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Clinical research

Anti-HERG activity and the risk of drug-induced arrhythmias and sudden death

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Aims Drug-induced QTc-prolongation, resulting from inhibition of HERG potassium channels may lead to serious ventricular arrhythmias and sudden death. We studied the quantitative anti-HERG activity of pro-arrhythmic drugs as a risk factor for this outcome in day-to-day practice.
Methods and results All 284 426 case reports of suspected adverse drug reactions of drugs with known anti-HERG activity received by the International Drug Monitoring Program of the World Health Organization (WHO-UMC) up to the first quarter of 2003, were used to calculate reporting odds ratios (RORs). Cases were defined as reports of cardiac arrest, sudden death, torsade de pointes, ventricular fibrillation, and ventricular tachycardia ($n = 5591$), and compared with non-cases regarding the anti-HERG activity, defined as the effective therapeutic plasma concentration ($ETCP_{unbound}$) divided by the HERG IC_{50} value, of suspected drugs. We identified a significant association of 1.93 (95% CI: 1.89–1.98) between the anti-HERG activity of drugs, measured as $\log_{10}$ ($ETCP_{unbound}/IC_{50}$), and reporting of serious ventricular arrhythmias and sudden death to the WHO-UMC database.
Conclusion Anti-HERG activity is associated with the risk of reports of serious ventricular arrhythmias and sudden death in the WHO-UMC database. These findings are in support of the value of pre-clinical HERG testing to predict pro-arrhythmic effects of medicines.

Introduction

Drug-induced prolongation of the QTc-interval usually results from concentration-dependent blocking of cardiac HERG potassium channels.[1,2] An excessively prolonged QTc-interval can, under the right circumstances, lead to a polymorphic ventricular arrhythmia known as torsade de pointes (TDP). When TDP is sustained, symptoms arising from impaired cerebral circulation, such as dizziness, syncope, and/or seizures, may become manifest. TDP can subsequently degenerate into ventricular fibrillation and, not uncommonly, cardiac arrest or sudden death may occur. It is not clear what percentage of TDP arrhythmias are non-sustained and what percentage degenerate into ventricular fibrillation. Over the last decade, this adverse reaction has attracted considerable clinical and regulatory interest and has been the most common cause of withdrawal, or restriction of the use, of drugs on the market.

In 1997, the Committee for Proprietary Medicinal Products (CPMP) of the European Union adopted a 'Points to

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Consider' document which made recommendations for non-clinical and clinical approaches to assess the risk of QTc-interval prolongation and TDP for non-cardiovascular drugs.[3] The strategies described are now being harmonized by the International Conference of Harmonization (ICH), and a draft version of the 'Note for Guidance' document is currently available.[4] Based on these regulatory recommendations, most new drugs are tested nowadays for their ability to block HERG potassium channels and rapid potassium currents (I_{Kr}). However, there is still much debate going on within the pharmaceutical industry, as well as regulatory authorities, on the predictive value of HERG channel binding and the risk of cardiac arrhythmias. For example, collaborating researchers from several pharmaceutical industries recently published an extensive overview of 100 QTc-prolonging drugs and their ability to bind to HERG-channels in relation to free-plasma concentrations.[5] These authors related this anti-HERG activity to the torsadogenic propensities of the drugs. Drugs were assigned to one of the following five categories of decreasing torsadogenicity: (i) anti-arrhythmic drugs, (ii) drugs withdrawn or suspended due to TDP risk, (iii) drugs with measurable TDP risk in humans or many TDP case reports in published literature, (iv) isolated TDP case reports, and (v) no published reports of TDP in humans, but with a certain degree of suspicion because of, for example, therapeutic class, drug interactions, etc. The clinical relevance of this type of categorization, however, remains to be confirmed.

We therefore studied the magnitude of anti-HERG activity in relation to pro-arrhythmic risk, defined as the occurrence of serious ventricular arrhythmias and sudden death, in day-to-day practice, using drug safety data obtained from the World Health Organization (WHO) adverse drug reactions database.

