# In silico assessment of nifedipine effects on human heart cells: pharmacokinetic-pharmacodynamic analyses at the population level

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## Abstract

This study aimed to utilise the value of integrating in vitro data and physiologically based pharmacokinetic (PBPK) models to quantitatively estimate the impact on pharmacokinetics (PK) and pharmacodynamics (PD). The objective was to predict pharmacodynamics (electrocardiogram (ECG) parameters) of nifedipine (NIF) after an oral administration by simulation. The computational models were performed for human transmural ECGs to model drug-induced changes in QT interval as well as changes in T-wave morphology. The differences in QTc interval due to NIF in healthy volunteers both males and females were predicted by the Cardiac Safety Simulator, providing a mechanistic understanding of clinical observation.

## Introduction

NIF is a $Ca^{2+}$ channel blocker used in the treatment of various cardiovascular diseases, with the pharmacological target in the vascular smooth muscles [1]. Two case studies of the PK-PD relation of NIF were analyzed: The first simulation study was designed using the drug exposure compound file and population data available in the Simcyp simulator, and plasma concentration data was exported from Simcyp to the Cardiac Safety Simulator (CSS) in order to analyse the PK-PD effect of the compound at the population level. In the second case a clinical study was mimicked [2] by utilizing CSS to support *in silico* assessment.

## Methods

The minimal PBPK Model was applied for the PK simulations in the Simcyp simulator. The PK model input (trial design) parameters are presented in Table 1. The half-maximal inhibitory concentration (IC50) and Hill coefficient (h) data (Table 2) describing drug triggered ionic current modification were used as input parameters addition to multiple free (unbound) drug plasma concentrations (µM). The computational models were derived from the ten Tusscher Panfilov 2006 (tT2006) human ventricular model [3] by proportionally changing ionic currents based on the *in vitro* measurements. To assess the antiarrhythmic potency of the NIF, the CSS platform (V2.1) was used to simulate normal (control) signal and drug-induced alterations in cardiac AP conduction at the population level (i.e. Sim-NEurCaucasian, North European Caucasian) [4]. The modelling approach for this study is described in Figure 1.

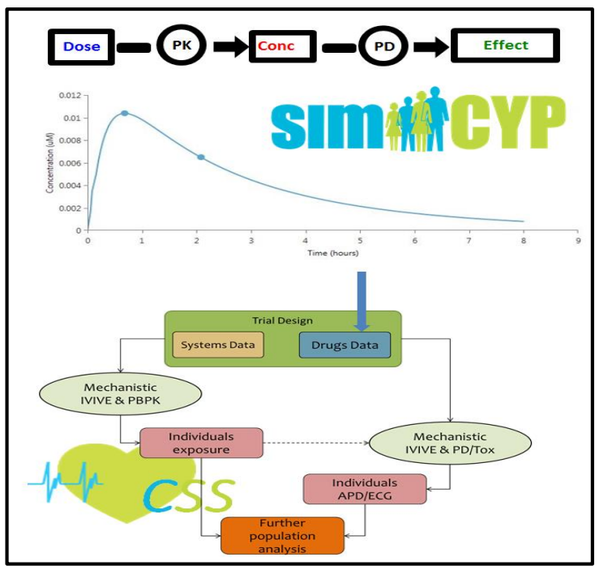


**Figure 1. Population-specific simulation schematic representation of combination of PK and PD model (using Simcyp and CSS simulators).**

**Table 1. Input parameters (trial design) used in Simcyp population-based simulator (V15 R1)**

| Trial Design | |
|---|---|
| Population Name | Sim-Healthy Volunteers |
| Population Size | 15.00 |
| Number of Trials | 3.00 |
| No. of Subjects per Trial | 5.00 |
| Start Day/Time | Day 1, 09:00 |
| End Day/Time | Day 1, 17:00 |
| Study Duration (h) | 8.00 |
| Sampling Time | Pre-defined Uniform |

**Table 2. Inhibitory actions of NIF on ion channels *in vitro***

| Effects of NIF on cardiac transmembrane ion currents | | |
|---|---|---|
| Ion Channel current | | Inhibitory Potency $I_{C50}$ (µM) |
| Inward | $I_{Na}$ | 88.5 (h = 0.71) [5] |
| | $I_{CaL}$ | 0.012 (h = 1.02) [5] |
| Outward | $I_{Kr}$ | 22* (h = 0.8) [5] |
| | $I_{Ks}$ | 360 (h = 0.97) [6] |

## Results: Cardiac electrophysiological characteristics

The PBPK model was used to simulate the PK property of NIF to predict the PD response on cardiac electrophysiological characteristics. The effect of NIF on the AP of human ventricular epicardial cells and ECG waves are shown in Figure 3. The simulation results show that NIF significantly shortened the APDs and QTc intervals in a concentration-dependent manner compared against control.

