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Simcyp

Assessing the role of local heart tissue concentration in bottom-up mechanistic prediction of QT prolongation by moxifloxacin using PBPK-QSTS modeling

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Objectives

1. Bottom up prediction of QT prolongation and TdP risk for moxifloxacin (MOXI)
2. Estimate the relevant exposure in bio-phase
3. Translate *in vitro* hERG IC_{50} to clinical ECG level with QSTS model
4. To study the impact of uncertainty/lab-to-lab variability in *in vitro* hERG IC_{50} value on model outcome
5. To verify the model performance to simulate the torsade de pointes (TdP) event

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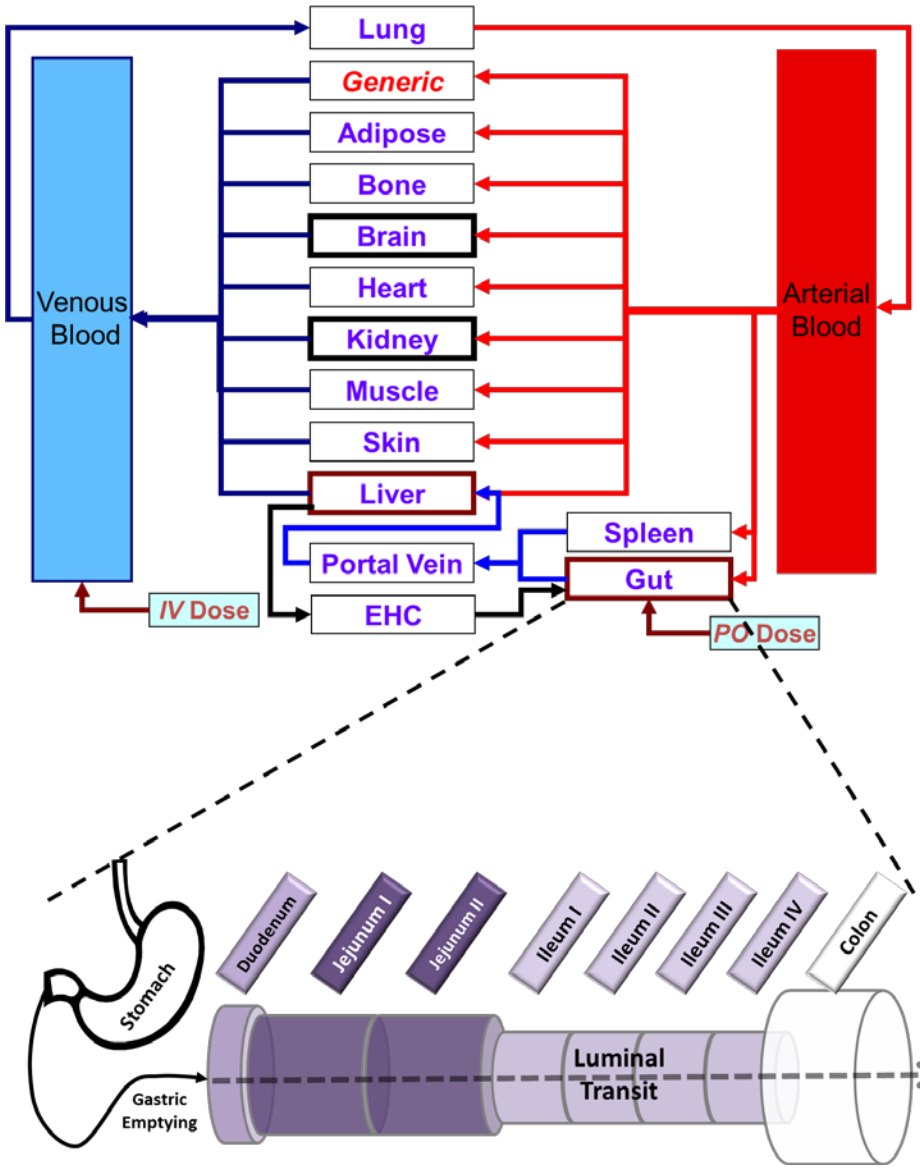
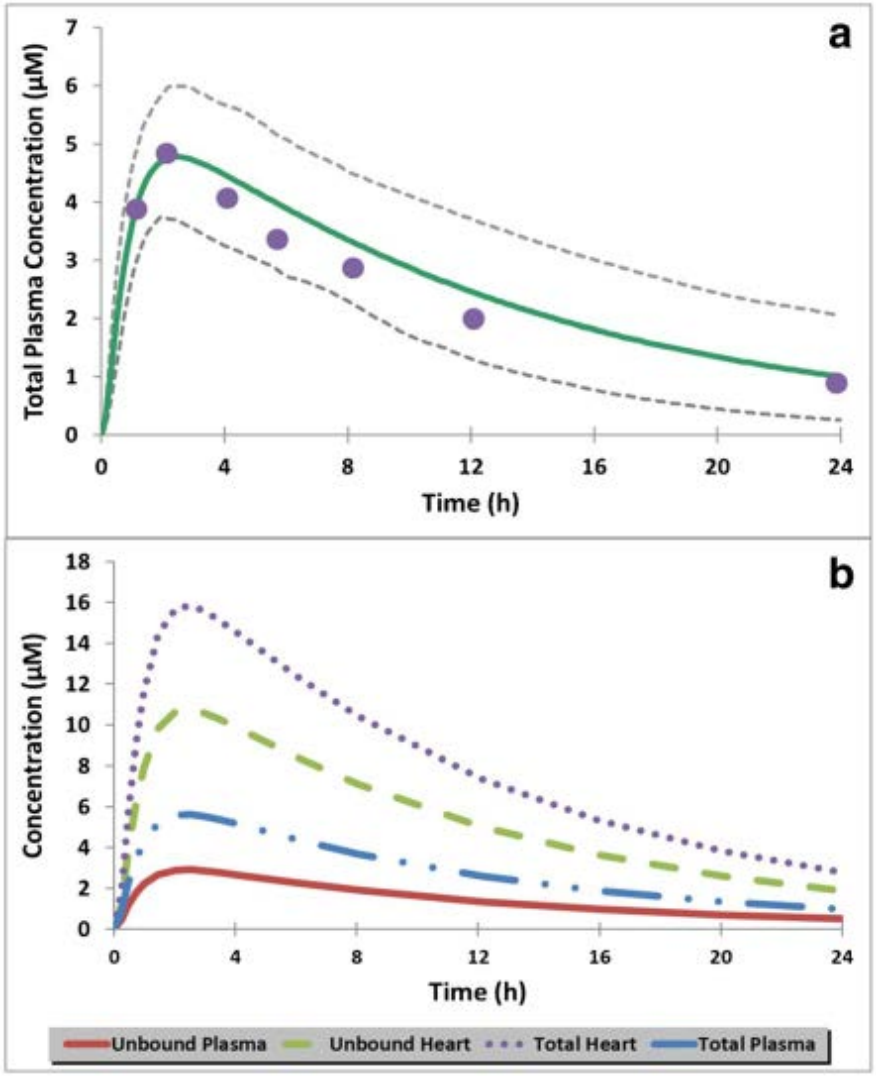
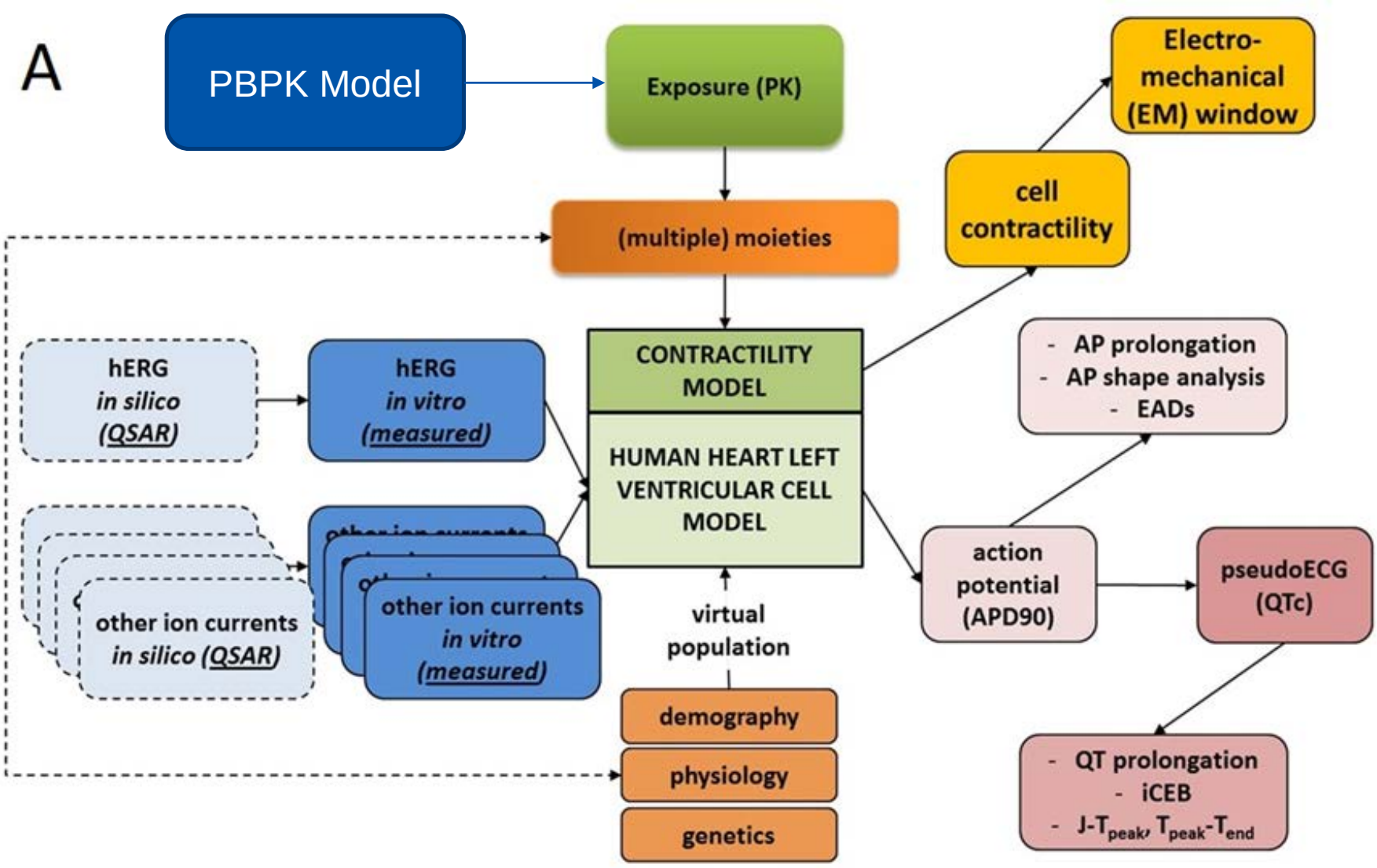
PBPK Model including Mechanistic Absorption model

