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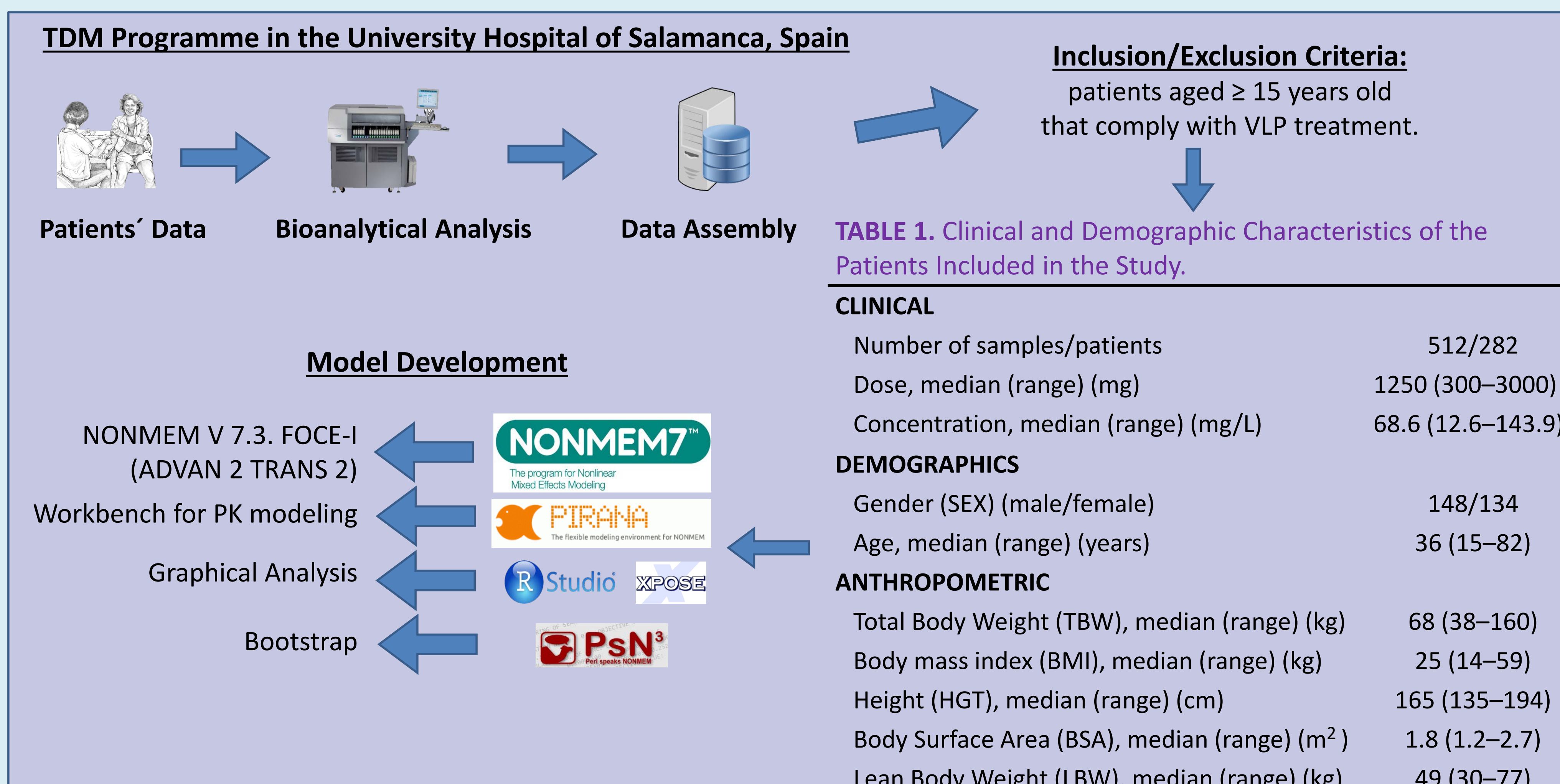
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OBJECTIVE

The main goal of this study was to evaluate the effect of anthropometric covariates on the clearance (CL) of valproic acid (VLP) in adult patients to develop a population pharmacokinetics (PoPK) model.