Methods

Setting

Data from the International Drug Monitoring Program of the WHO were used.[6] The database of this program is maintained by the Uppsala Monitoring Centre (WHO-UMC) and contains summaries of case reports originally submitted by healthcare professionals to national pharmacovigilance centres in more than 70 countries all over the world. At the end of 2003, this database contained more than 3 million individual case reports of suspected adverse drug reactions (ADRs) regarding specific, but anonymous, patients. The reports contain administrative data, patient data, ADR data, medication data, and other information. The information in these reports is not homogenous, at least with regard to origin, completeness of documentation, or the likelihood that the suspected drugs caused the adverse events.

For this study all reports up to the first quarter of 2003 of a previously published list of 52 pro-arrhythmic drugs, for which information on both effective free therapeutic plasma concentrations ($ETCP_{unbound}$) as well as inhibition of HERG/I_{Kr} currents were available[5] (Appendix 1) were used.

Design

A widespread method for quantitative signal detection in spontaneous reporting systems is the calculation of reporting odds ratios (RORs) as a measure of disproportionality. This method compares the exposure to certain (characteristics of) drugs among case reports of interest with that among all other reports (non-cases), and is comparable to a case–control design (data analysis).

In the WHO-UMC database the case reports of interest were identified by means of the WHO-ART adverse reaction terms: 'cardiac arrest', 'sudden death', 'torsade de pointes', 'ventricular fibrillation', and 'ventricular tachycardia'.[7] The anti-HERG activity of the study drugs was regarded as the exposure. Anti-HERG activity was defined as the free plasma concentrations attained during clinical use ($ETCP_{unbound}$) divided by the concentration which inhibits 50% of the potassium channels (IC_{50}). When multiple HERG-binding properties or free plasma concentrations have been described in the literature, the lowest IC_{50} and the maximum $ETCP_{unbound}$ were used.[5] Per ADR-report, anti-HERG activities of all study drugs which were assigned as 'suspect' were assessed. If multiple study drugs were reported, anti-HERG activities were summed using the following formula:

$$\text{Sum}_{\text{anti-HERG activity}} = \left(\frac{\text{ETCP}_{\text{unbound}}}{\text{IC}_{50}}\right)_A + \left(\frac{\text{ETCP}_{\text{unbound}}}{\text{IC}_{50}}\right)_B + \ldots\ldots + \left(\frac{\text{ETCP}_{\text{unbound}}}{\text{IC}_{50}}\right)_Z.$$

The $ETCP_{unbound}/IC_{50}$ ratio of the study drugs varied from less than 0.0003 to 40, and a $\log_{10}$ transformation was used. This exposure measure can be regarded as the therapeutic/toxic ratio of a drug or drug combination. It was expected that, with increasing $ETCP_{unbound}/IC_{50}$ ratio, the risk of an adverse event of interest increases.

Potential confounders

The association between anti-HERG activity and the study outcome may be confounded by secondary factors including age, sex, several concomitant diseases (heart disease, pulmonary disease, diabetes mellitus), pharmacokinetic drug–drug interactions (defined as clinically relevant cytochrome P450 interactions by Flockhart *et al.*[8]), concomitant use of drugs which may lower blood potassium levels, year of reporting, and time since first marketing. When multiple study drugs were reported, in the analyses, the shortest latency period between marketing and reporting was used.

For the assessment of concomitant diseases, proxies derived from the available information provided by the reporters were used (*Table 1*). Time since marketing was calculated as the year of reporting minus the year of first marketing (Appendix 1).

Data analysis

To estimate the association between anti-HERG activity and serious ventricular arrhythmias, and sudden death, RORs were calculated. This method normally compares the exposure odds with certain drugs among case reports of interest with the exposure odds among all other reports, as a measure of background risk, and is calculated like a normal odds ratio (*Table 2*). In the present study, anti-HERG activity is modelled as a continuous exposure variable. The advantage of this method is that it is straightforwardly applicable and adjustment for covariates is possible in logistic regression analysis.[9] A ROR

Table 1 Definition of cardiac disease, diabetes mellitus, and pulmonary disease

Disease	Definition
Cardiac disease	Concomitant medication of cardiac drugs (ATC-code C01, verapamil, or diltiazem) or, Pre-disposing or contributing conditions marked as ischaemic heart disease, heart failure, cardiac dysrhythmias, conduction disorders, heart valve replacement, or cardiac pacemaker
Diabetes mellitus	Concomitant medication of anti-diabetic drugs (ATC-code A10) or, Predisposing or contributing conditions marked as diabetes
Pulmonary disease	Concomitant medication of anti-asthmatic drugs (ATC-code R03) or, Predisposing or contributing conditions marked as chronic bronchitis, emphysema, asthma, or COPD

Table 2 Calculation of the reporting odds ratios (ROR).

