Age Is a Statistically Significant Predictor of the Within Subject Variability in Dabigatran Pharmacokinetics

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Objective

To quantify the magnitude and to identify potential predictors of the observed within subject variability (WSV) of dabigatran in bioequivalence (BE) studies.

Methods

The WSV in the area under the curve from time 0 to infinity (AUC_{inf}) and the maximum concentration (C_{max}) of 17 replicated BE studies including a total of 815 healthy volunteers were analyzed in R using meta-analysis. In these studies each subject received repeated treatment of the reference product in two periods. Age, body weight, height, body mass index, sex, race, the number of subjects per study and region were evaluated as possible predictors of the observed WSV using meta-regression (MR). In case that the MR identifies a study-level predictor, a non-linear mixed effect (NLME) model was developed in NONMEM using individual data to assess whether or not the slope of the predictor was statistically different from 0. Moreover, the impact of extreme values in the computation of WSV was evaluated. Extreme values were defined herein as 3 times the interquartile distance of C_{max} and AUC_{inf} at individual level between periods.
WSV was computed as follows:

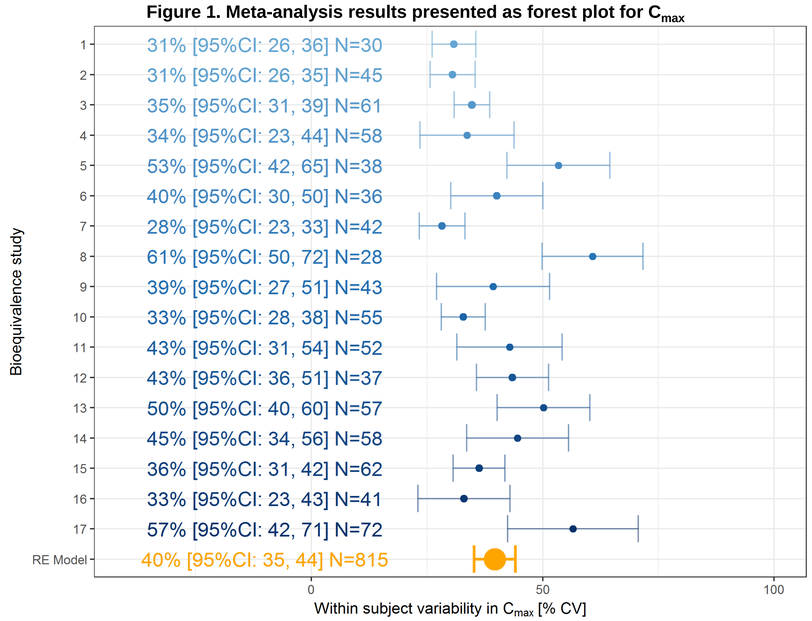
$$S^2_{WR} = \sum_{i=1}^{m}\sum_{j=1}^{n_i}\frac{\left(D_{ij}-\overline{D_i}\right)^2}{2(n-m)} \qquad \text{Equation 1}$$

where *i* is the number of *m* sequences used in the study, *j* is the number of n_i subjects in the i^{th} sequence, and D_{ij} is the individual difference between C_{max} or AUC_{inf} following repeated administration of the reference product for the i^{th} sequence and j^{th} subject.