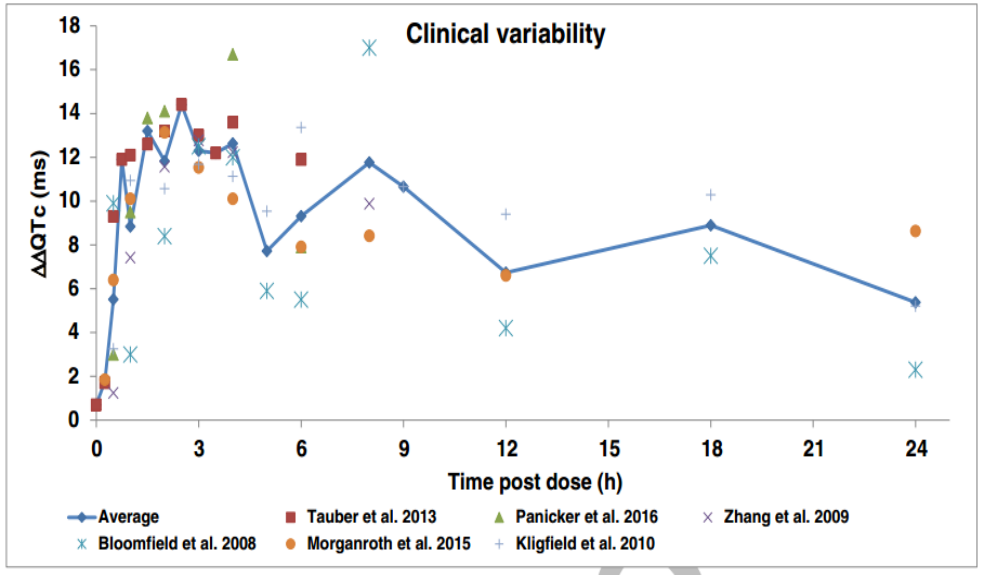




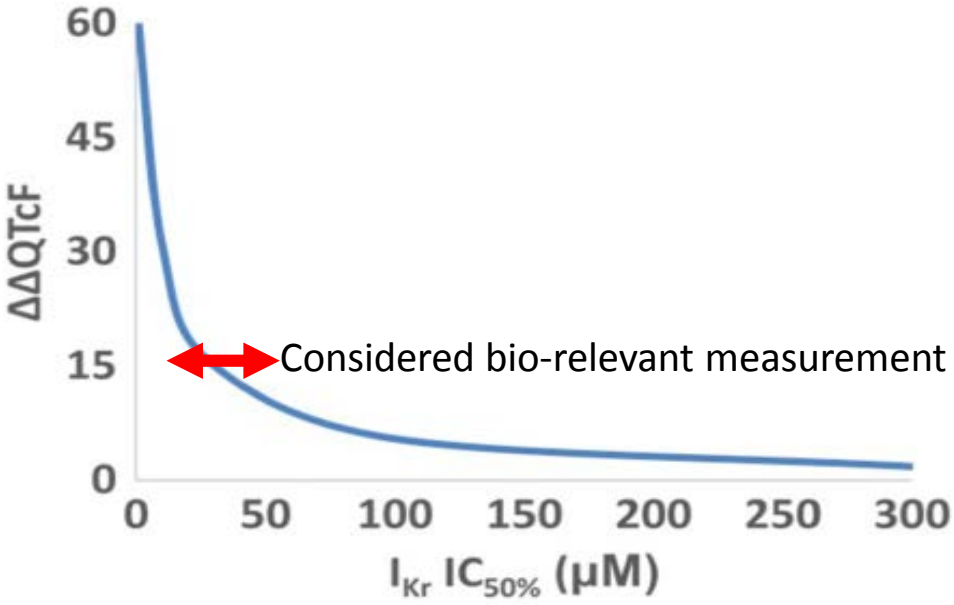
PBPK-QSTS Approach for QT prolongation/TdP risk assessment



What is reference point?