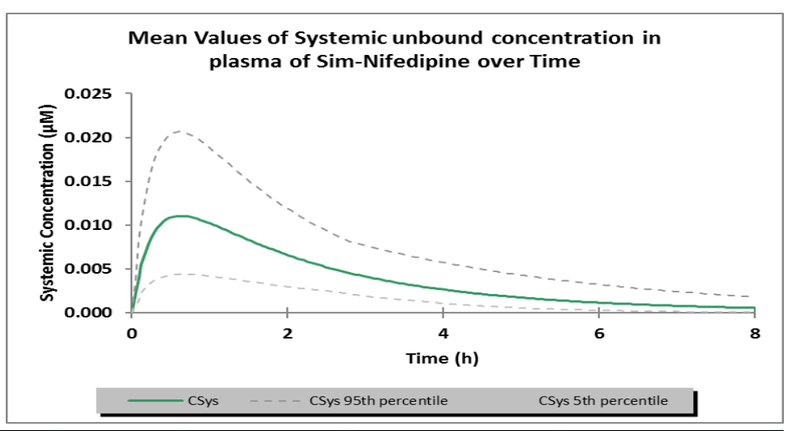


**Figure 2. Simulated mean plasma concentration (µM) time profile for 10 mg single dose of NIF in healthy volunteers.**

| | From (h) | To (h) | TMax (h) | CMax (µM) | AUC (µM.h) |
|---|---|---|---|---|---|
| CuPlasma (µM) | 0.00 | 8.00 | 0.64 | 0.011 | 0.031 |

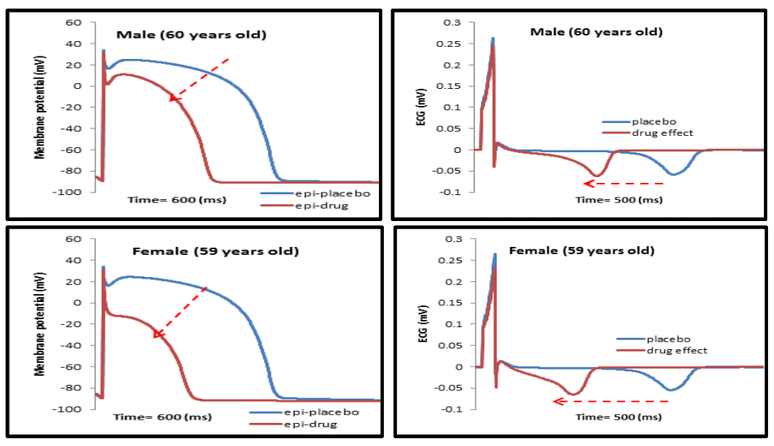


**Figure 3. Concentration-dependent effects of NIF on cellular AP (left-hand side panels) and 1D ECG (right-hand side) waveform conducted by using the tT2006 human (male/female) ventricular cell model. Arrows pointing into AP and ECG are showing shortening of the repolarization phase.**