Results

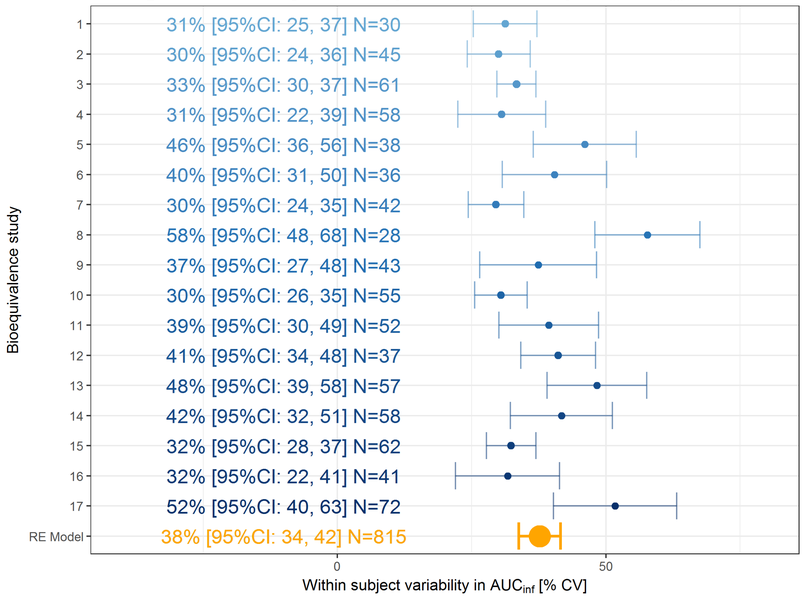
The WSV of C_{max} expressed as coefficient of variation was 40% (95%CI: 35%, 44%). Among the 17 studies, WSV ranged from 28% to 61%. The magnitude of the heterogeneity was quantified to be high (I^2-statistic = 85.0%; *Q*-statistic = 77.6; p < 0.001; df = 16).

Figure 1. Meta-analysis results presented as forest plot for C_{max}



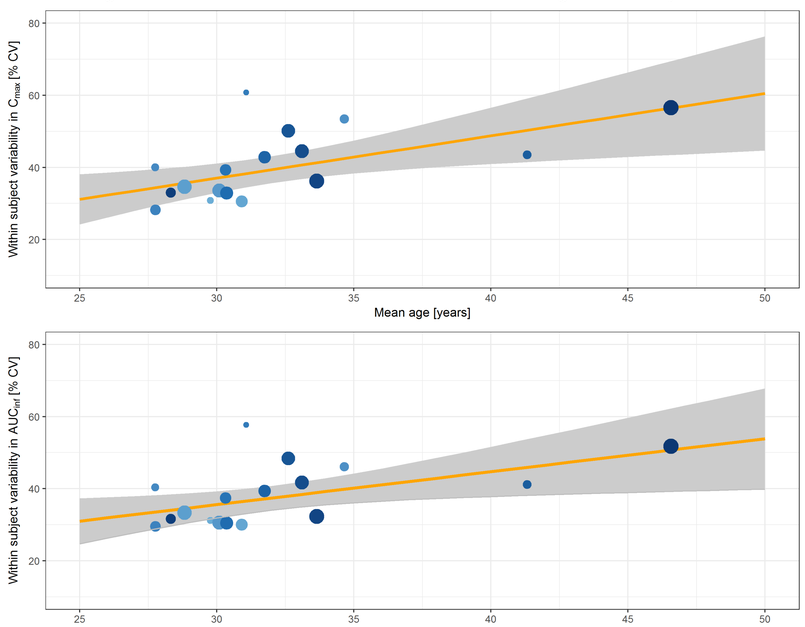
Regarding the AUC_{inf}, WSV was 38% (95%CI: 34%, 42%) ranging from 30% to 58%. The magnitude of the heterogeneity was quantified to be also high (I^2-statistic = 81.7%; *Q*-statistic = 67.2; p < 0.001; df = 16).

Figure 2. Meta-analysis results presented as forest plot for AUC_{inf}



For the range of mean ages of the evaluated studies (27.8 to 46.6 years), the mean age was found to be a statistically significant predictor of WSV for both C_{max} (p = 0.007) and AUC_{inf} (p = 0.018). The mean age explained a significant fraction of the total amount of heterogeneity for both C_{max} (p < 0.007; r^2 = 0.373) and AUC_{inf} (p = 0.018; r^2 = 0.307).

