Title: **Pharmacokinetic-Pharmacodynamic Model of Unfractionated Heparin and aPTT From Real-World Adult Clinical Data.** ***Authors:*** Brooks, J (1) Hughes, J (1), Faldasz, J (1), Bamberg, K (2), Constable, J (2), Keizer, RJ (1). ***Affiliations:*** (1) InsightRx, (2) Northern Arizona Healthcare

Background: The use of unfractionated heparin (UFH) continuous IV infusion for anticoagulation using routine therapeutic drug monitoring with activated partial thrombosplastin clotting time (aPTT) is common within hospital settings. UFH is eliminated via multiple pathways including a saturable pathway and a slower, unsaturable pathway thought to be driven by renal function. There are currently no published clinically usable, population PKPD models available for adults to predict aPTT. In this study, we aim to develop a population PKPD model utilizing real-world, adult intravenous UFH and aPTT data collected from patients within a hospital setting.

Methods: Real-world adult patient clinical data from Northern Arizona Healthcare was provided including UFH dosing rates and aPTT measurements. Goodness of Fit (GOF) plots, individual prediction plots, and a visual predictive check (VPC) were used to assess the developed model. Model predictive error was assessed using the Perl-speaks-Nonmem tool *proseval* to calculate mean percentage error (MPE - %) and normalized root-mean square error (nRMSE - %).

Results: A total of 100 patients with 937 aPTT measurements were included in the model building dataset. aPTT was modeled as a direct effect linked to a core 1-compartment PK model, including baseline. Several covariates improved the model fit including approximated fat-free mass (dOFV: -44.5254, $p<0.01$), eGFR as approximated by the Cockcroft-Gault (CG) method using fat-free mass (dOFV: -8.64, $p<0.01$), and a decreasing relationship between UFH dosing rates and aPTT effect over time (dOFV: -15.6850, $p<0.01$). Several other effects including a nonlinear elimination pathway, disease-state effect on UFH-aPTT relationship, and an indirect PK-PD relationship were explored but did not improve the model. VPC and GOF plots suggest a well-fitting model. Model predictive performance with MPE of -4.8% (95% CI: -7.3 — -2.7%) and nRMSE of 35.9% (95% CI: 33.4 - 38.4%).

Conclusions: A robust population PKPD model for predicting aPTT in adults receiving UFH was developed. Predictions were significantly enhanced by incorporating covariates including fat-free mass, eGFR, and time on UFH. Predictive accuracy suggests a clinically useful advancement in personalized UFH dosing.

Key Words: Heparin, PK-PD, Model-Informed Precision Dosing