Variability in reported QT prolongation after 400mg Moxifloxacin oral dose

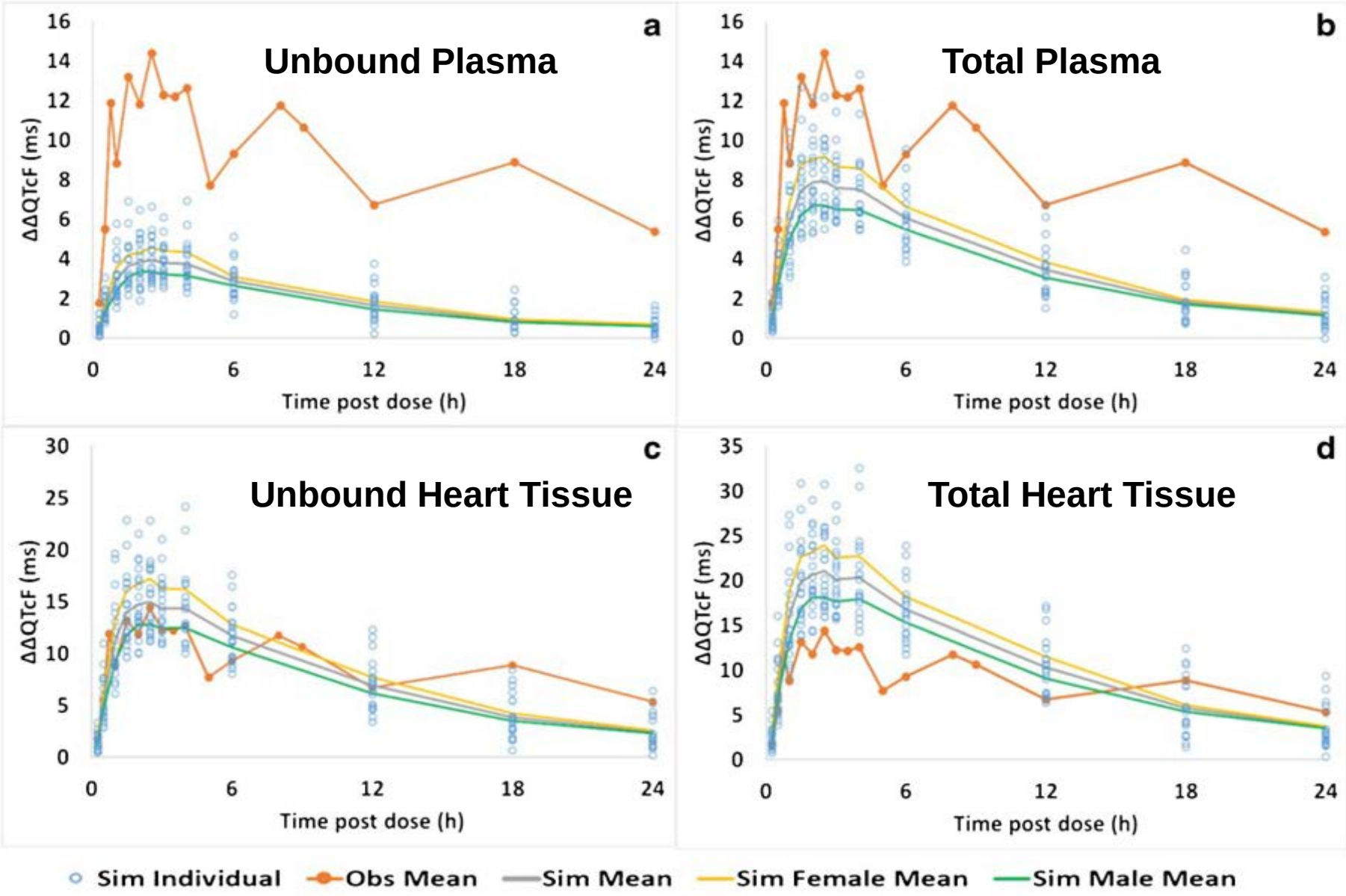


Impact on in vitro hERG IC50 on model outcomes

Uncertainty/variability in in vitro input could affect interpretation

Strong need to standardise or select a common reference *in vitro* protocol to move forward

