Introduction
Cardiovascular toxicity is one of the leading causes of early and late attrition during the drug development process, as well as a major contributor to withdrawals of marketed drugs. Cardiovascular safety concerns arise from a variety of mechanisms, including direct myocyte injury, activation of apoptotic and necrotic changes, alteration of ion homeostasis or the signaling pathways or influence on the transcription factors i.e. kinase inhibitors. Cardiac arrhythmia is one of the most frequent cardiac safety liabilities responsible for toxic effect, often recognized in the late stage of clinical development and during post-marketing surveillance. Torsade de Pointes (TdP) is a syndrome of polymorphic ventricular arrhythmia occurring in the setting of marked prolongation of the ECG QT interval. Such cardiac safety risks have led to the withdrawal of many approved drugs from the market and is a leading cause of drug attrition during development. The recently approved drugs for multi-drug resistant pulmonary tuberculosis (e.g. bedaquiline) tend to influence parameters which may be pro-arrhythmic. Therefore algorithms for the drug-related cardiac risk assessment are needed.

Objective
The aim of the current work was to develop the in silico-based models for the early prediction of the cardiac risk propensity with the use an in vitro to in vivo extrapolation (IVIVE) approach. One of the assumptions was to develop systems which can be utilized at various stages of the drug development, and therefore working on different set of available information.

Materials and Methods
There were two different approaches applied during the models development as presented below on Figure 1.

Biophysically detailed computational models (BDMM) of cardiomyocytes in combination with appropriate in vitro cardiac ion channel inhibition data of the drug has recently been identified as a potentially efficient and economic approach to identify the arrhythmia risk and in turn reduce or avoid clinical studies

The Simcyp Cardiac Safety Simulator (CSS) with biophysically-detailed myocyte models (BDMM) describing electrophysiology of the human left ventricular cardiomyocytes was utilized. The input data include:

A. Ionic channel inhibitory effects as measured by patch clamp assay (e.g., $i_{Ks}$ for Ikr, $i_{Ca}$, $i_{Na}$, $i_{Cl}$ and other currents if available in the literature)

B. Drug concentrations of parent and/or active metabolites obtained from clinical studies or simulated using PBPK models such as Simcyp, and individual subject covariates

Simulation results (pseudoECG signal and its derivatives - QRS, QT, J-Tpeak, Tpeak - Tend, and EMW - Electro-Mechanical Window) were used to either develop empirical classifiers or directly to assess cardiac clinical consequences by mimicking the clinical trials.

Main references


Materials and Methods cont.

The empirical classifiers were built with the use of decision trees algorithms with 96 drugs used as the learning dataset. 9 active concentrations were tested (0, 0.0001, 0.001, 0.01, 0.1, 1, 10, 100, 500 μM). The simulated endpoint which was assumed to be the surrogate of the drugs proarrhythmia potency was defined as the ICEB (index of cardiac electrophysiological balance, where ICEB = $Q_T/Q_R$). 12 known drugs, 6 TdPs (Amiodarone, Citalopram, Clarithromycin, Dofetilide, Moxifloxacin, Quinidine) and 6 TdP (Fexofenadine, Propanolol, Verapamil, Hydrodolosalot, Ranolazine, Vardenal) were chosen as the validation dataset. 2 anti-TB drugs (Bedaquiline, Moxifloxacin) were tested.

For the simulations mimicking clinical results free plasma concentration was assumed to be the active fraction surrogate. In opposite to the above described empirical model development, here whenever possible known active metabolites (i.e. dolastron-hydrodolosalot, quinidine - 3-CH$_2$ quinidine) were also accounted for. The simulated/calculated endpoints were supposed to mimic those originally reported in the original scientific report derived from the literature.

Results and Discussion
The most robust empirical model built with the use of alternative decision tree (Adtree – Figure 2) algorithm, utilizing electromechanical window (EMW) and ICEB was able to correctly classify 85 out of 96 records during the internal validation step (89% of accuracy), and 10 out of 12 (citalopram and quinidine classified incorrectly) external validation compound (81% of accuracy) for their TdP propensity (Figure 3).

![Figure 2. Decision tree structure.](image)

During the population simulation, the final endpoints depended on those reported in the original works. Regardless of the endpoint, the obtained results matched well the clinical observations in all cases. The input data included the literature derived, in vitro measured ionic currents inhibition for bedaquiline and its main metabolites M2 (Table 1).

<table>
<thead>
<tr>
<th>Drug</th>
<th>$i_{Ks} (mM)$</th>
<th>$i_{Ca} (mM)$</th>
<th>$i_{Na} (mM)$</th>
<th>$i_{Cl} (mM)$</th>
<th>EMW (ms)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bedaquiline</td>
<td>0.7</td>
<td>0.7</td>
<td>0.7</td>
<td>0.7</td>
<td>39.9</td>
</tr>
<tr>
<td>Moxifloxacin</td>
<td>0.7</td>
<td>0.7</td>
<td>0.7</td>
<td>0.7</td>
<td>39.9</td>
</tr>
</tbody>
</table>

Table 1. In vitro measured ionic current inhibition for bedaquiline and its main metabolites

The exposure data were simulated with the use of Simcyp Simulator (V12.1) as presented on Figure 4.

![Figure 4. Individual concentration - seven beats were simulated with the use of Simcyp Simulator and Eq1-PBP model.](image)

For bedaquiline the predicted vs observed QTcF (derived from the simulated ECG QT value corrected for the heart rate with the Fridericia algorithm, where $QTcF = QT/HR^{0.5}$) values (ms) were: -4.1 vs -4.7 and 6.4 vs 3.8 for the 1st and 7th day of treatment respectively.

Results and Discussion
An in silico modelling and simulation approach that considered ECG changes beyond QT was proposed as a tool for the drugs and drugs combination cardiac safety assessment. This approach allows for the early screening as well as testing of clinical scenarios.