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Multiple categories of non-cardiac QT-prolonging drugs are associated with increased risk of out-of-hospital cardiac arrest: real-world data from a population-based study

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Aim Drugs causing QT-prolongation as off-target effect [non-cardiac QT-prolonging drugs (QT-drugs)] increase the risk of out-of-hospital cardiac arrest (OHCA). Such drugs are categorized in multiple clinically widely used CredibleMeds.org lists. Category 1 ('known risk of Torsade de Pointes') and category 2 ('possible risk of Torsade de Pointes') are of particular clinical relevance. However, a category-stratified analysis of OHCA-risk is presently unavailable.

Methods and results We conducted a case–control study with OHCA-cases from presumed cardiac causes included from the ARREST registry in the Netherlands (2009–2018) that was specifically designed to study OHCA, and age/sex/OHCA-date matched non-OHCA-controls. Adjusted odds ratios for OHCA (OR_{adj}) of QT-drugs from categories 1 or 2 were calculated, using conditional logistic regression. Stratified analysis was performed according to sex, age, and presence of cardiovascular drugs (proxy for cardiovascular disease). We included 5473 OHCA-cases (68.8 years, 69.9% men) and matched them to 20 866 non-OHCA-controls. Compared with no use of non-cardiac QT-drugs, drugs of both categories were associated with increased OHCA-risk, but seemingly weaker for category 2 {category 1: case 3.2%, control 1.4%, OR_{adj} 1.7 [95% confidence interval (CI): 1.3–2.1]}; [category 2: case 7.3%, control 4.0%, OR_{adj} 1.4 (95% CI: 1.2–1.6)]. The increased risk occurred in men and women, at all ages (highest in patients aged ≤50 years), and both in the presence or absence of cardiovascular drug use.

Conclusion Both category 1 and category 2 QT-drugs are associated with increased OHCA-risk in both sexes, at all ages, and in patients taking or not taking cardiovascular drugs.

Keywords Sudden cardiac arrest • Out-of-hospital cardiac arrest • Non-cardiac QT-prolonging drugs • ESCAPE-NET

Introduction

Out-of-hospital cardiac arrest (OHCA) accounts for 50% of all deaths from cardiovascular causes in industrialized countries.[1] Most OHCA events result from cardiac arrhythmia (ventricular tachycardia/ventricular fibrillation) secondary to disruptions in cardiac electrophysiology.[2] Drugs that impair cardiac repolarization and prolong the QT interval of the ECG (QT-drugs) may induce such disruptions and cause OHCA by blocking cardiac ion channels, in particular, potassium channels.[3] This block is the designed mode of action of some cardiac drugs (drugs used to treat cardiac conditions), in particular, Vaughan–Williams class 1 and 3 antiarrhythmic drugs.

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What's new?

- This is the first study to specifically investigate the category-stratified risk of out-of-hospital cardiac arrest (OHCA) of non-cardiac QT-prolonging drugs from CredibleMeds.org categories 1 ('known risk of Torsade de Pointes') and 2 ('possible risk of Torsade de Pointes').
- Use of non-cardiac QT-prolonging from both categories 1 and 2 is associated with increased OHCA-risk.
- The increased OHCA-risk occurs in both sexes and age groups (highest in patients aged ≤50 years), and in patients with or without cardiovascular disease.

Importantly, it also occurs as off-target effect of numerous drugs prescribed to treat non-cardiac conditions (non-cardiac QT-drugs). This is clinically relevant, because non-cardiac QT-drugs are often prescribed, and prescribers (typically, non-cardiologists) have limited awareness of this potential risk and/or the means to take risk-mitigating actions (e.g. cardiologic workup to identify vulnerable individuals). Accordingly, several studies showed an increased OHCA-risk in patients receiving non-cardiac QT-drugs drugs,[4–7] e.g. antipsychotics,[5] antidepressants,[6] and antibiotics.[7] With the aim of minimizing this adverse drug effect and individualizing drug prescription, researchers of the Centre for Education on Research and Therapeutics at the University of Arizona Health Sciences Center (AZCERT) developed an internet-based registry (www.CredibleMeds.org) which provides up-to-date lists of all QT-drugs.[8–10] In this registry, QT-drugs are classified into four risk categories based on their reported potential to cause Torsade des Pointes (TdP), the ventricular tachycardia that results from excessive QT-prolongation.[8–10] This registry has become an invaluable tool for practicing clinicians, patients, and investigators involved in OHCA research, and is used as a clinical decision support tool in healthcare, particularly when non-cardiac drug use is considered.[8,9] Yet, it is unknown whether the classification into these categories reflects OHCA-risk on a population level. Filling this knowledge gap is clearly needed given the widespread use of the CredibleMeds lists.[8,9] Therefore, we aimed to investigate the association between OHCA-risk and use of non-cardiac QT-drugs from the two highest risk categories [category 1 ('known risk of TdP') and 2 ('possible risk of TdP')] using real-world data from a large population-based OHCA-registry.

