Comparison of Proarrhythmia Classification Models

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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 assumed 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.

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

Reference	Category	
	TdP +	TdP-
Redfern 2003	Category 1: Repolarisation-prolonging (Class Ia and Class III) antiarrhythmics (which have IKr block as an integral pharmacodynamic mechanism, and QT prolongation as an intended, desirable effect).	Category 4: Drugs for which there have been isolated reports of TdP in humans.
	Category 2: Drugs that have been withdrawn or suspended from the market in at least one major regulatory territory due to an unacceptable risk of TdP for the condition being treated.	Category 5: Drugs for which there have been no published reports of TdP in humans. This category also contains some drugs (e.g. ketoconazole) which are associated with drug interactions leading to TdP, but which have not been associated with cases of TdP when used alone.
	Category 3: Drugs that have a measurable incidence of TdP in humans, or for which numerous case reports exist in the published literature.	
Mirams 2011	Category 1: Class Ia and III anti-arrhythmics; generally associated with a large, but acceptable, risk of TdP.	Category 4: Drugs for which there have been isolated case reports of TdP.
	Category 2: Drugs that have been withdrawn from the market (by at least one major regulatory authority) due to unacceptable TdP risk.	
	Category 3: Drugs with a measurable incidence of TdP, or for which numerous case reports exist.	Category 5: Drugs for which there have been no published reports of TdP.
Okada 2015	Category 1: Repolarisation-prolonging (Class Ia and Class III) antiarrhythmics (which have IKr block as an integral pharmacodynamic mechanism, and QT prolongation as an intended, desirable effect).	Category 4: Drugs for which there have been isolated reports of TdP in humans.
	Category 2: Drugs that have been withdrawn or suspended from the market in at least one major regulatory territory due to an unacceptable risk of TdP for the condition being treated.	Category 5: Drugs for which there have been no published reports of TdP in humans.
	Category 3: Drugs that have a measurable incidence of TdP in humans, or for which numerous case reports exist in the published literature.	
Guo 2013	Positive observations in the clinic.	Negative observations in the clinic.
	Equivocal results are reported, or the positive events are observed only in overdose.	Non-TdP type arrhythmia.
Champeroux 2005	Group A: drugs with numerous or several reports (>2 cases) of TdP.	Group B: drugs causing QT prolongation and/or TdP only, the latter at a very low frequency (≤2 cases).
		Group C: drugs without reports of TdP or QT prolongation.
Yap 2004	Category 1-3 according to CredibleMeds (former ArizonaCERT 2003) plus TdP agents collected from Micromedex, Drug Information Handbook, Meyler's Side Effects of Drugs, and a list of agents compiled by De Ponti et al. 2001.	243 TdP with no reported case of TdP in humans; obtained from the search of Micromedex, Drug Information Handbook, and American Hospital Formulary Service (AHFS) for agents.
CredibleMeds 2016	Known Risk of TdP - these drugs prolong the QT interval AND are clearly associated with a known risk of TdP, even when taken as recommended.	Possible Risk of TdP - these drugs can cause QT prolongation BUT currently lack evidence for a risk of TdP when taken as recommended.
	Conditional Risk of TdP - drugs associated with TdP BUT only under certain circumstances of their use (e.g. excessive dose, in patients with conditions such as hypokalemia, or when taken with interacting drugs) OR by creating conditions that facilitate or induce TdP (e.g. by inhibiting metabolism of a QT-prolonging drug or by causing an electrolyte disturbance that induces TdP).	
