

# Application of a PBPK Model of Rivaroxaban to Prospective Simulations of Drug-Drug-Disease Interactions with Protein Kinase Inhibitors in CA-VTE

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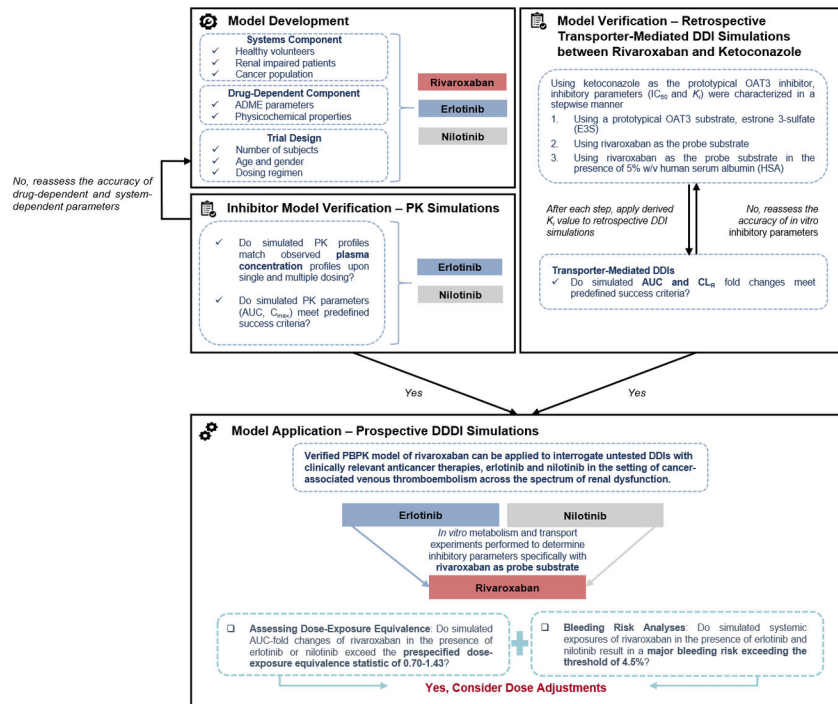
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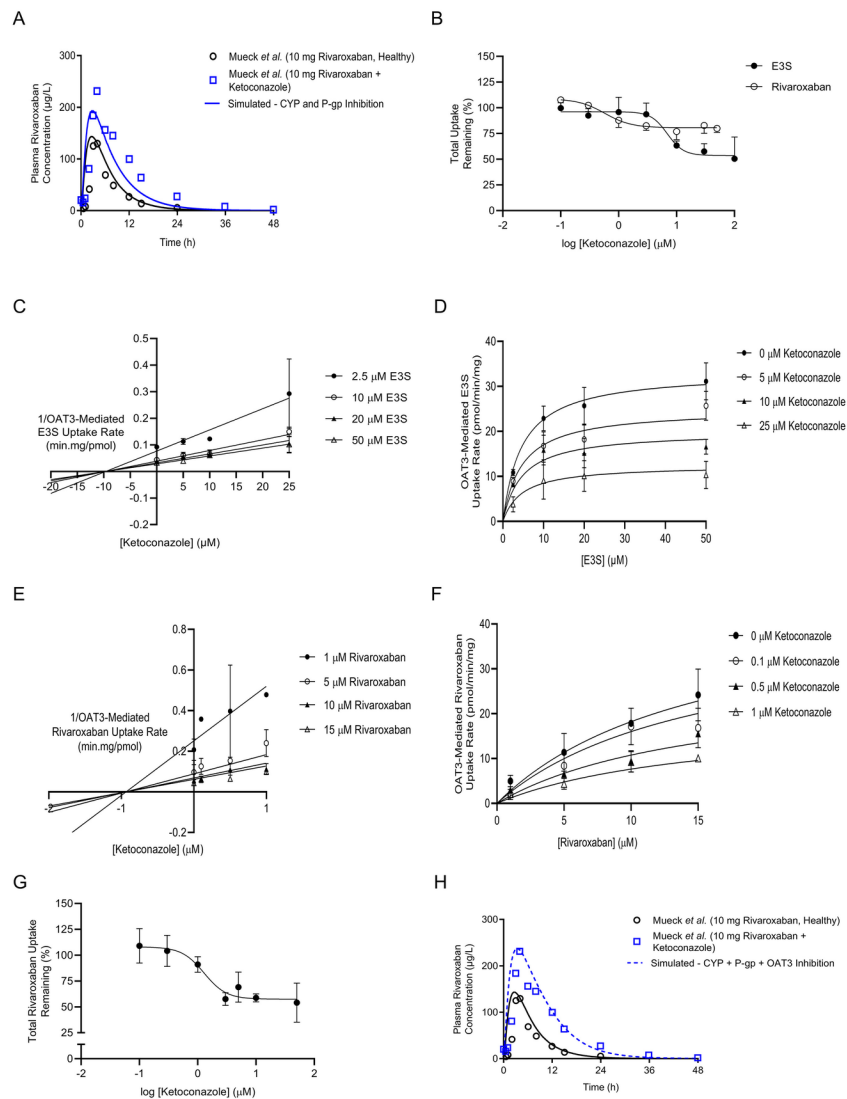
## Abstract

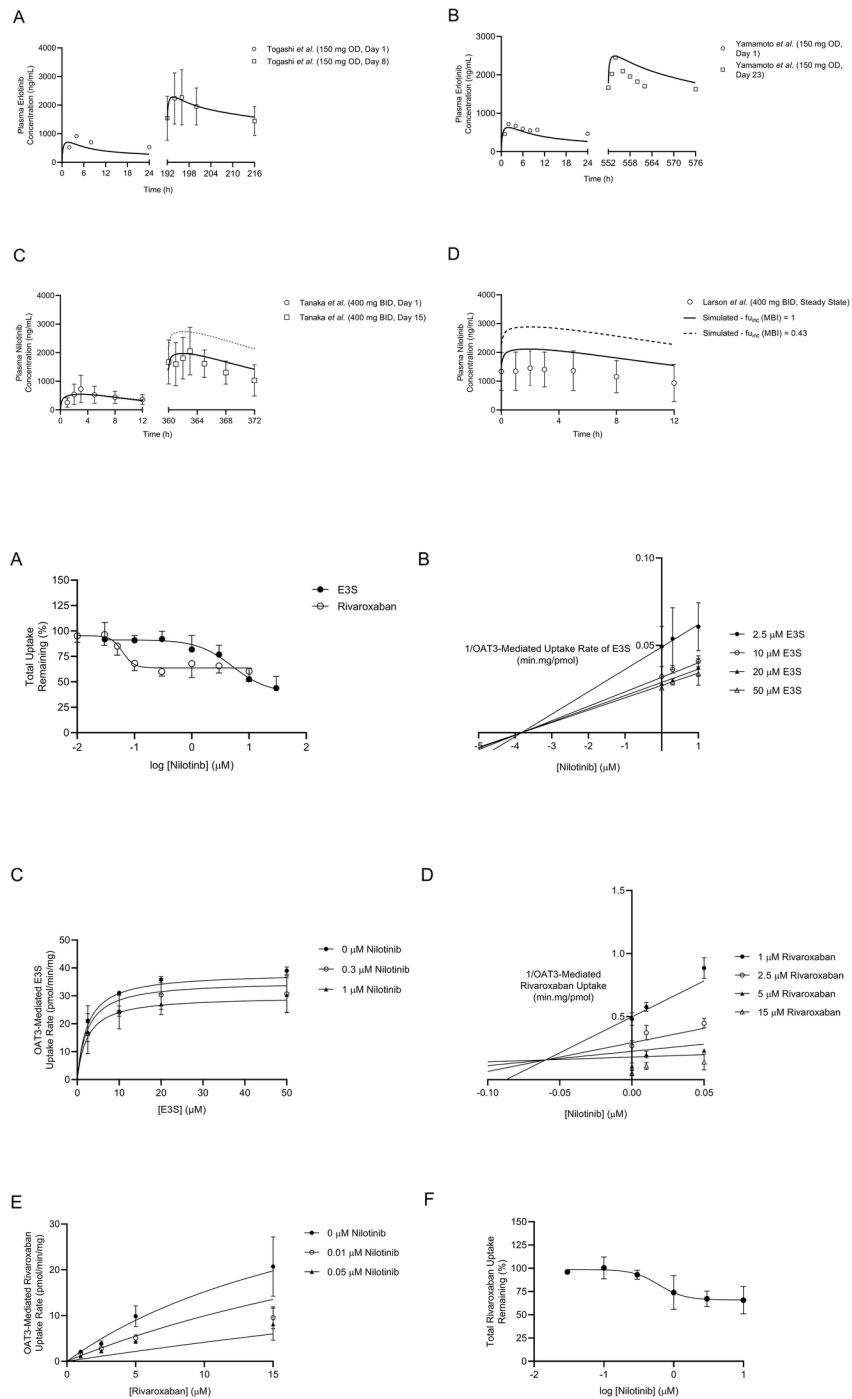