Methods

Study design and setting

We conducted a population-based case–control study. Cases were individuals who suffered OHCA from presumed cardiac causes included in the AmsteRdam REsuscitation STudies (ARREST[11]) registry study in 2009–2018. This registry includes all Emergency Medical Services (EMS) attended victims of OHCA from presumed cardiac causes, excluding OHCAs from obvious non-cardiac causes (e.g. drowning, trauma), those from which data on drug use could not be retrieved (patient's pharmacy could not be retrieved or refused participation), and those of surviving patients who did not consent to their data being used. Each eligible OHCA-case was matched with up to five non-OHCA-control sampled from the PHARMO Database Network[12] using exact matching on year of birth, sex, and index-date (OHCA-date). This study was conducted based on the principles expressed in the Declaration of Helsinki. Written informed consent was obtained from those who survived the OHCA. The Medical Ethics Review Board of the Academic Medical Center, Amsterdam, approved the study, including the use of data from patients who did not survive OHCA.

Data sources

Cases

The ARREST registry[11] is an ongoing population-based registry that prospectively enrols all EMS-attended OHCAs from one large region in the Netherlands (North Holland province, covering both urban and rural areas and containing 2.4 million individuals) in co-operation with all dispatch centres, ambulance personnel, and hospitals in the study region according to Utstein recommendations. After each suspected OHCA, ARREST study personnel is notified by the dispatch centre. The EMS personnel routinely provide dispatch forms and run sheets, and call the ARREST study centre to provide information on the location and circumstances of OHCA. All OHCAs were deemed to have a cardiac cause unless an obvious non-cardiac cause was documented. Complete data on drug use in the year before OHCA were obtained from drug-dispensing records from the patient's community pharmacy using standardized protocols. A detailed description of the ARREST registry is provided elsewhere.[11]

Controls

The PHARMO Database Network is a population-based network of healthcare databases that combine different healthcare settings, including community pharmacies and hospitals.[12] For this study, we obtained complete drug-dispensing records in the year before the index-date for the controls.

Exposure of interest

We defined the use of non-cardiac QT-drugs (following the Anatomical Therapeutic Classification System) as having a drug-dispensing record within 90 days before index-date, since, in the Netherlands the average repeat prescription length for drugs used for chronic disease is 90 days. For antimicrobial, gastrointestinal, and antiemetic drugs, we shortened this exposure period to ≤14 days (antimicrobial agents) or 7 days (gastrointestinal, antiemetic drugs) prior to index-date, because these drugs are generally prescribed for shorter periods. A list of non-cardiac QT-drugs was retrieved from the www.crediblemeds.org (accessed date 10 July 2019) website,[10] which classifies QT-drugs into four risk categories based on their ability to cause TdP.[8–10] For this study, we analysed OHCA-risk of non-cardiac QT-drugs. Exposure of interest was defined as use of non-cardiac QT-drugs from categories 1 and/or 2. Category 1 drugs are defined at www.crediblemeds.org as 'drugs that prolong the QT interval and are clearly associated with a known risk of TdP, even when taken as recommended'. Category 2 drugs are defined as 'drugs that can cause QT prolongation but currently lack evidence for a risk of TdP when taken as recommended'. The OHCA-risk of QT-drugs from categories 3 ('Conditional risk of TdP') and 4 ('Drugs to avoid in congenital Long QT syndrome') was not analysed.