Predicted QT prolongation with various bio-phase inputs



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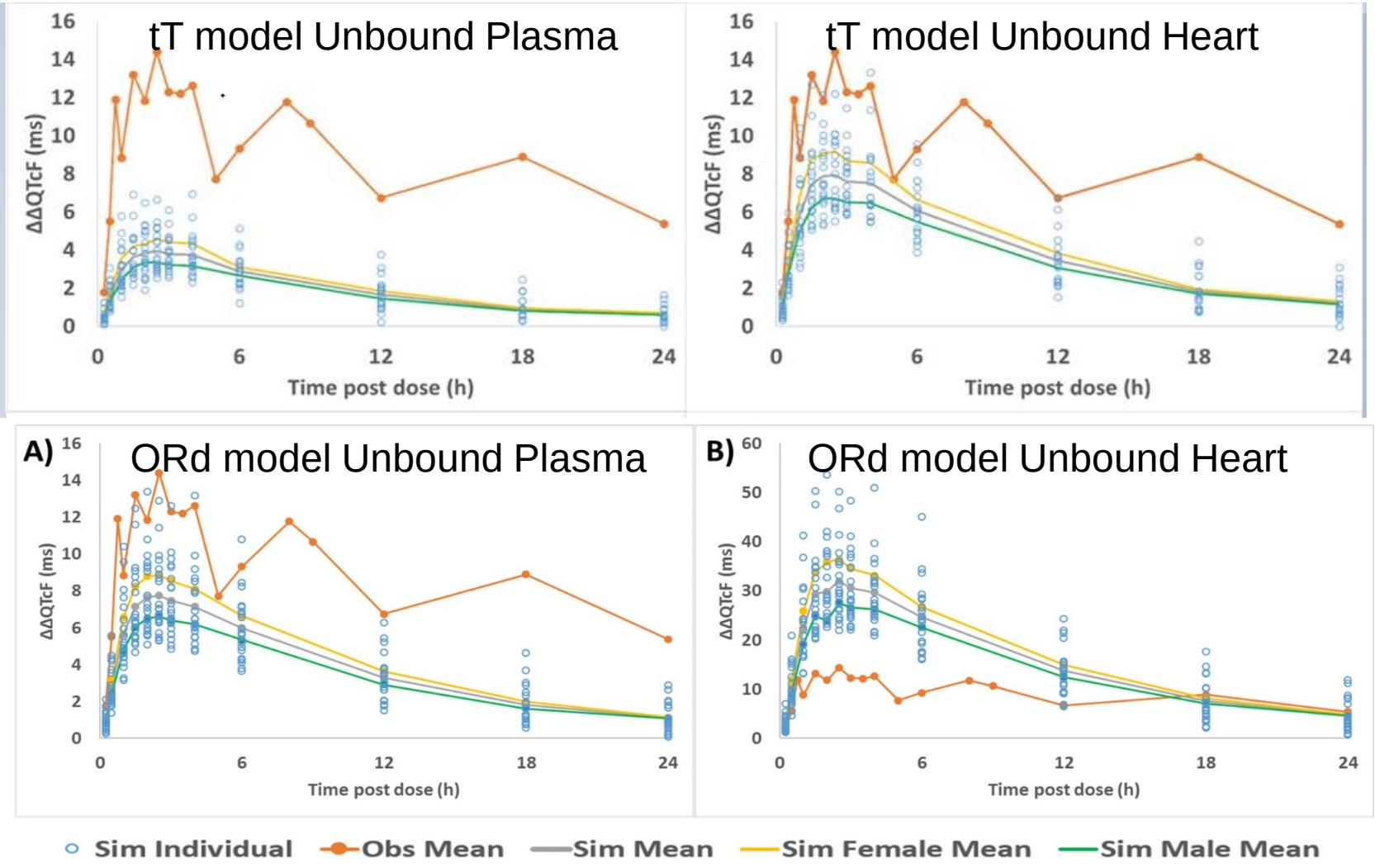
Impact of QST model selection



- ten Tusscher 2006 model shows unbound heart tissue exposure as bio-relevant
- O'hara-Rudy 2011 model shows total plasma exposure as bio-relevant

