QT/TDP Risk Screen: A Web-based Tool for the Early Identification of Drug-Induced Proarrhythmic Risk

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PURPOSE

It is well recognized that **early identification** of **drug-induced proarrhythmic safety risks** is crucial to drug development for **ethical**, **animal sparing** and **costs reduction** considerations[1]. The availability, however, of **easily accessible**, **user-friendly** tools for **real time assessments** of the **proarrhythmic potential** of compounds has been lacking. The novel **Tx index**[2], implemented in the presented web-based tool, was applied to a dataset of **84 drugs compounds**.

METHODS

QT/TdP Risk Screen is based on **206,766 cellular simulations** of compound-induced effects on **Action Potential Duration (APD)** in isolated **Endo-, Mid-,** and **Epi-cardial cells** and on **7,072 tissue simulations** on **QT prolongation** in a **1D-virtual tissue**[3]. Simulations were performed by blocking the **slow** and **fast** components of the **delayed rectifier current** (IK_s and IK_r, respectively) and the **L-type calcium current** (ICa_L) at different concentration levels. Based on these simulations, **four Tx indices** were defined as the ratio of **drug concentration** leading to a **10% prolongation** of the APD_{Endo}, APD_{Mid}, APD_{Epi} or **QT interval** over the maximum Effective Free Therapeutic Plasma Concentration (EFTPC), respectively. A dataset of **44 non-torsadogenic** and **40 torsadogenic** drug compounds was used to validate the performance of the tool. **hERG test** (positive response: hERG pIC50 > 6) was applied to the **84 compounds** to compare performances[2] (Figure 1). QT/TdP Risk Screen was built and integrated on the **cloud-based InSilicoTrials platform**, in compliance with the highest standards of **security** and **privacy**.

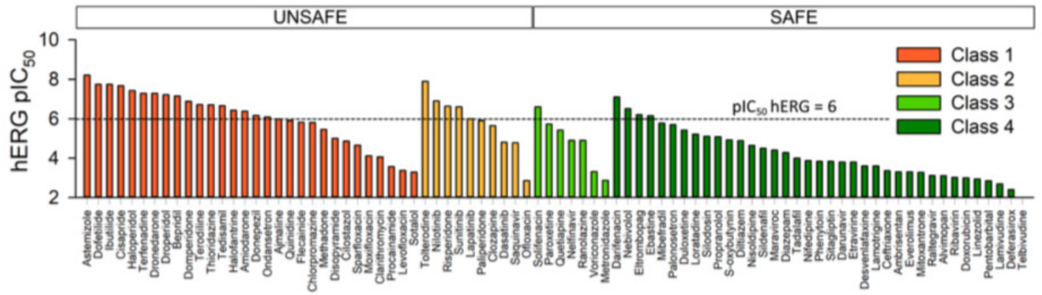

Figure 1. ***Torsadogenic risk classification of the 84 compounds using pIC50 hERG > 6***. *CredibleMeds* categories: *Class 1*, compounds with risk of TdP; *Class 2*, compounds with possible risk of TdP; *Class 3*, compounds with conditional risk of TdP; and *Class 4*, drugs that should be avoided by patients with congenital Long QT Syndrome.

References

[1] Chi KR *Nat. Rev. Drug Disc.* (2013) 12, 565-567; [2] Romero L et al. *J. Chem. Inf. Model.* (2018) 58, 867−878. [3] O'Hara T et al. *PLoS Comput. Biol*. (2011) 7(5): e1002061 doi: 10.1371/ journal.pcbi.1002061. [4] Sager, PT et al. *Am. Heart J.* (2014) 167, 292−300. [5] Cantilena L et al. *Clin. Pharmacol. Ther.* (2006) 79, P29.

RESULTS

Receiver operating characteristic (ROC) curves were constructed on the **four estimated Tx indices** for each compound in the dataset to enable the identification of **torsadogenic potential cut-off values**[2]. These were identified as **8**, **8**, and **6.4** for **Tx-APD_{Endo}**, **Tx-APD_{Mid}**, **Tx-APD_{Epi}** and as **9.2** for **Tx-QT**, respectively. The classification of the **84 compounds** resulted in an accuracy ranging between **87%** and **88%** for the **four Tx** indices **Tx-APD_{Endo}**, **Tx-APD_{Mid}**, **Tx-APD_{Epi}** and **Tx-QT** (Figure 2). The classification of the **84 compounds** resulted in an accuracy ranging between **87%** and **88%** for the **four Tx indices Tx-APD_{Endo}**, **Tx-APD_{Mid}**, **Tx-APD_{Epi}** and **Tx-QT** (Table 1).

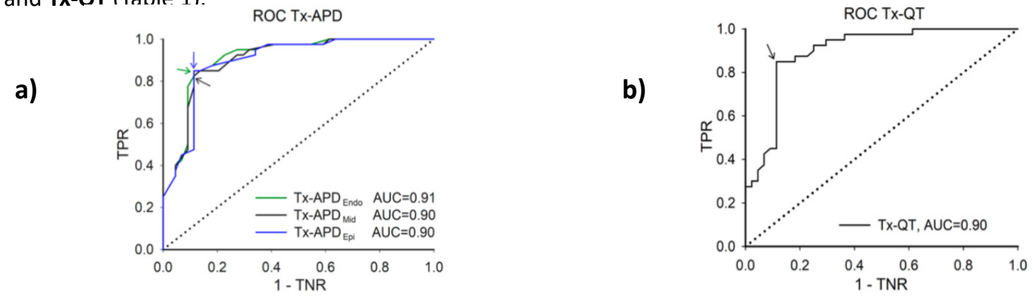

Figure 2. ***In silico isolated cellular Tx-APD and Tx-QT assays***. **a)** ROC curves for the Tx-APD and optimal cut-off points where sensitivity and specificity are maximal (arrows) for the Tx-APD_{Endo} (green), Tx-APD_{Mid} (black), and Tx-APD_{Epi} (blue) (8, 8, and 6.4, respectively). **b)** ROC curve for the Tx-QT and optimal cut-off point where sensitivity and specificity are maximal for the Tx-QT (arrow, 9.2). The area under the curve (AUC) values are also indicated.

Endo			Mid			Epi			QT		
Tx	TdP+	TdP-	Tx	TdP+	TdP-	Tx	TdP+	TdP-	Tx	TdP+	TdP-
+	34	5	+	34	6	+	34	5	+	34	5
-	6	39	-	6	38	-	6	39	-	6	39
A	TPR	TNR	A	TPR	TNR	A	TPR	TNR	A	TPR	TNR
0.87	0.85	0.89	0.86	0.85	0.86	0.87	0.85	0.89	0.87	0.85	0.89

Table 1. ***Confusion matrices for the Tx-APDs and Tx-QT.*** The values of the true positive rate (TPR), true negative rate (TNR), and accuracy (A) are also indicated.

CONCLUSIONS

hERG block alone exhibits poor predictive performance[4]. When applying the ***in vitro*** **hERG test** to the **84 compounds**, it exhibited a **TPR** of **55%**, a **TNR** of **89%**, and an **A** of **73%**, in close agreement with previous studies[5]. In comparison, the ***in silico*** **Tx** tests described in this study yield **TPRs** of **85%**, **TNRs** of **86%-89%** and **As** of **86%–87%**. This method does not include drug effects on Na+ channels, which is related to the misclassification of 3 compounds (quetiapine, ranolazine, and lamotrigine - significant Na+ channels blockers at EFTPC). Future work will include this channel. The presented web-based tool is a **highly innovative method** for an **accurate torsadogenic risk assessment**. Each assessment required only a **few seconds** of **computational time**.