STRHIPS: A SAFETY TRIAL TOOL BASED ON HUMAN INDUCED PLURIPOTENT STEM CELLS TO EVALUATE DRUG-INDUCED ARRHYTHMIAS

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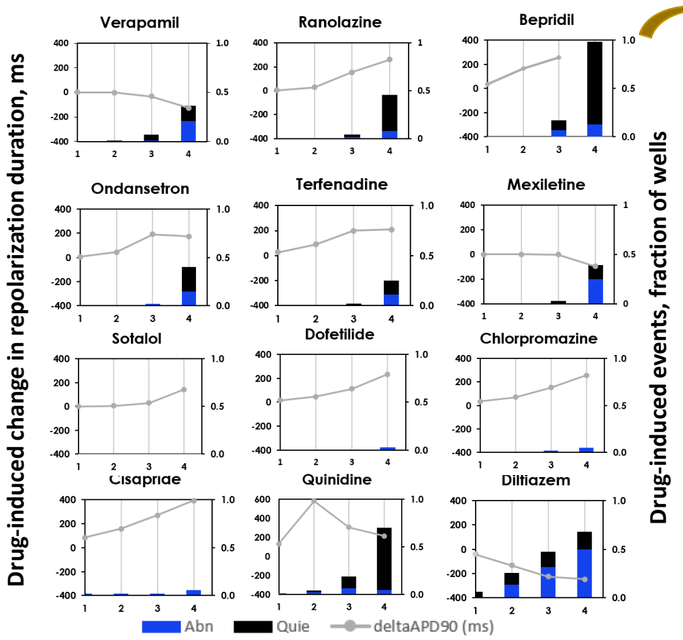
BACKGROUND

- The CiPA paradigm[1] foresees the integration of preclinical assessments of drug effects on multiple isolated cardiac ion channels in patch clamp assays and the corresponding *in silico* reconstruction of the human ventricular action potential with cellular studies performed on human induced pluripotent stem cell-derived cardiomyocytes (hiPSC-CMs) to predict the proarrhythmic liability of drug candidates[2].
- The assessment of hiPSC-CM electrophysiological variability in control and "dosed" cells by means of populations of *in silico* hiPSC-CMs is rapidly becoming a relevant component of the CiPA paradigm.
- Objective: to evaluate the performance of the new web-based tool STrhiPS (Safety Trials on hiPS, strhips.insilicocardio.com) on the CiPA training set drugs[1]

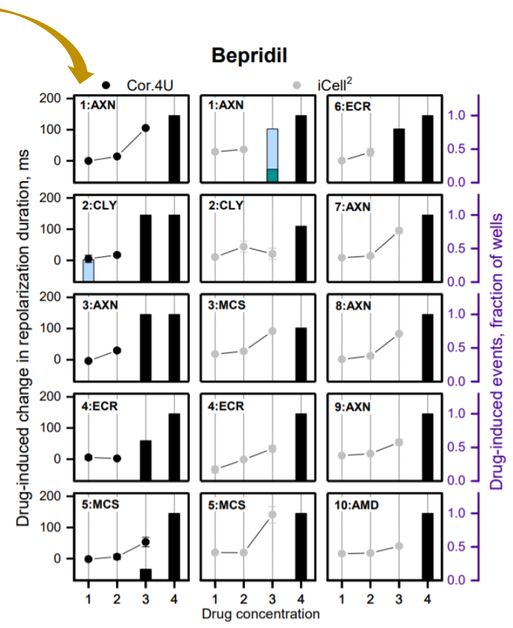
METHODS

- STrhiPS is based on a population extension of the *in silico* hiPSC-CMs Paci model[3].
- It was applied to the 12 CiPA training compounds, 4 compounds for each CiPA TdP category: High (H), Intermediate (I), Low/No (N) risk.
- Experimental conditions similar to those of the CiPA multisite study were simulated: 4 different concentrations, 110 cells, no pacing applied.
- Percentage of block for each of the main ion channels (I_{Kr}, I_{CaL}, I_{Na}, I_{NaL}, I_{to}, I_{K1}, I_{Ks}), and biomarkers (Action Potential Duration (APD), and others) values in both absence and presence of the compound were estimated in the population.
- Drug-induced repolarization abnormalities or cessation of spontaneous beating were reported.
- STRhiPS is available on cloud-based platform built on the Microsoft Azure cloud environment, in compliance with the highest standards of security and privacy.

RESULTS



Simulated effects of 12 'CiPA' drugs at 4 increasing concentrations



Exp data from Blinova et al.[3]

- Simulations required 8 to 9 minutes per compound, and automatic computation of biomarkers and detection of abnormalities was possible in 99% of cells
- Impact on biomarkers was qualitatively consistent with the blocking profile of each drug: APD was shortened in all N drugs except for ranolazine (as in [3]), prolonged in I and H drugs.
- Abnormalities confirmed to be rarely observed at low/therapeutic concentrations (0.9% of cells at concentrations 1 and 2).
- For several drugs the results pattern was fully consistent with the experiments (see Bepridil in figure). For few of them some discrepancies were observed (e.g. sotalol induced AP prolongation but not abnormalities).

CONCLUSIONS

- The web based, user-friendly STRhiPS enabled an *in silico* population-based analysis of the proarrhythmic risk of the 12 CiPA training compounds.
- The results indicated that the tool can support the design and interpretation of *in vitro* experiments.

1. Li, Z. et al. (2017). *Circ Arrhythm Electrophysiol*.
2. Paci, M. et al. (2018). *Front. Physiol*.
3. Blinova, K., et al. (2018). *Cell Rep*.