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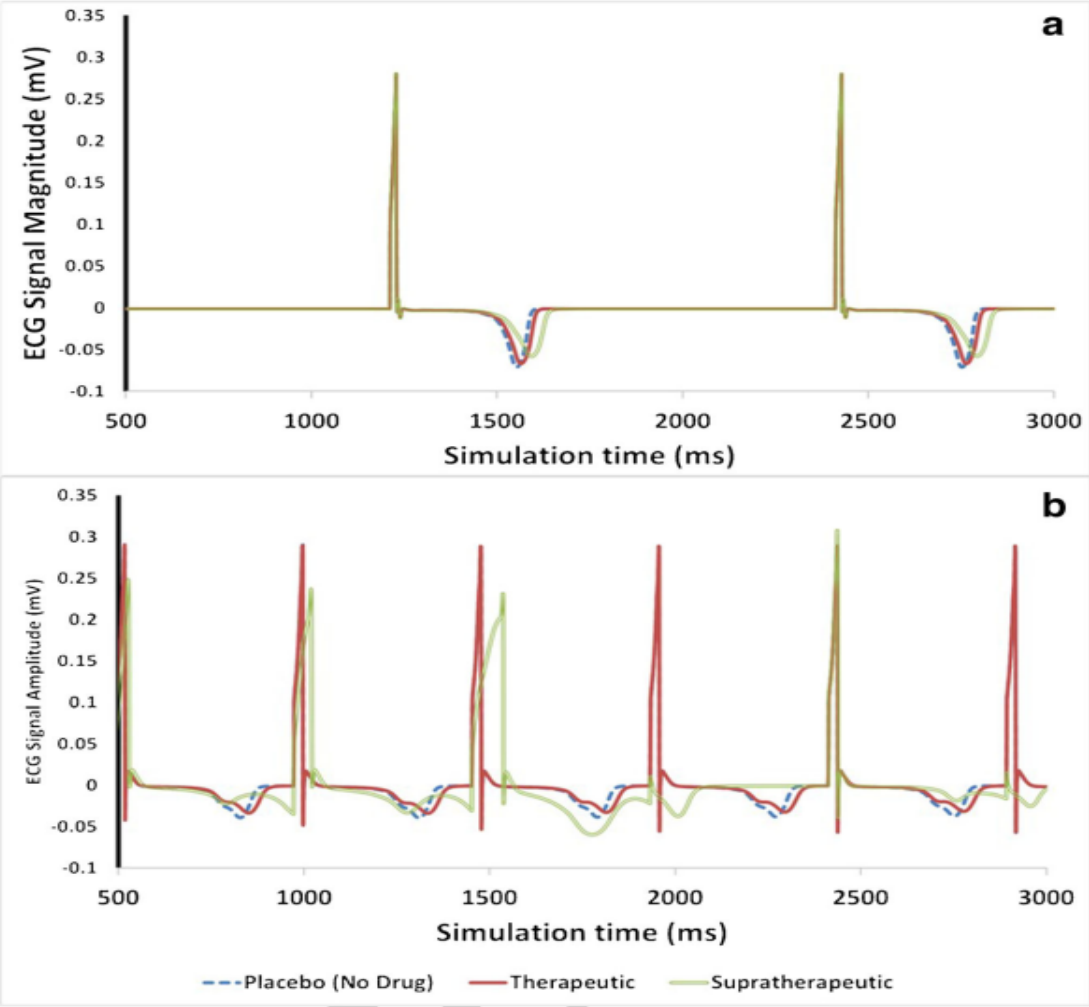
TdP is multi-factorial event



Simulated pseudoECG traces after therapeutic (red thick line), supra-therapeutic (double green continuous line) exposure of MOXI to

(A) healthy physiology

AND

(B) with tachycardia and hypokalaemia

FAERS database mining indicates almost all TdP cases where MOXI was involved were multi-factorial and TdP occurred when combined with other risk factors e.g. hypokalemia and abnormal heart rate.