	Reports with the suspected ADR	Reports without the suspected ADR
Reports with the suspected drug (exposed)	A	B
All other reports (non-exposed)	C	D

A: Number of reports of drug-induced arrhythmias associated with a given drug.
B: Number of reports of other adverse drug reactions associated with a given drug.
C: Number of reports of drug-induced arrhythmias associated with other drugs.
D: Number of reports of other adverse drug reactions associated with other drugs.
ROR = (A/C)/(B/D) = AD/BC.

significantly higher than one indicates a disproportionate share of a certain drug in a certain ADR and hence an increased risk of this ADR of interest. RORs were calculated using unconditional multivariable logistic regression, adjusting for the potential confounding factors mentioned above (age, sex, several concomitant diseases, pharmacokinetic drug–drug interactions, concomitant use of drugs which may lower blood potassium levels, year of reporting, and time since first marketing). The linearity assumption for continuous variables was assessed by comparing plots of observed odds as well as fitted odds against the variable of interest. All statistical analyses were performed using SPSS 10.0 statistical software (SPSS Inc., Chicago, IL, USA). Two-sided significance tests with an alpha of 0.05 were used (2×0.025). Since we only tested a single hypothesis, and subgroup analyses as well as analyses of different case definitions were only used to strengthen this hypothesis, all analyses were performed at a significance level of alpha of 0.05.

Subgroup analyses

In order to study whether the association differed among several sub-populations of the study population, separate RORs were calculated for sub-groups based on gender, age, type of drugs used, part of the world where reports originated, time since marketing (to study the Weber effect[10]), and reporting date (to study the influence of mass media attention[11]).

Different case-definitions

Since we used a composite study outcome, we also looked at the five different endpoints separately. Cardiac arrest, sudden death, TDP, ventricular fibrillation, and ventricular tachycardia are the most precisely defined serious outcomes which may result from drug-induced QTc-prolongation in the WHO-ART terminology. Other, less well-defined terms, such as cardiac fibrillation, and ventricular arrhythmias, however, may also include study outcomes of interest. We therefore also calculated RORs using these two latter case definitions. The association of anti-HERG activity with QTc-prolongation, a precursor for drug-induced arrhythmias, and syncope, one of the clinical symptoms, were also assessed. As a negative control, we studied the association between anti-HERG activity and two randomly picked study outcomes, without proven association with HERG: hepatitis and skin ulcer.

Missing values

The WHO-UMC data are summaries of case reports of suspected ADRs, originally submitted to national pharmacovigilance centres. However, reports such as these often do not contain a full medical history, and data on confounders may be incomplete or lacking. To assess the presence of concomitant diseases, use was made of the information in the field 'predisposing or contributing conditions' (shown in 2% of the reports), as well as known co-medication (shown in 50% of the reports).

Age and gender of the patient were unknown in 20% and 9% ADR reports respectively. Unknown gender was analysed as a separate category. Missing ages were imputed based on the mean age of patients of the same gender, using the same drugs.

Results

During the study period, the WHO received 284 426 reports of ADRs of 49 of the 52 study drugs. The greatest number of these reports concerned fluoxetine, followed by nifedipine and ciprofloxacin (Appendix 1). A total of 5591 reports concerned serious ventricular arrhythmias and/or sudden death (2533 cardiac arrests, 1085 ventricular fibrillations, 1675 ventricular tachycardias, 1031 TDP, and 468 sudden deaths), in which cisapride was the most frequently mentioned suspected drug (>10%). Reports could include more than one ADR term of interest, consequently the numbers do not add up. Ibutilide had the highest proportion of case reports of serious ventricular arrhythmias, and/or sudden death, among all ADR reports concerning this drug (85%). *Table 3* summarizes the characteristics of the case reports of serious ventricular arrhythmias and sudden death (cases), plus all other reports. Cases had a significantly higher $ETCP_{unbound}/IC_{50}$ ratio, patients were older, and ADRs were reported more recently than other reports. In significantly more cases, heart disease was marked as a predisposing factor. Both cases and other reports concerned a slight preponderance of females.