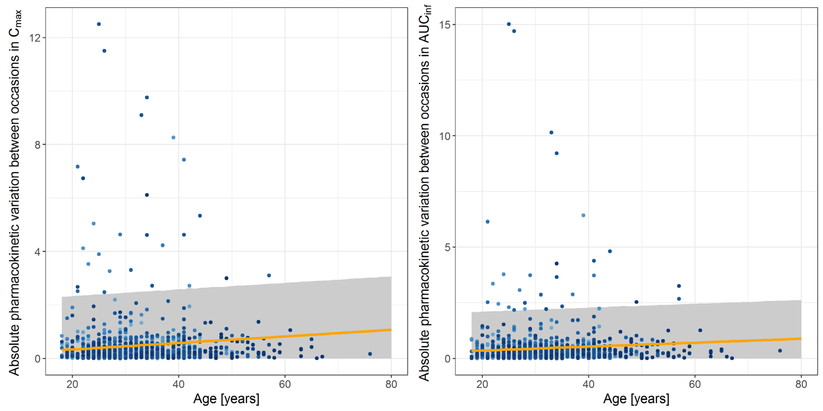
Figure 3. Association between the WSV and the mean age of the subjects



Body weight, height, body mass index, sex, race, the number of subjects per BE study and region were not found to be predictors of the WSV (p>0.05).

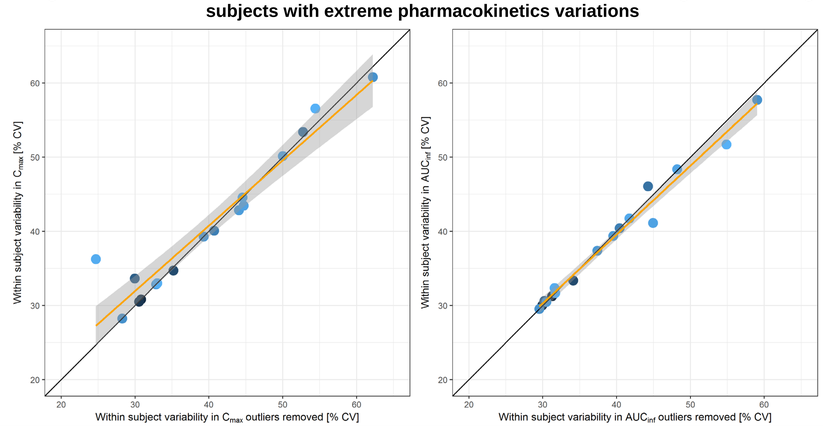
The NLME model developed confirmed that the slope of the relationship between WSV and mean age was statistically significant different from 0 supporting the MR finding. For C_{max} and AUC_{inf}, the slopes were estimated to be 0.012 (95%CI: 0.007; 0.017) and 0.009 (95%CI: 0.003; 0.014), respectively.

Figure 4. Association between the within subject pharmacokinetic variation and the mean age



PK changes between periods in C_{max} and AUC_{inf} higher than 53.3% and 51.2% were considered extreme. A total of 53 (6.5%) and 58 subjects (7.1%) were removed to compute WSV. For C_{max}, Pearson's statistic was computed to be (r = 0.959; p < 0.001). The 95%CI ranged from 0.886 to 0.985. For AUC_{inf}, Pearson's statistic (95%CI) was computed to be 0.991 (0.973; 0.997). Overall, these results suggests small impact of the subjects with extreme PK variations in the computation of the WSV.

Figure 5. Correlation between dabigatran's within subject variability including and excluding subjects with extreme pharmacokinetics variations



Conclusions

Large heterogeneity was observed across studies. Age was found to be a statistically significant predictor of the observed WSV of dabigatran. Sponsors may expect larger WSV with an increase in the mean age of the recruited subjects. Of note, significant heterogeneity on the WSV of dabigatran's PK parameters remains after adjusting the effect of age. This analysis indicates that the design of BE studies for highly variable drugs has significant uncertainty in the expected value of the WSV even in cases where large amount of data are available.

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