He 2012	Drugs with clinical studies and/or case reports of causing TdP were identified as TdP+.	Drugs which had no clinical studies and case reports of TdP or similar symptom (QT prolongation, ventricular tachycardia or ventricular fibrillation etc) and had been used by a large number of patients. Drugs used to treat common diseases such as flu, diabetes, hypertension, bacterial infection etc) and at least 30 years of market presence.
Liu 2006	Known ability to prolong QTc and/or induce TdP in humans.	Established cardiac safety in clinical usage.
Haverkamp 2001 Camm 2004	Class A (high torsadogenic potency) Drugs which are potent blockers of currents prolonging myocardial repolarization. Documented action potential prolongation and the induction of early afterdepolarizations. The drugs are either antiarrhythmic drugs of which the mechanisms of antiarrhythmic drug action is based on prolongation of repolarization or the IC_{50} for this effect is in the same range as the IC 50 for the therapeutic action. Documented QT prolongation has been documented at therapeutic doses/concentrations and cases of TdP induced by the drug alone (in the absence of concomitant therapy prolonging repolarization and/or hypokalemia).	Class D (torsadogenic potential not clear) Drugs which block repolarizing ion currents *in vitro* but which have so far not been shown to prolong repolarization in other *in vitro* models (e.g. papillary muscle fibres or isolated hearts) or the concentrations necessary for this effect were far above the clinical concentrations. Prolongation of the human QT interval has not been demonstrated in systematic randomized studies. Cases of TdP in association with treatment with the drug may have been reported. However, the causal relation between the event and the drug is not clear.
	Class B (medium high torsadogenic potency) Drugs which prolong myocardial repolarization (i.e. cardiac action potential duration and QT interval) at higher doses, or at normal doses with concurrent administration of drugs that inhibit drug metabolism (e.g. by inhibiting the cytochrome P450 metabolism). Their IC_{50} for this prolongation of repolarization is above the IC_{50} for the therapeutic effect. Cases of TdP induced by the drug alone have been documented. However, TdP is usually associated with metabolic inhibition and/or the presence of other risk factors.	
	Class C (low torsadogenic potency) Drugs that prolong action potential duration and QT interval at high doses/concentrations which are clearly above the therapeutic range. Their effect on repolarization becomes only manifest during overdose, intoxication or in the presence of severe metabolic inhibition. Cases of TdP have been documented. However, in almost all so far available published cases, several factors which are well known to increase the propensity of TdP, i.e. risk factors, were present.	
Colatsky 2016 (CIPA)	High risk: Compounds Identified as High Risk for Manifesting Human TdP.	Very low risk: Compounds Identified as No or Very Low Risk for Manifesting Human TdP.
	Intermediate risk: Compounds Identified as Intermediate Risk for Manifesting Human TdP.	
Lawrence 2006	Category 1 drugs include repolarization prolonging (Class Ia and Class III) antiarrhythmics (which have IKr block as an integral pharmcacodynamic mechanism and QT prolongation as an intended desirable effect).	Category 4 drugs are those for which there have been isolated reports of TdP in humans.
	Category 2 drugs include those that have been withdrawn or suspended from the market due to an unacceptable risk of TdP.	
	Category 3 drugs are those that have a measurable incidence of TdP in humans or for which numerous case reports exist.	Category 5 includes drugs for which there have been no published reports of TdP in humans.
Guns 2012 Johannesen 2014 Antzelevich 2004 Kramer 2013 Cummins Lancaster/Sobie 2016	No re-scaling required.	