The crude logistic regression analysis revealed a positive association between anti-HERG activity and the risk of serious ventricular arrhythmias, and sudden death. The

Table 3 Characteristics of reports of cardiac arrest, sudden death, TDP, ventricular tachycardia, or ventricular fibrillation (cases) and other reports (non-cases)

	Cases ($n = 5591$)		Non-cases ($n = 278\,835$)		P[a]
$ETCP_{unbound}/IC_{50}$ (mean, SD)	2.24	5.9	0.69	3.6	<0.001
Age (mean, SD)	57.3	18.7	49.6	19.5	<0.001
Gender					
Male (*n*, %)	2 314	41.4	105 902	38.0	<0.001
Female (*n*, %)	2 976	53.2	147 699	53.0	
Unknown (*n*, %)	301	5.4	25 234	9.0	
Reporting year (mean, SD)	1 996	6.0	1 994	6.4	<0.001
Pulmonary disease (*n*, %)	154	2.8	6 037	2.2	0.003
Heart disease (*n*, %)	2 540	45.4	58 269	20.9	<0.001
Diabetes mellitus (*n*, %)	225	4.0	6 029	2.2	<0.001
Drug–drug interaction (*n*, %)	332	5.9	6 132	2.2	<0.001
Use of potassium lowering drugs[b] (*n*, %)	670	12.0	16 170	5.8	<0.001
Years since marketing (mean, SD)	20.8	16.7	19.0	15.6	<0.001

[a]ROR *P*-value of univariable logistic regression of characteristic and composite endpoint.
[b]Non-potassium-sparing diuretics, laxatives, systemic beta-agonists, systemic corticosteroids.

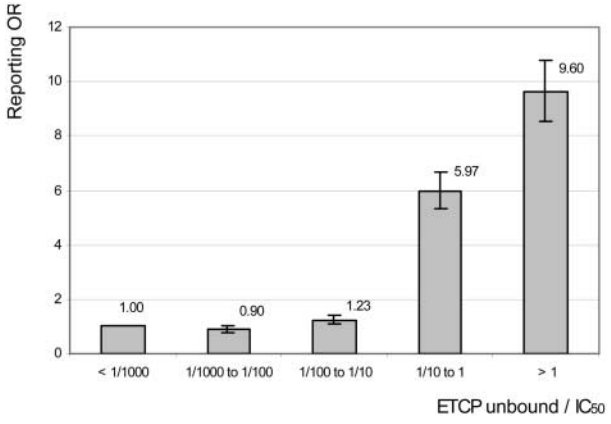

Figure 1 The association between $ETCP_{unbound}/IC_{50}$ ratio and the composite endpoint (cardiac arrest, sudden death, TDP, ventricular tachycardia, or ventricular fibrillation).

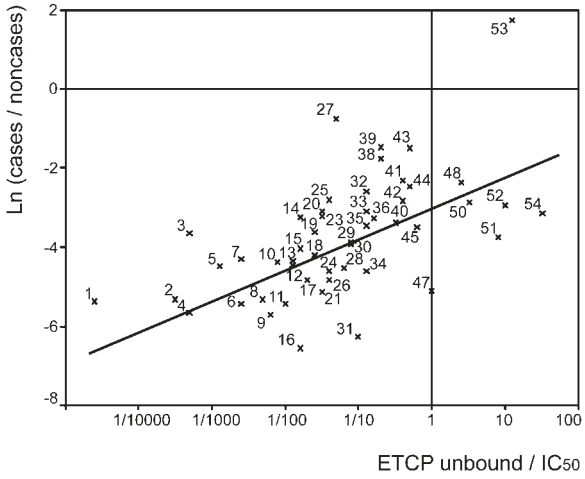

Figure 2 The association between $ETCP_{unbound}/IC_{50}$ ratio and the composite endpoint for the individual drugs (Appendix 1).

ROR for the $\log_{10}$ $ETCP_{unbound}/IC_{50}$ ratio was 1.93 (95% CI 1.89–1.97). After adjustment for age, gender, year of reporting, heart disease, diabetes mellitus, pulmonary disease, pharmacokinetic drug–drug interactions, concomitant use of potentially potassium-lowering drugs, and years between marketing and report, the ROR changed marginally 1.93 (95% CI 1.89–1.98).