METHODS

- ✓ Serum concentrations of VLP were taken from patients included in the TDM program.
- ✓ Inclusion/exclusion criteria were previously applied.
- ✓ The PK analysis was performed with NONMEM.
- ✓ Proportional error models were assumed to describe interindividual and residual variabilities.
- ✓ The analysed covariates are described in table 1.
- ✓ The predictive capacity was evaluated using a Bootstrap technique.



RESULTS

- ✓ All evaluated anthropometric covariates showed the significant influence on CL/F_{VLP} and its inclusion in the model can explain part of the interindividual variability. See table 2.
- ✓ The goodness of fit in the final model (TBW on CL) is better than with basic model. See figure 1.
- ✓ The results obtained in the Bootstrap analysis show acceptable performance of the proposed model. See table 3.

TABLE 2. Summary of Covariates Analyses.

Covariates ^a on the CL/F_{PBT}	Forward Inclusion Method		ω^2 (RSE(%))	σ^2 (RSE(%))
	ΔOFV ^b	P Value		
Basic model	----	----	0.0653 (15)	0.0571 (10)
TBW	100.32	< 0.05	0.0373 (18)	0.0576 (10)
HGT	54.02	< 0.05	0.0496 (13)	0.0571 (10)
BMI	43.97	< 0.05	0.0517 (17)	0.0573 (11)
BSA	108.51	< 0.05	0.0358 (19)	0.0575 (10)
LBW	106.16	< 0.05	0.0362 (17)	0.0576 (10)

RSE (%), percentage of relative standard error.

^a covariates were include by allometric function.

^b Reduction in the objective function value (OFV) compared with basic model.

- ✓ Due to correlation of anthropometric covariates, the inclusion of only one of them in the PoPK final model is acceptable.
- ✓ In comparison with the others covariates, the TBW is the easiest to obtain in clinical practice. Moreover, in general, the volume (V) of liposoluble drugs correlates better with the TBW and justifies the difference observed in the CL in overweight patients, for whom when using the TBW measure as body size, the size is one V higher than when the LBW or BSA is used.