Results and Discussion

18 different classification schemes for 646 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, hydroxizine and mefloquine). For 16 (e.g. fluvoxamine, olanzapine and mexiletine) and 42 (e.g. propafenone, moxifloxacin 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 where 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.

Figure 1. *Results of various sources analysis for the contradictory results classifications.*

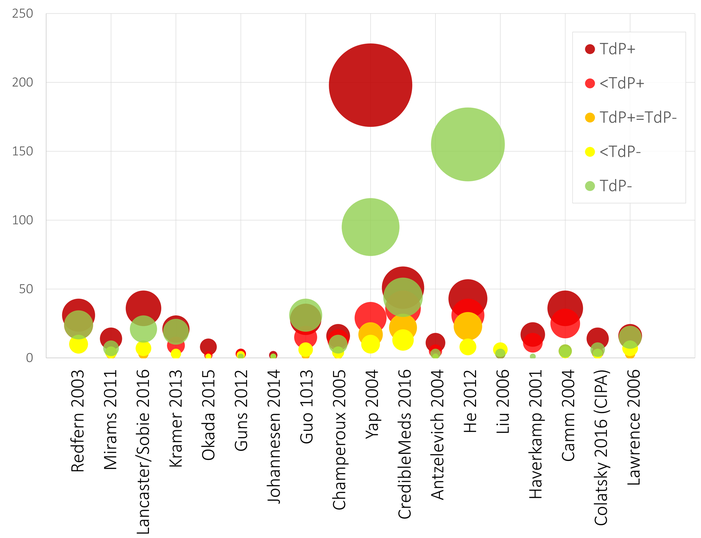

Table 2. *Total number of models/classification schemes for chemical entities with contradicting classification.*

Compounds with ambiguous classification	Number of classification schemes where a compound was classified as	
	TdP+	TdP-
adenosine-phosphate	1	1
amantadine	3	1
amiodarone	11	2
amitryptiline	5	3
atazanavir	1	1
azithromycin	5	1
chloralhydrate	2	1
chloroquine	3	3
ciprofloxacin	3	4
clarithromycin	9	3
clomipramine	2	1
clozapine	4	3
cocaine	3	1
desipramine	3	6
diphenhydramine	3	5
dobutamine	1	1
dolasetron	1	1
domperidone	5	2
donepezil	2	2
doxepin	4	1
dronedarone	2	1
encainide	1	1
erythromycin	8	1
felbamate	1	2
flecainide	8	1
fluconazole	3	1
fluoxetine	3	2
fluvoxamine	1	3
foscarnet	1	3
fosphenytoin	1	1
furosemide	1	2
gatifloxacin	2	1
gemifloxacin	1	1
granisetron	1	1
hydroxyzine	1	1
iloperidone	1	1
imipramine	6	4
isradipine	2	1
ketanserin	3	2
ketoconazole	4	3
lapatinib	1	1
loperamide	1	1
mefloquine	2	2
mesoridazine	3	1
metronidazole	1	3
mexiletine	1	5
mibefradil	3	4

Compounds with ambiguous classification	Number of classification schemes where a compound was classified as	
	TdP+	TdP-
miconazole	1	1
mizolastine	2	1
moexipril	1	1
moracizine	1	1
moxifloxacin	8	4
nefazodone	1	1
nelfinavir	2	1
nicardipine	1	2
nilotinib	3	1
nortriptyline	2	1
ofloxacin	1	1
olanzapine	1	5
ondansetron	4	1
paliperidone	3	1
papaverine	3	1
pazopanib	1	1
pentamidine	8	1
perhexiline	1	1
probucol	4	1
promethazine	2	1
propafenone	5	4
quetiapine	3	3
ranolazine	2	5
risperidone	5	5
ritonavir	1	1
saquinavir	1	4
sertindole	11	1
sparfloxacin	8	2
spiramycin	1	1
sulfamethoxazole	1	1
sultopride	1	1
sunitinib	4	1
tacrolimus	3	2
tamoxifen	1	5
telithromycin	1	1
tetrabenazine	1	1
tiapride	1	1
tizanidine	1	1
toremifene	1	1
trimethoprim	2	1
trimipramine	1	1
troleandomycin	1	1
vardenafil	1	2
venlafaxine	2	1
zimeldine	2	1
ziprasidone	3	1
zolmitriptan	1	1

The presented results clearly point out to the need of establishing a new, general, standardized classification system of the drug proarrhythmic propensity. It is quite likely that the it will be dynamic in nature as the knowledge about drugs changes but having general framework could help to manage existing and develop new classification models.

It is worth mentioning that the current analysis does not include information from the wide range of pre-clinical studies which are conducted for the compounds under development. In this work neither animal studies nor *in vitro* conducted ionic currents inhibition studies were considered.

References Available upon request.

Acknowledgement B.W. acknowledges support from the Polish National Science Center (Grant No. 2013/11/D/NZ7/01583).