When taking an $IC_{50}/ETCP_{unbound}$ ratio of 30, corresponding to a $ETCP_{unbound}/IC_{50}$ ratio of 0.033, as a cut-off point, as suggested by Redfern *et al.*,[5] the adjusted ROR for a ratio over 0.033 vs. a ratio below 0.033 was 3.68 (95% CI 3.47–3.91). This indicates that drugs which bind to HERG potassium channels at levels less than 30 times the therapeutic levels, have a three to four times stronger association with serious ventricular arrhythmias and sudden death as an adverse reaction, compared with drugs which bind to HERG potassium channels at concentrations more than 30 times the therapeutic levels.

In *Figure 1*, anti-HERG activities of the study drugs were grouped into five categories. Adjusted RORs were calculated for these categories using an $ETCP_{unbound}/IC_{50}$ ratio of $<$ 1/1000 as the reference category. The ROR of 5.97 indicates that for drugs for which the IC_{50} is 1 to 10 times higher than the $ETCP_{unbound}$ the risk of reporting serious ventricular arrhythmias and sudden death is six times higher compared with drugs for which the IC_{50} is more than 1000 times higher than the $ETCP_{unbound}$ (reference category).

In *Figure 2*, anti-HERG activities of all individual drugs are plotted against the odds of case-events (cases/non-cases), together with a line describing the fitted logistic model. The label numbers represent the drugs in Appendix 1. Drugs that least followed the predicted pattern were ibutilide (#53), bepridil (#27), amiodarone (#3), sotalol (#39), flecainide (#38) and terfenadine taken concomitantly with CYP3A4 inhibiting drugs (#43) (for which the odds were higher than expected), and aprindine (#47), ketoconazole (#31), and mefloquine (#16) (for which the odds were lower than expected). From this figure it can also be seen that the odds of terfenadine taken concomitantly with CYP3A4 inhibiting drugs (#43)

were much higher than the odds of terfenadine alone (#14). And similarly, that the odds of iv erythromycin (#33) were much higher than the odds of erythromycin taken through other routes of administration (#6).

Subgroup analysis and different study outcomes

Adjusted RORs in studied sub-groups varied between 1.6 and 3.5 and were all significantly higher than one (*Table 4*). The association was stronger in females, patients aged <65, reports of non-anti-arrhythmic drugs, and reports from North American countries. The association decreased when a drug had been longer on the market, and was more pronounced after 1 January 1998 than before that date.

When the five study outcomes were regarded separately, adjusted RORs varied between 1.7 and 2.6. QTc-prolongation, a precursor for drug-induced arrhythmias, was also strongly associated with anti-HERG activity (adjusted ROR 2.7). When less well-defined endpoints were used, the association weakened. Anti-HERG activity showed no association with either of the negative control endpoints: hepatitis and skin ulcer (*Table 4*).

Discussion

We identified a significant association of 1.93 (95% CI 1.89–1.98) between the anti-HERG activity of drugs, measured as $\log_{10}$ ($ETCP_{unbound}/IC_{50}$), and reporting of serious ventricular arrhythmias and sudden death, to the WHO-UMC database.

Our findings support the hypothesis that anti-HERG activity is associated with risk of serious ventricular arrhythmias, and sudden death, in daily clinical practice. As expected, drugs which bind to HERG potassium channels in concentrations close to therapeutic plasma concentrations, have a high risk of reports of serious ventricular arrhythmias and sudden death, probably indicating a pro-arrhythmic effect. The smaller the margin between IC_{50} (toxic drug level) and $ETCP_{unbound}$ value (therapeutic drug level), the higher the risk (*Figure 1*). The ORs in this study represent a relative risk, but do not estimate the actual pro-arrhythmic risk in day-to-day practice. They reflect the disproportionality of serious ventricular arrhythmias, and sudden death, as an ADR among all possible ADRs of a certain drug. The overall OR of 1.93 indicates that for every single unit increase in the $\log_{10}$ (e.g. from 1/1000 to 1/100, from

Table 4 Association between $\log_{10}$ ($ETCP_{unbound}/IC_{50}$) and serious ventricular arrhythmias or sudden death for several sub-groups and between $\log_{10}$ ($ETCP_{unbound}/IC_{50}$) and several study endpoints

