, this study contributes to the understanding of the PK and PD relationships of commonly used antihypertensive drugs and their combinations and could support the development of FDC therapies against hypertension, providing a foundation for future clinical trials and therapeutic strategies.

References

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