**Background and Purpose** Rivaroxaban is emerging as a viable anticoagulant for the pharmacological management of cancer associated venous thromboembolism (CA-VTE). Being eliminated via CYP3A4/2J2-mediated metabolism and organic anion transporter 3 (OAT3)/P-glycoprotein-mediated renal secretion, rivaroxaban is susceptible to drug-drug interactions (DDIs) with protein kinase inhibitors (PKIs), erlotinib and nilotinib. Physiologically based pharmacokinetic (PBPK) modelling was applied to interrogate the DDIs for dose adjustment of rivaroxaban in CA-VTE. **Experimental Approach** The inhibitory potencies of erlotinib and nilotinib on CYP3A4/2J2-mediated metabolism of rivaroxaban were characterized. Using prototypical OAT3 inhibitor ketoconazole, *in vitro* OAT3 inhibition assays were optimized to ascertain the *in vivo* relevance of derived inhibitory constants ( $K_i$ ). DDIs between rivaroxaban and erlotinib or nilotinib were investigated using iteratively verified PBPK model. **Key Results** Mechanism-based inactivation (MBI) of CYP3A4-mediated rivaroxaban metabolism by both PKIs and MBI of CYP2J2 by erlotinib were established. The importance of substrate specificity and nonspecific binding to derive OAT3-inhibitory  $K_i$  values of ketoconazole and nilotinib for the accurate prediction of DDIs was illustrated. When simulated