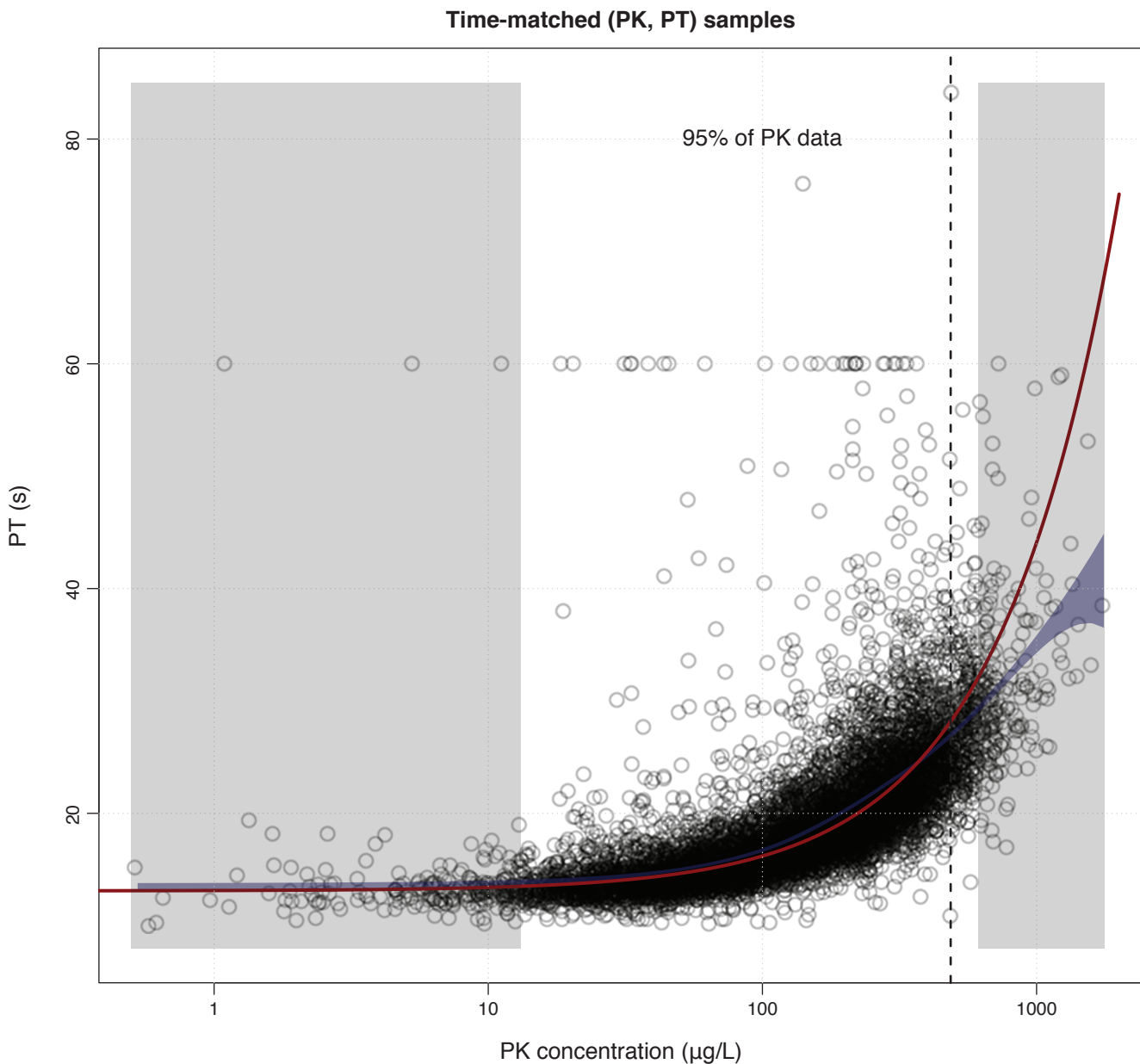


Figure S2 Time-matched PK, PT samples from the PK–PT dataset^a. The blue shaded area represents the 95% confidence band of the LOESS regression. The red line represents the estimated linear relationship. The grey shaded area represents the area where the lower and upper 2.5% of data are located. The vertical dashed line shows the upper 99th percentile of observed concentrations for patients receiving 20 mg rivaroxaban.



PK, pharmacokinetic, PT, prothrombin time.

^aThe PK/PT relationship was assessed using the population PK–PT dataset. Inspection of time-matched PK, PT samples revealed a strong association between PK and PT, where PT increases with increasing PK concentration. The relationship seems to follow a direct linear correlation with a saturation of the PK/PT effect only at the highest observed rivaroxaban plasma concentrations. Hence, a linear model was assumed to be appropriate.

The model is given by

$$PT(t) = (PT_0 + PT_1 \text{Conc}(t)) \cdot (1 + \varepsilon),$$

with $PT_0 = \theta_0 \exp(\eta_0)$ and $PT_1 = \theta_1 \exp(\eta_1)$, where $\text{Conc}(t)$ is the predicted rivaroxaban plasma concentration using the final population PK model; θ_0 and θ_1 represent the typical baseline and slope parameter of the linear relationship, respectively; η_0 and η_1 represent the associated inter-individual variability terms assumed to be normally distributed (with mean 0); and ε represents the proportional residual error term, assumed to be normally distributed (with mean 0). No covariate analysis on the PK/PT relationship was conducted. PT baseline and slope were estimated (RSE% in brackets) as 13.1 s (0.27%) and 0.031 s/µg/L (1.11%), with IIV of CV% 7.76 (13%) and CV% 38.2 (9.5%), respectively, and a residual unexplained error of CV% 11.4 (12.8%). Due to the small IIV at baseline – actually smaller than the estimated residual unexplained variability for the PT data, the individual baseline values in the Phase 3 studies were also not used to enhance the PT-adjusted exposure.