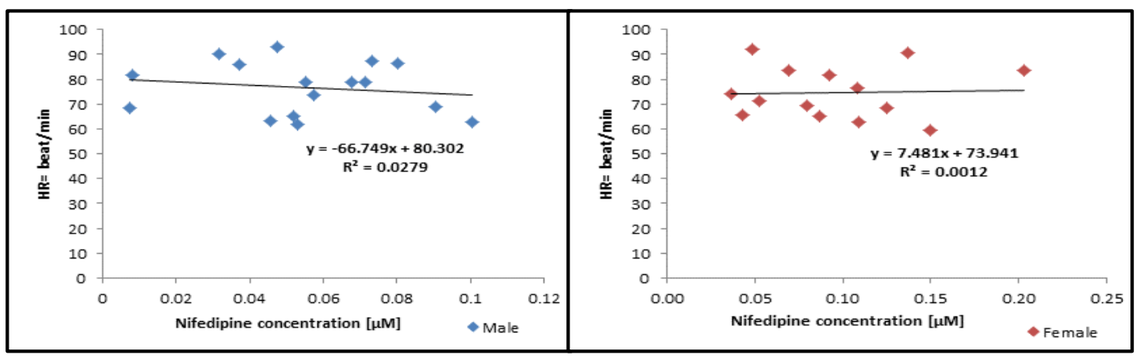


**Figure 4. Concentration-dependent effects of NIF on HR (blue male, red female) at population level.**

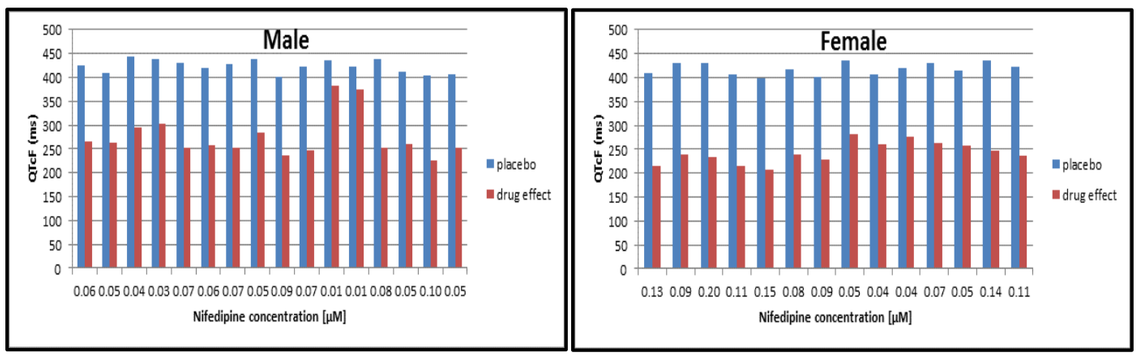


**Figure 5. The QTc Interval changes at the subject-specific from baseline.**

**Table 3. Endpoints (ECG parameters) generated by the CSS for the placebo (base) and the presence of the drug (NIF)**

| ECG parameters (average value (ms) of all subjects) | | | |
|---|---|---|---|
| | QTcF (M/F) | TpeakTend (M/F) | JTpeakc (M/F) |
| base | 423.85/418.51 | 59.22/59.3 | 273.8/269.70 |
| drug | 275.1/242.83 | 46.34/46.3 | 162.95/135.31 |

**Table 4. The percentage of the variation on the endpoints after simulation of different NIF plasma concentrations at the population level.**

| sex | *The coefficient of determination of the model $R^2$ (% of the changes (reduction)) | | | HR (b/m) |
|---|---|---|---|---|
| | ΔQTcF | ΔTpeakTend | ΔJTpeakc | |
| M | 83% | 42% | 84% | 76.64 |
| F | 50% | 61% (increased) | 69% | 74.66 |

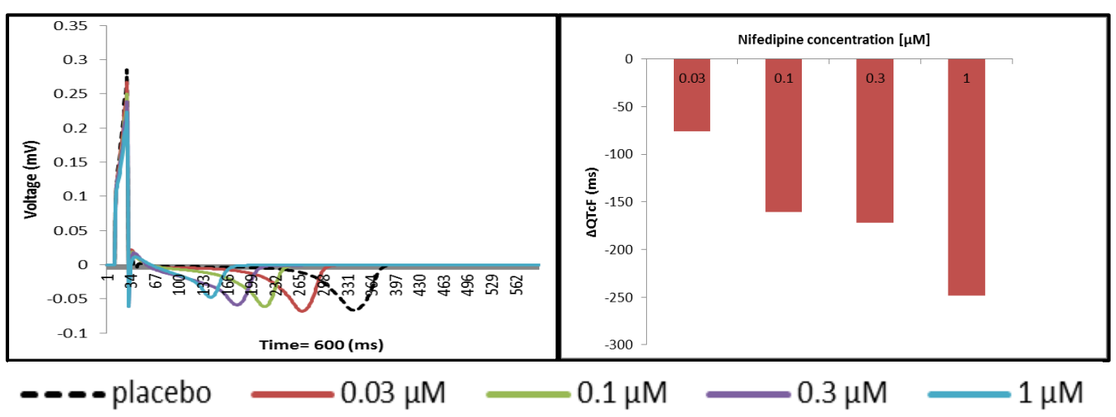


**Figure 6. Left-hand side panel: the representative ECG traces of the placebo and with increasing concentrations of NIF (data taken from [2]); right-hand side panel: bar graph showing changes in ΔQTcF at increasing concentrations of NIF.**

## Discussion and conclusions

- The utility of PBPK-PD modeling in early cardiac safety screening in linking drug concentration at the probable site of action with toxicological and/or therapeutic effects.
- *The in silico* model (e.g Figure 6.) was successful in recovering the experimental observation [2].
- Future work: the interaction effect of a high concentration of NIF (1 µM) that might reduce proarrhythmic dose-dependent effects of drugs which increase the risk of QT interval prolongation.

## References

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