rivaroxaban exposure variations with concomitant erlotinib and nilotinib therapy were evaluated using published dose-exposure equivalence metrics and bleeding risk analyses, dose reductions from 20 mg to 15 mg and 10 mg in normal and mild renal dysfunction, respectively, were warranted. **Conclusion and Implications** We established the PBPK-DDI platform to prospectively interrogate and manage clinically relevant interactions between rivaroxaban and PKIs in patients with underlying renal impairment. Rational dose adjustments were proposed, attesting to the capacity of PBPK modelling in facilitating precision medicine.

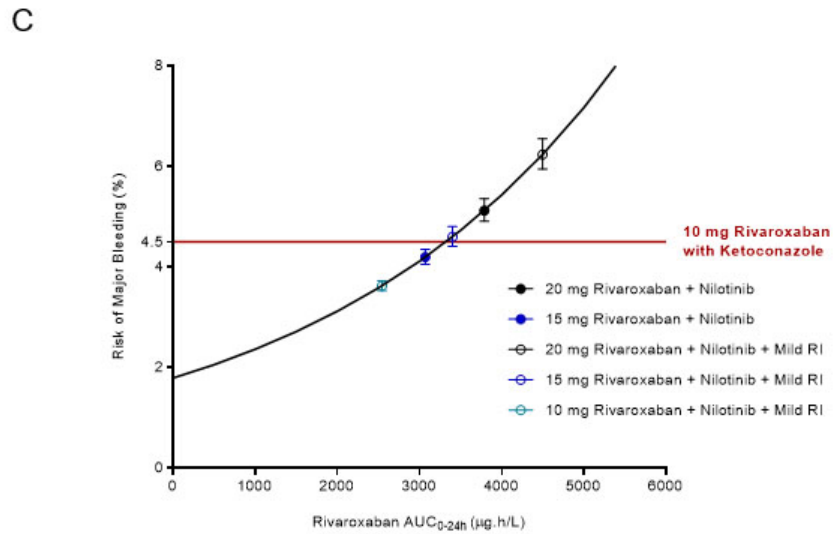
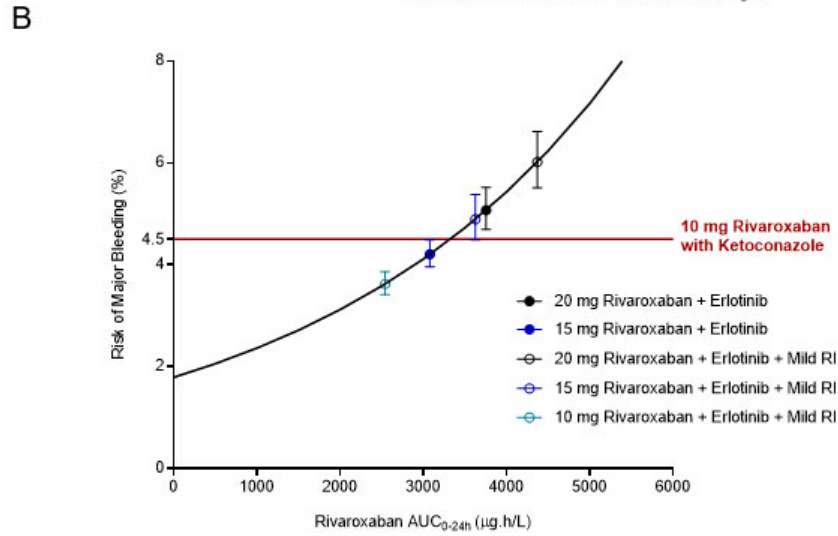
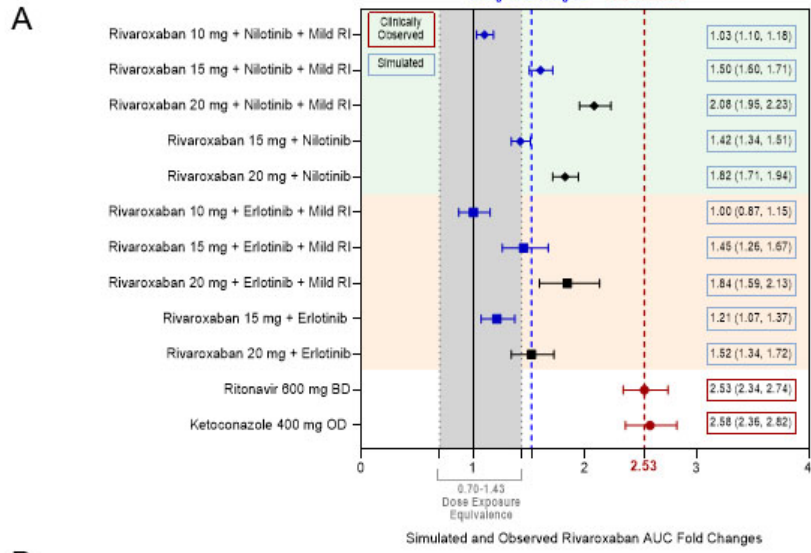
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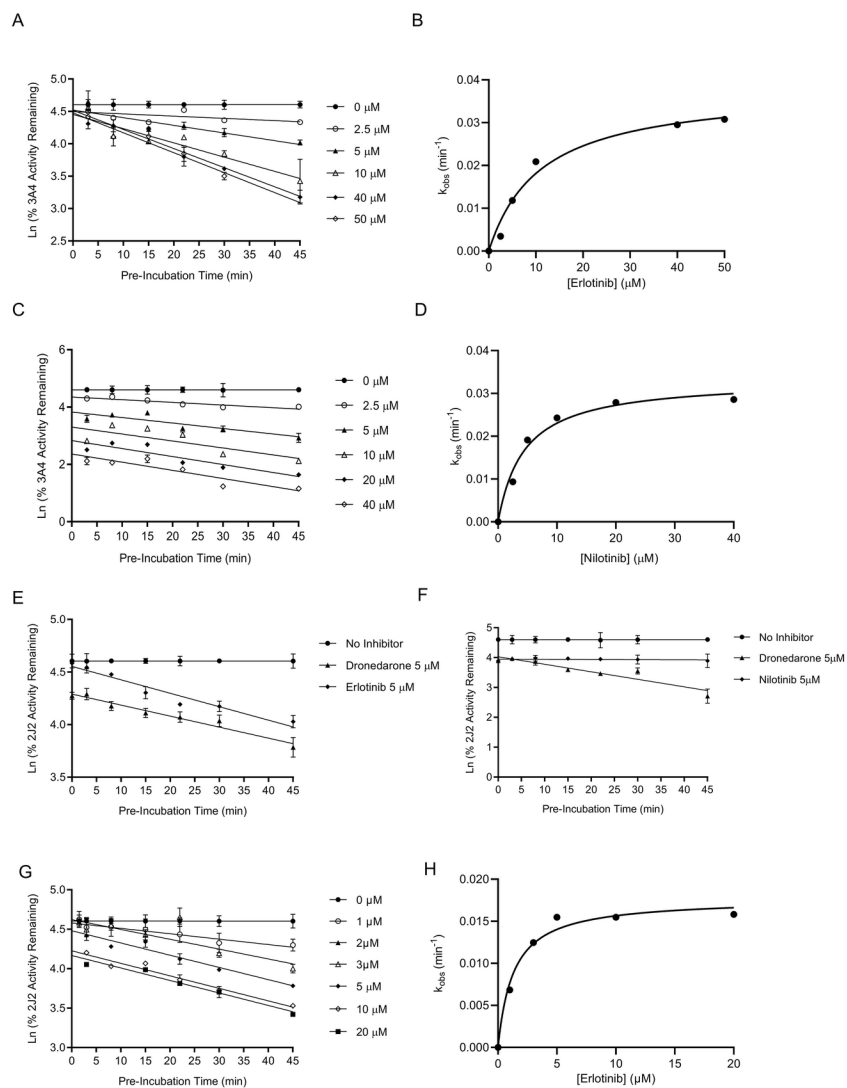


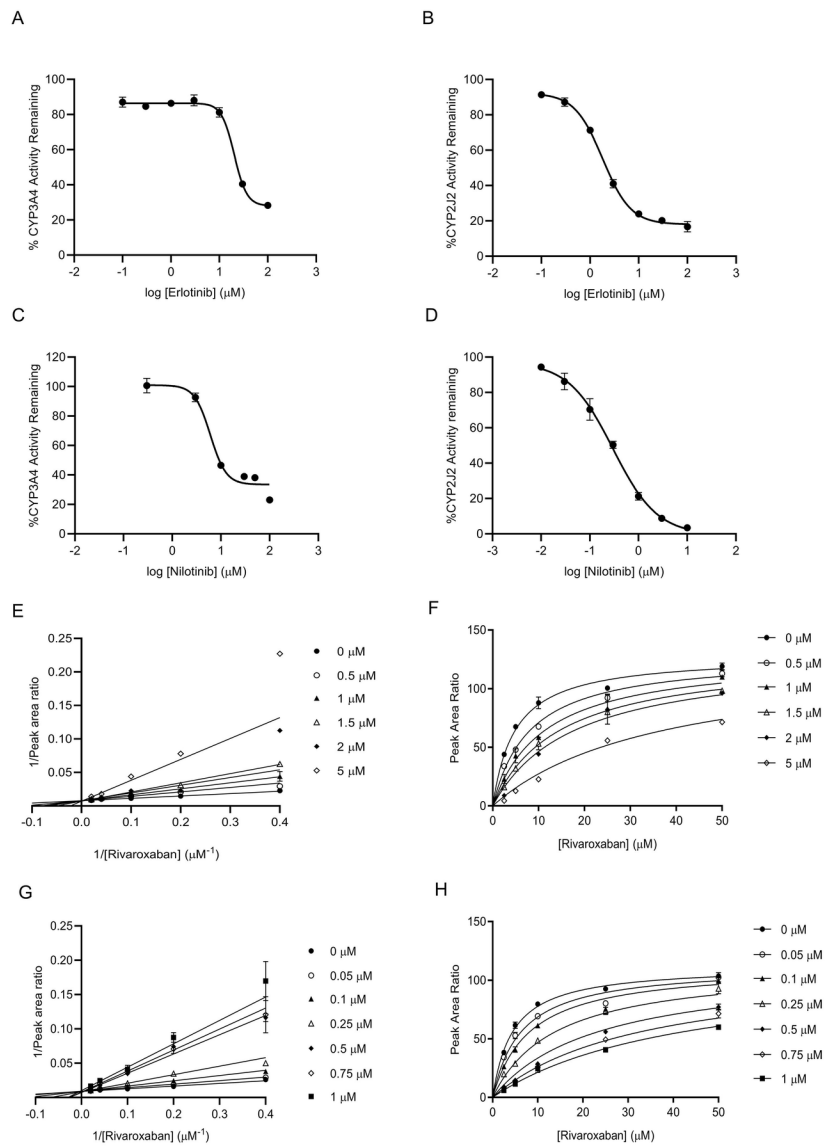
