# Population pharmacokinetic analysis of concentration data after implantation of sirolimus-eluting Bx Velocity stent in patients


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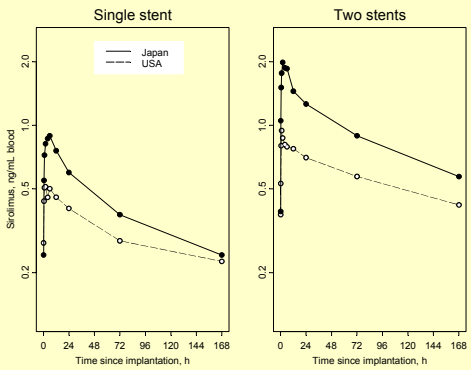
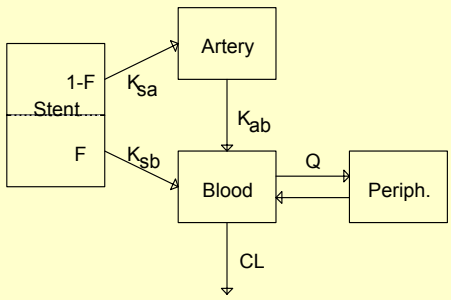
**Objectives:** The Bx Velocity, sirolimus-eluting balloon-expandable stent has shown remarkable results in terms of reducing the occurrence of in-stent restenosis following coronary intervention. The current work was aimed to elucidate the sirolimus (SL) pharmacokinetics in patients with de novo coronary artery lesions.

**Data:** Two PK trials were conducted in the US (19 patients) and in Japan (20 patients). After implantation of one or two stents (149.4 - 177.7 μg SL/stent), blood samples were collected serially and assayed for SL using a validated liquid chromatography method.



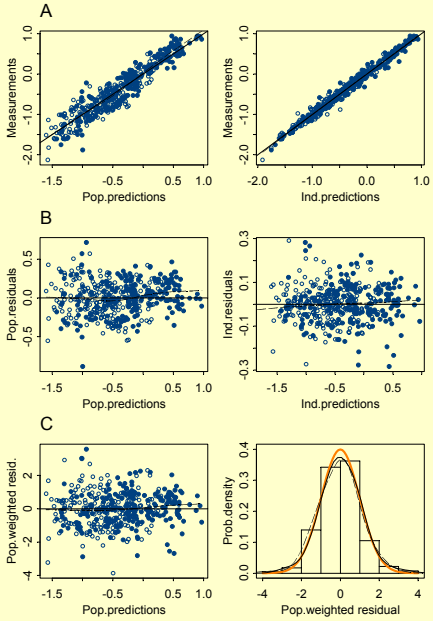

**Methods:** NONMEM V software and the first-order conditional estimation method was used to fit mixed-effects models to concentration-time data. The transform-both-side approach was applied, and concentrations were converted into natural logarithms. The constant-variance residual error model was used, and the log-normal distribution was assumed for all individual PK parameters except fractions that were supposed to follow the normal distribution in the logit domain.

**Model:** The structural model was based on previous animal data and mechanistic considerations. It assumed two-compartment (CMT) linear disposition of SL and included also the stent CMT and the artery tissue CMT. The fraction F of the total drug amount is released from the stent CMT to the blood stream. The rate is controlled by the rate constant $K_{sa}$. The rest of the drug (1-F) is released to the artery tissue with the rate constant $K_{sa}$. From the artery the drug is transferred to blood ($K_{ab}$). Other parameters are listed below:
CL: Total blood clearance
Vc: Volume of the central CMT
Vp: Volume of the peripheral CMT
Q: Inter-CMT exchange flow




**Results:** In a typical patient of 77 kg body weight, CL was 1.3 L/h (5.3) and Q 0.67 L/h (20), both increased with body weight. In parentheses standard errors of estimates (% CV) are given. $K_{sa}$ differed between studies: it was 0.0039 $h^{-1}$ (12) and 0.0064 $h^{-1}$ (8) in the US and Japan studies, respectively. The remaining parameters did not depend on patient characteristics: Vc was 0.22 (20), Vp 59 L (27), F 0.091 (18), $K_{ab}$ 0.051 $h^{-1}$ (11), and $K_{ab}$ 1.8 $h^{-1}$ (15), respectively. Thus the observed difference in concentration-time profiles is related to a formulation factor rather than to the inter-ethnic diversity. Due to the limited number of patients in the trial random inter-individual variability could be estimated in CL (18%), Vc (49%), Vp (86%), and Q (34%) only. $T_{1/2}$ was assessed via simulation using individual Bayesian parameter estimates. It was found to be substantially longer (210 and 150 h in the US and Japan studies, respectively) than after oral SL administration (62 to 82 h, literature data). No data after extravascular administration that would allow $T_{1/2}$ estimation are available in the literature.

**Goodness-of-fit:** The model provided a good fit to the data as confirmed by the plot of measurements and (population and individual) predictions. Note: units are logarithmic. Neither population nor individual residuals show any specific pattern (open and closed circles correspond to the US and Japanese data, respectively). The distribution of weighted population residuals does not deviate much from normality (lower right panel: yellow bold line shows the density curve of the standard normal distribution).




**Conclusion:** SL-eluting stent releases more than 90% of the drug directly to the artery tissue, and $T_{1/2}$ is controlled primarily by the release rate. Simulated SL amounts in various compartments following stent implantation are shown below. Parameter values of typical US (black lines) and Japanese (yellow lines) patients were used. The stent and peripheral compartment amounts are adjusted to fit the range (divided by 200 and 20, respectively). As predicted by the model, at 168 h since implantation (the last sampling time), approx. 50% of SL still persists in the artery., yellow lines correspond to Japanese data. Thus the pharmacokinetic findings are in accordance with clinical efficacy data demonstrating-long term restenosis prevention.