Introduction

There are various nonclinical and clinical models available to assess proarrhythmic potential of drugs under development, on the basis of generated surrogate markers. Neither IKr inhibition nor AP/QT prolongation are perfect predictors, and the ventricular proarrhythmia (TdP) should be the end point of primary concern in the cardiac safety assessment. Multiple classification schemes for categorizing drugs (into 2-5 classes depending on the assessed scale) are available, and various classification models were built with their use. There is a wide range of available mathematical algorithms, which can be applied to assess the potential cardiac risk of drugs or drug candidates. Yet it is a well known that the predictive power of any classification model depends not only on the algorithm utilized for the model development, but also the data quality, and the database integrity. For the TdP risk assessment model, accurate classification of the compounds is crucial. These classifications are not consistent, an individual compound is sometimes assigned to an opposing class depending on the chosen scheme. As a consequence, it is neither possible to directly compare the predictive effectiveness of the models nor classify the compound of interest.

Objective

The aim of the current work is to present and compare various classification schemes proposed in publicly available scientific sources and list the compounds which were differently categorized depending on the selected scheme.

Materials and Methods

A literature search was performed using the traditional tools and publically available databases. PubMed, Google Scholar, ScienceDirect and the Internet via the Google search engine were used to search for the drug classifications and the models developed to assess cardiac safety of the drugs. Multiple combinations of relevant keywords were applied, these included: proarrhythmic, classification, model, drugs, torsadogenic, TdP, risk and prediction. Algorithms and models specializing in the prediction of HERG inhibition, QT prolongation and proarrhythmia endpoints different than TdP propensity were excluded from the analysis.

To allow for a direct comparison all classifications with more than two classes were re-scaled to binary classifications. This procedure was based on the class descriptions given in the original texts. The class descriptions and the final classification after binarization are presented in Table 1.

Results and Discussion

18 different classification schemes for 464 compounds were identified in the literature search. After re-scaling to binary classification, 552 compounds (85% of the identified compounds) were consistently classified either as torsadogenic (110 as TdP+) or safe (340 as TdP-). However, 398 out of 552 compounds (72%) appear in one classification only. For 94 compounds (38% of those which were present in at least 2 classifications) contradictory results were found. 36 out of the 94 compounds were equally often indicated as proarrhythmic and safe (e.g. donepezil, hydroxyzine and mifeprone). For 16 (e.g. fluvoxamine, olanzapine and mexiteline) and 42 (e.g. propafenone, mexloflaxin and amiodarone) compounds TdP+ and TdP- class respectively was indicated more frequently. 6 of these classifications were directly used during the development of the in silico predictive models of various character. It is worth noting that all the above-mentioned models were developed and validated with the use of different datasets at least some of the compounds were differently classified between databases used for model development. There is also a group of chemical entities which were not used for the in silico models development, yet their categorization differs depending on the classification scheme. Both groups are presented in Table 2.

Table 1. Original TdP risk classes and results of binarization procedure

Table 2. Total number of models/classification schemes for chemical entities with contradicting classifications.