$\log_{10}$ ($ETCP_{unbound}/IC_{50}$)	OR_{crude}	95%	CI	OR_{adj} [a]	95%	CI
Overall[b]	1.93	1.89	1.97	1.93	1.89	1.98
Subgroups[b]						
Males	1.74	1.68	1.80	1.76	1.70	1.83
Females	2.08	2.02	2.14	2.08	2.01	2.15
Age <65	2.08	2.02	2.14	2.06	1.99	2.12
Age ≥65	1.66	1.60	1.71	1.78	1.71	1.84
Anti-arrhythmic drugs	1.39	1.34	1.44	1.73	1.66	1.80
Other medication	2.02	1.97	2.08	2.01	1.96	2.07
Europe	1.85	1.78	1.93	1.79	1.72	1.87
North America	2.05	1.99	2.10	2.03	1.97	2.09
Rest of the world	1.60	1.46	1.76	1.58	1.42	1.77
1st year after marketing	3.56	2.91	4.34	3.50	2.48	4.94
≤5 years after marketing	2.91	2.72	3.11	2.06	1.88	2.26
>10 years after marketing	1.71	1.67	1.75	1.83	1.78	1.88
>20 years after marketing	1.46	1.41	1.50	1.59	1.54	1.65
Reported before 1 Jan 1998	1.79	1.74	1.84	1.74	1.67	1.80
Reported after 1 Jan 1998	2.29	2.21	2.37	2.20	2.12	2.28
Different case-definitions						
Cardiac arrest	1.80	1.74	1.86	1.80	1.74	1.86
Sudden death	1.62	1.50	1.75	1.74	1.60	1.89
TDP	2.21	2.10	2.32	2.34	2.22	2.49
Ventricular tachycardia	2.04	1.96	2.12	2.01	1.92	2.10
Ventricular fibrillation	2.34	2.23	2.45	2.61	2.47	2.76
QT-prolongation	2.27	2.18	2.37	2.73	2.61	2.86
Cardiac fibrillation	1.63	1.20	2.21	1.57	1.14	2.17
Ventricular arrhythmia	1.54	1.44	1.65	1.48	1.38	1.59
Syncope	1.24	1.21	1.28	1.23	1.19	1.26
Hepatitis	1.02	0.99	1.05	0.97	0.94	1.00
Skin ulcer	1.06	0.91	1.24	1.06	0.92	1.24

[a]Adjusted for age, gender, year of reporting, heart disease, diabetes mellitus, pulmonary disease, metabolic drug–drug interactions, concomitant use of potassium-lowering drugs, and years between marketing and report.

[b]Composite endpoint: cardiac arrest, sudden death, TDP, ventricular tachycardia, ventricular fibrillation.

1/100 to 1/10, etc) of the therapeutic/toxic ratio of a drug, the risk of reporting serious ventricular arrhythmias, and sudden death, doubles.

Previously, several studies have shown that female gender is a rather strong predictor for drug-induced TDP, since ~70% of the published case reports concerned women.[12,13] In the present study, we found that (of the ADR reports with known gender of the patient) 56% of the case patients were female, compared with 58% of the patients experiencing other ADRs. We used, however, a composite endpoint which included, apart from TDP: cardiac arrest, sudden death, ventricular fibrillation, and ventricular tachycardia. When we focused solely on the ADR-reports of TDP, we found that more than 68% of these reports concerned females.

General limitations of the dataset should be discussed. First, the study was restricted to drugs for which HERG binding properties as well as therapeutic free plasma concentrations have been studied, and published. The number of drugs being tested for HERG-activities is still increasing and these analyses should be repeated when more data are available. Secondly, the $ETCP_{unbound}/IC_{50}$ ratios were based on therapeutic plasma levels at recommended doses. The case reports in the WHO-UMC database, however, do not disclose in sufficient detail the doses used by these patients. Plasma levels may increase when pharmacokinetic drug–drug interactions occur or alternative routes of administration are used. Specific anti-HERG activities were only known for terfenadine plus CYP3A4 inhibitors, and iv erythromycin. Uncertainty of actual plasma levels may have influenced our results.