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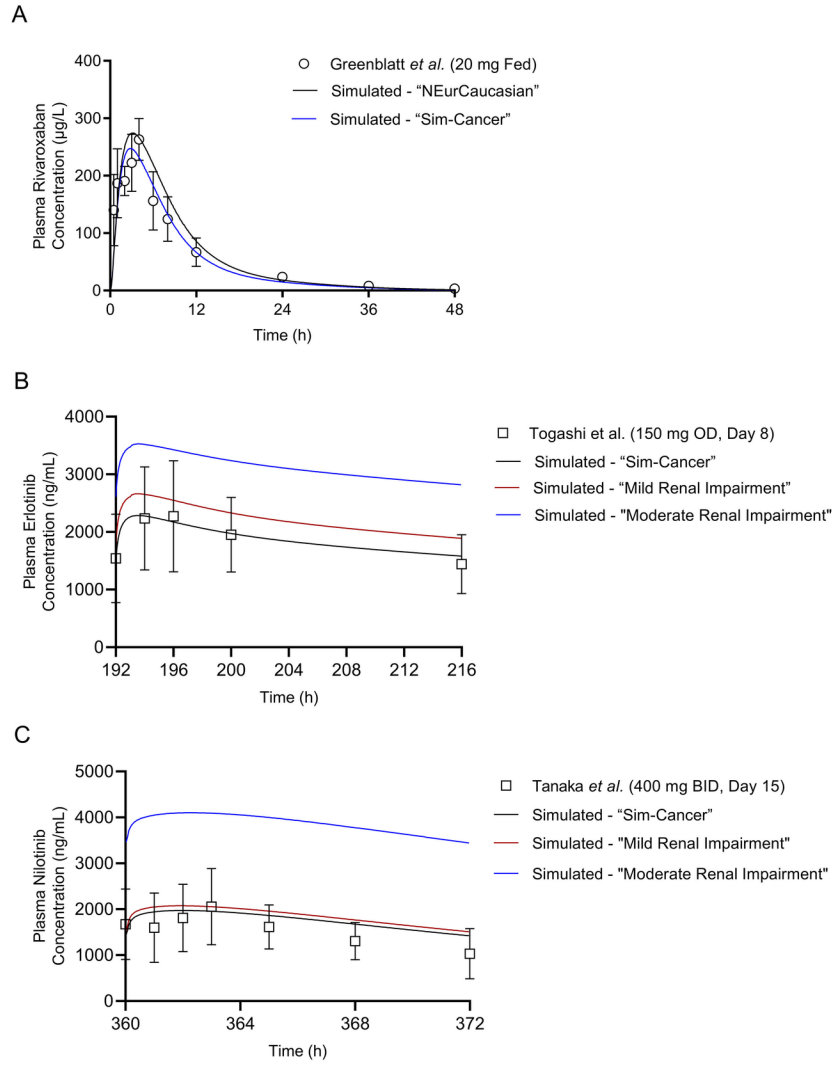
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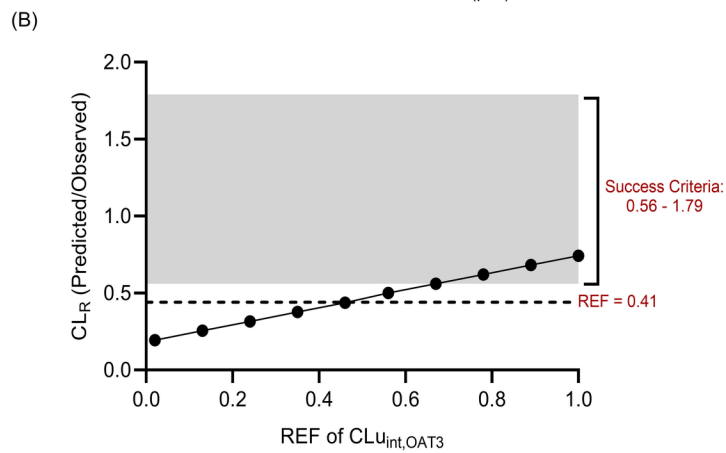
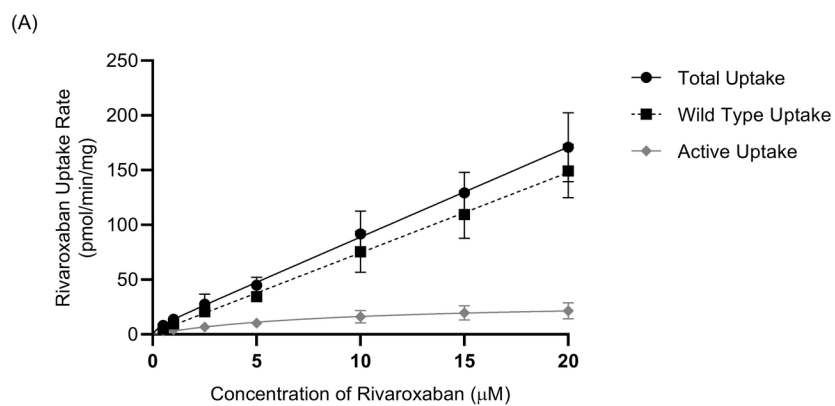
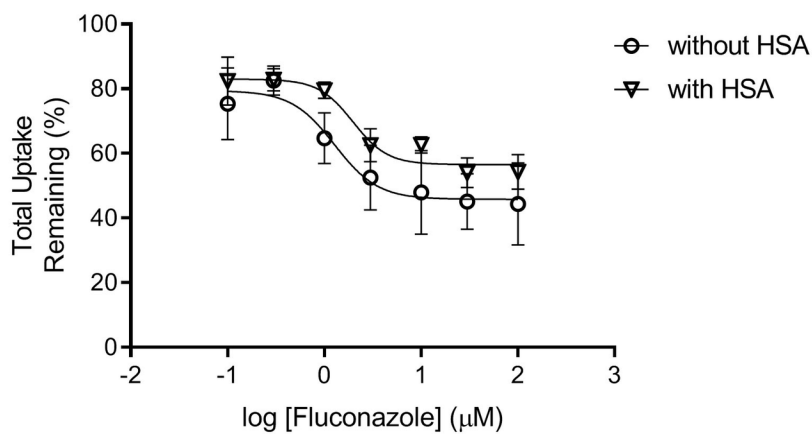
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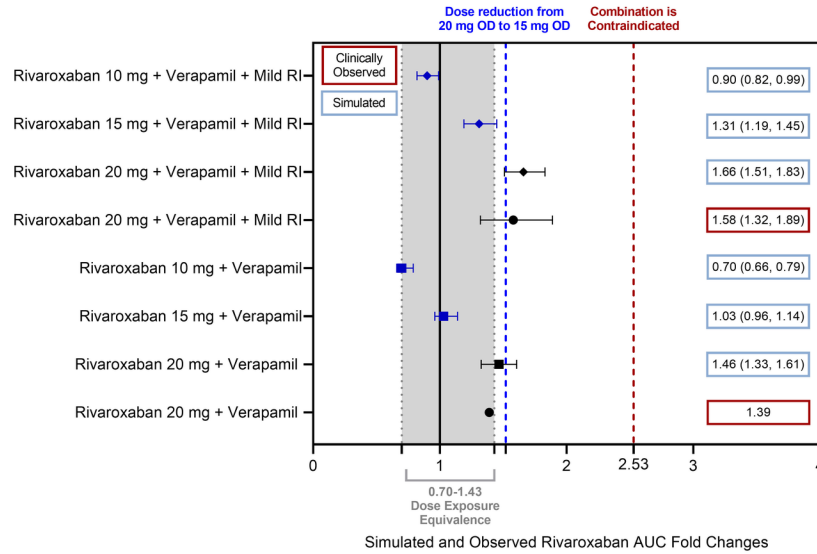












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