Towards Bridging Translational Gap in Cardiotoxicity Prediction: an Application of Progressive Cardiac Risk Assessment Strategy in TdP Risk Assessment of Moxifloxacin

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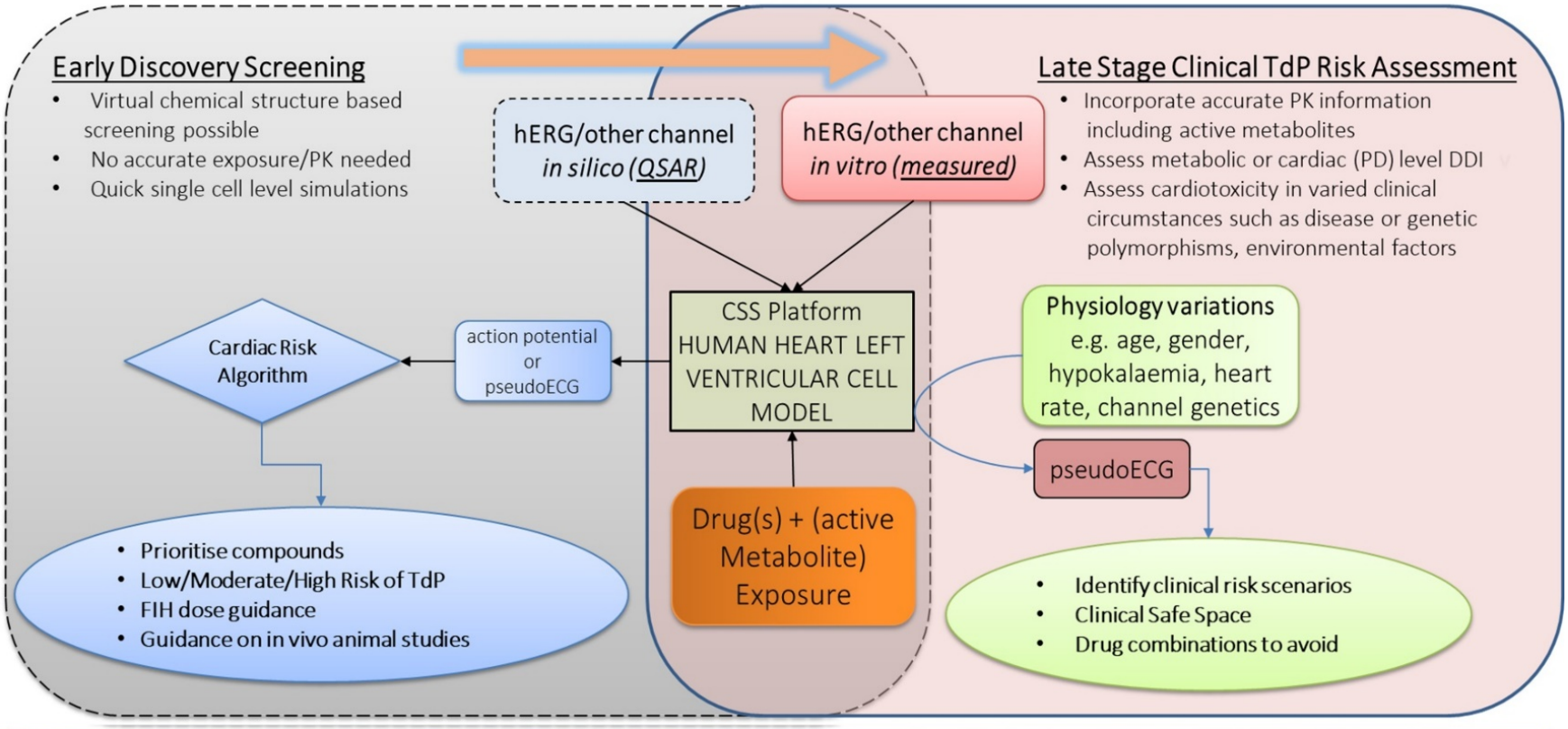

Quantitative approach for cardiac risk assessment and interpretation in tuberculosis drug development

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THANK YOU