The method of reaction proportion signalling has several drawbacks. ADRs were reported on a voluntary basis, and therefore represented only a fraction ($<$10%) of the actual adverse events that occurred.[14,15] Selective under- and over-reporting of particular ADRs within the overall under-reporting can lead to misinterpretations when comparing drugs with respect to ADRs. ADRs which are more likely than others to be reported are ADRs of relatively new drugs[10,16] severe ADRs,[14,16] and ADRs which are not listed in the summary of product characteristics.[14] All these aspects can be seen in the subgroup analyses we performed. The association was stronger shortly after marketing, and it was less well pronounced among patients taking anti-arrhythmic drugs, for which the pro-arrhythmic side-effects have been already described (*Table 4*). The association weakens when the study event is less severe (syncope vs. ventricular arrhythmia). Another factor which may have influenced our results is selective reporting as a result of media attention. This factor has been described previously for the association between cardiac arrhythmias and the use of anti-histamine drugs,[11] and similarly in our study the association between exposure and outcome is stronger after 1 January 1998 than before.

We did not, of course, study the effects of individual drugs, but the *in vitro* anti-HERG activities of drugs, and combinations of drugs. These molecular properties of drugs are unlikely to be known by healthcare providers in daily practice. We therefore think that we have used a more objective exposure measure, which is less susceptible to recognized bias. Moreover, all sub-group analyses point in a similar direction and negative control outcomes which should not be related to anti-HERG activity (hepatitis, skin ulcer) are indeed unrelated to the exposure. We therefore believe that our findings represent a true connection.

There were several drugs that appeared not to follow the predicted association. Their observed cases/non-cases ratios were relatively high or low compared with the ratios fitted by our logistic model (Appendix 1, *Figure 2*). For ibutilide, bepridil, amiodarone, sotalol, and flecainide, the cases/non-cases ratio is higher than expected. These drugs are prescribed to patients with cardiac diseases and therefore 'confounding by indication' may have caused this relatively high fraction of 'case-events'. In addition, only less than 200 case reports were used to estimate the ratio for ibutilide and bepridil. Slightly more than 300 case reports were used to estimate the cases/non-cases ratio for combination of terfenadine and CYP3A4 inhibiting drugs. This relatively high ratio may have been caused by selective reporting of ADRs due to media attention for cardiac arrhythmias associated with the combined use of these drugs. For ketoconazole, mefloquine, and aprindine the fraction of 'case-events' in the WHO-UMC database is much lower than expected, based on anti-HERG activity. These drugs could be regarded as drugs with 'false positive' anti-HERG activities. For ketoconazole this effect was described before.[5] However, the low ratio may also be explained by the fact that there were relatively many ADR reports of 'skin and appendages disorders' as well as 'liver and biliary system disorders', competing with the ADRs of our interest to stand out disproportionately against all other case reports. Both ADRs counted for 23% of all ADRs that were reported for ketoconazole, whereas the percentages among the case reports of all studied drugs together were 12 and 4%, respectively. Similarly the relatively high proportion of case reports of 'psychiatric disorders' (31% for mefloquine vs. 13% overall) and 'central and peripheral nervous system disorders' (25% for mefloquine vs. 14% overall) could have competed with the ADRs of our interest.

Drugs that bind to HERG potassium channels in concentrations close to or lower than therapeutic plasma concentrations (i.e. have a high $\log_{10}$ $ETCP_{unbound}/IC_{50}$ ratio) have a high risk of reports of serious ventricular arrhythmias, and sudden death, in the WHO-UMC database, indicating a higher pro-arrhythmic risk. The higher the IC_{50} (toxic drug level) compared with the $ETCP_{unbound}$ value (therapeutic drug level), the higher this risk. These findings support the value of pre-clinical HERG testing for predicting pro-arrhythmic effects of medicines.