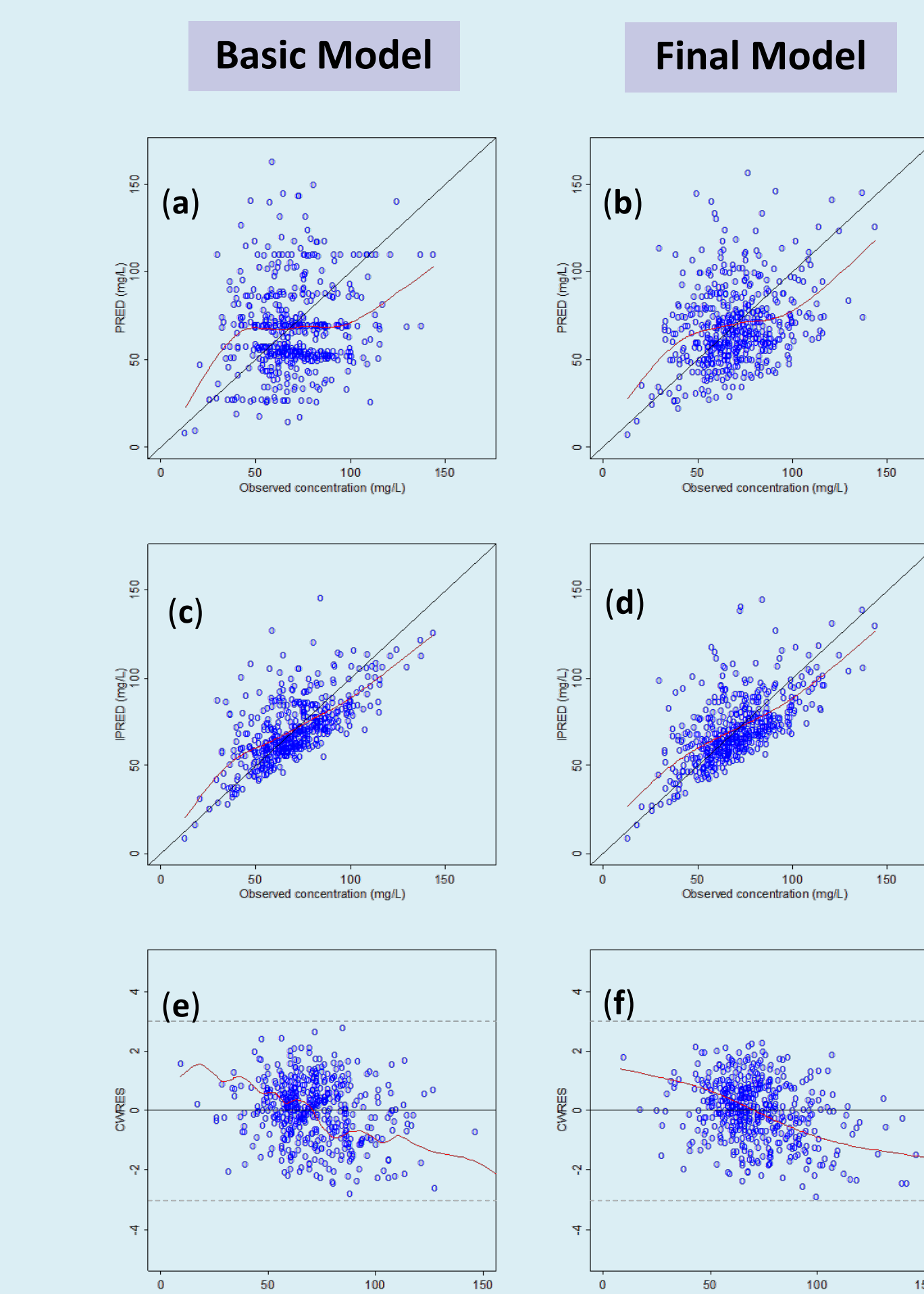


Figure 1. Goodness of Fit Plots.

a, b: Observed concentrations vs. Populational predicted concentrations (PRED).
c, d: Observed concentrations vs. Individual predicted concentrations (IPRED).
e, f: IPRED vs. Conditional weighted residuals (CWRES).
NOTE: Non significant shrinkage.

TABLE 3. The Final Parameter Estimates from NONMEM and the Bootstrap Analysis.

Parameter	NONMEM		Bootstrap Analysis	
	Estimate	RSE (%)	Mean	95 % CI
Ka (h ⁻¹)	4.1**	----	----	----
V/F (L/kg)	0.20**	----	----	----
CL (L/h)	0.568	2.0	0.569	0.550 – 0.588
TBW*	0.815	10.7	0.820	0.679 – 0.954
ω^2	0.0373	18.3	0.0372	0.026 – 0.049
σ^2	0.0576	10.3	0.0570	0.047 – 0.067

1000 Bootstrap runs. RSE (%), percentage of relative standard error. CI, confidence interval.

* Effect of the covariates on the CL of VLP. ** Fixed respectively [1-3].

FINAL MODEL:

$$CL/F_{VLP} \text{ (L/h)} = 0.57 \cdot (TBW/68)^{0.82}$$

$$\omega^2_{CL/F} = 0.037 \text{ (CV=18 \% ; shrinkage= 27 \%)}$$

$$\sigma^2 = 0.058 \text{ (CV=10 \% ; shrinkage= 16 \%)}$$

The standard estimation errors were ≤ 11 % for all parameters.

CONCLUSION

The TBW, the BSA and the LBW are anthropometric covariates that explain the biggest part of interindividual variability on CL/F_{VLP} . However, according to the characteristics of liposolubility of VLP the inclusion of TBW in the model is considered to be suitable; This variable also has the advantage of being more easily obtainable in clinical practice. The final model that includes the TBW on CL/F_{VLP} seems to be appropriate for clinical application in TDM. However, we consider it to be necessary to carry out an external validation of this model to verify its applicability, especially in overweight or obese patients.

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