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Appendix 1 Study drugs and anti-HERG activities

Drug name	1st year marketed (17)	$ETCP_{un\text{-}bound}$ (nM)	IC_{50} (μM)	Ratio[a]	log^{10} (ratio)	Cases	Non-cases
1. Nifedipine	1975	7.7	275	0.00003	−4.6	94	20 437
2. Nitrendipine	1985	3.02	10	0.00030	−3.5	3	610
3. Amiodarone	1962	0.5	1	0.00050	−3.3	271	10 467
4. Cetirizine	1987	56	108	0.00052	−3.3	18	5 217
5. Diphenhydramine	1946	34	30	0.00113	−2.9	37	3 296
6. Erythromycin	1952	170	72.2	0.00235	−2.6	54	12 173
7. Loratadine	1988	0.45	0.173	0.00260	−2.6	58	4 265
8. Ciprofloxacin	1987	5 281	966	0.00547	−2.3	72	14 936
9. Chlorpheniramine	1968	11	1.6	0.00688	−2.2	13	3 915
10. Amitriptyline	1961	41	4.66	0.00880	−2.1	92	7 301
11. Fluoxetine	1986	29	3.1	0.00935	−2.0	203	45 834
12. Risperidone	1993	1.81	0.15	0.0121	−1.9	143	12 254
13. Diltiazem	1973	122	10	0.0122	−1.9	145	11 282
14. Terfenadine	1982	0.29	0.02	0.0145	−1.8	200	5 162
15. Ebastine	1990	5.1	0.3	0.0170	−1.8	2	112
16. Mefloquine	1986	95.2	5.6	0.0170	−1.8	12	8 399
17. Tamoxifen	1973	21	1	0.0210	−1.7	69	8 504
18. Olanzapine	1996	5.2	0.231	0.0225	−1.6	136	8 994
19. Mizolastine	1998	8.7	0.35	0.0249	−1.6	6	222
20. Pimozide	1969	0.43	0.015	0.0287	−1.5	22	482
21. Imipramine	1958	106	3.4	0.0312	−1.5	21	3 576
22. Tedisamil	—	80	2.5	0.0320	−1.5	0	1
23. Mibefradil	1997	12	0.35	0.0343	−1.5	95	2 370
24. Clarithromycin	1990	1 206	32.9	0.0367	−1.4	115	11 473
25. Cibenzoline	1985	976	23	0.0424	−1.4	13	214
26. Phenytoin	1938	4 360	100	0.0436	−1.4	118	14 578
27. Bepridil	1981	33	0.6	0.0550	−1.3	59	125
28. Fexofenadine	1996	345	5	0.0690	−1.2	24	2 224
29. Grepafloxacin	1997	2 087	27	0.0773	−1.1	6	287
30. Desipramine	1962	108	1.39	0.0777	−1.1	41	2 111
31. Ketoconazole	1981	177	1.9	0.0932	−1.0	9	4 734
32. Sertindole	1996	1.59	0.014	0.114	−0.9	20	266
33. Erythromycin i.v.	1952	8 516	72.2	0.118	−0.9	75	1 671
34. Domperidone	1978	19	0.16	0.119	−0.9	12	1 216
35. Haloperidol	1959	3.6	0.027	0.133	−0.9	247	7 864
36. Procainamide	1950	54 186	310	0.175	−0.8	101	2 652
37. Sematilide	—	4 449	25	0.178	−0.7	0	0
38. Flecainide	1982	753	3.91	0.193	−0.7	332	1 894
39. Sotalol	1974	14 733	74	0.199	−0.7	337	1 477
40. Astemizole	1983	0.26	0.0009	0.289	−0.5	68	1 974
41. Dofetilide	1999	2	0.005	0.400	−0.4	68	676
42. Disopyramide	1969	742	1.8	0.412	−0.4	110	1 843
43. Terfenadine & CYP3A4-inhibitor	1982	9	0.02	0.450	−0.3	60	264
44. Propafenone	1979	241	0.44	0.548	−0.3	97	1 146
45. Verapamil	1963	81	0.14	0.579	−0.2	332	10 788
46. Azimilide	1999	70	0.1	0.700	−0.2	0	0
47. Aprindine	1973	239	0.23	1.04	0.0	1	164
48. Cisapride	1988	4.9	0.002	2.45	0.4	596	6 278
49. Almokalant	—	150	0.05	3.00	0.5	0	0
50. Terodiline	1986	12	0.004	3.00	0.5	66	1 160
51. Sparfloxacin	1993	1 766	0.23	7.68	0.9	10	420
52. Quinidine	1918	3 237	0.3	10.8	1.0	181	3 399
53. Ibutilide	1996	140	0.01	14.0	1.1	154	27
54. Thioridazine	1958	979	0.033	29.7	1.5	152	3 520
>1 drug						421	4 581
Total						5 591	278 835

[a] $ETCP_{unbound}/IC_{50}$.

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