Covariates

We included cardiovascular disease and diabetes mellitus in our multivariable analysis, using drug proxies, because both are well-known risk factors for OHCA. Presence of cardiovascular disease was defined by use of following cardiovascular drugs within 6 months before index-date: beta-blockers, calcium blockers, renin–angiotensin system inhibitors, diuretics, nitrates, antithrombotics, and/or statins. Presence of diabetes mellitus

Table 1 Baseline characteristics of cases and controls

	OHCA-cases	Non-OHCA-controls
Total	5473	21 866
Mean age, years (standard deviation)	68.8 (14.0)	68.8 (14.0)
Male sex	3823 (69.9)	15 263 (69.8)
Cardiovascular drugs	3513 (64.2)	8548 (39.1)
Beta-blockers	1998 (36.5)	3839 (17.6)
Calcium channel blockers	902 (16.5)	2016 (9.2)
Antithrombotics	2299 (42.0)	4853 (22.2)
Diuretics	1590 (29.1)	2712 (12.4)
Renin–angiotensin system inhibitors	2073 (37.9)	4802 (22.0)
Nitrates	574 (10.5)	841 (3.9)
Statins	1843 (33.7)	4609 (21.1)
Antidiabetics	936 (17.1)	2145 (9.8)
Antiarrhythmic drugs Vaughan–Williams class 1 or 3	114 (2.1)	183 (0.8)
Anti-epileptic drugs	205 (3.8)	383 (1.8)
Antidepressant drugs	369 (6.7)	918 (4.2)
Antipsychotic drugs	186 (3.4)	279 (1.3)

Numbers are number (%) unless indicated otherwise. Use of cardiovascular drugs and/or antidiabetics was defined as use within 6 months before the index-date. Use of Vaughan–Williams class 1 or 3 antiarrhythmic drugs, anti-epileptics, antidepressants, and antipsychotics was defined as use within 90 days before the index-date.
OHCA, out-of-hospital cardiac arrest.

was defined as the use of any antidiabetic drug within 6 months prior to index-date. Furthermore, we included the use of Vaughan–Williams antiarrhythmic drugs class 1 or 3, antidepressants, antipsychotics, and anti-epileptics as confounders, as defined by having a drug-dispensing record within 90 days prior to index-date. We chose this period since we were interested in the current use in order to adjust for the direct cardiac electrophysiological effects of these drugs.[4–6] Cardiovascular drugs and antidiabetics were considered as a proxy for cardiovascular disease and diabetes mellitus, respectively, therefore the exposure window was set at 6 months prior to index-date.

Statistical analysis

Differences in baseline characteristics between cases and controls were tested using the χ^2 test for binary variables and the independent *t*-test for continuous variables. A two-sided *P*-value was considered significant. We used conditional (multivariable) logistic regression analysis to estimate the association between non-cardiac QT-drugs and OHCA-risk by calculating the odds ratio (OR) and 95% confidence interval (CI), employing two models. In model 1, estimates were calculated as crude ORs (univariate model). In model 2, estimates were adjusted for concomitant use of any drug listed in *Table 1* (multivariable model). We examined the association between OHCA and non-cardiac QT-drugs (category 1 or 2 or both) compared with no use of non-cardiac QT-drugs. We also examined whether patient profiles were different between users of category 1 drugs and users of category 2 drugs by assessing concomitant drug use as a proxy for comorbidities to identify whether differences in patient properties result in differences in *a priori* OHCA-risk of both drug categories. Next, we conducted stratified analysis according to age, presence of cardiovascular drugs, and age. We assessed potential interactions of non-cardiac QT-drugs from categories 1 or 2 with sex, age (≤50, 51–69, and ≥70 years), and use of cardiovascular drugs by consecutively entering the cross-products of the two factors into the multivariable models. In the stratified analyses assessing the association with OHCA in individuals with or without cardiovascular drugs use, we used multivariable logistic regression analyses additionally adjusted for age and sex, as matching is lost by sub-selecting all individuals with or without cardiovascular drugs use from the original case–control data set.

Results

Patient characteristics

We identified 10 077 OHCA-cases from presumed cardiac causes. From these, information regarding drug use could not be obtained for 3880 OHCA-cases, while 283 OHCA-cases were excluded because they were foreigners. We included 5473 OHCA-cases (mean age 68.8 year, 69.9% male, *Table 1*) and matched them to 20 866 non-OHCA-controls (*Figure 1*). Cases had a higher prevalence of cardiovascular drug use than controls (*Table 1*). Furthermore, the prevalence of the use of antidiabetics, antipsychotics, antidepressants, and anti-epileptics was higher among cases than controls.

Estimated odds ratios of out-of-hospital cardiac arrest for different categories of non-cardiac QT-drugs

Use of category 1 non-cardiac QT-drugs (case: 3.2% control: 1.4%) was associated with increased OHCA-risk [OR_{adj} 1.7 (95% CI 1.3–2.1), *Table 2*] when compared with no use of non-cardiac QT-drugs. This also applied to use of category 2 non-cardiac QT-drugs (case: 7.3% control: 4.0%), although OHCA-risk appeared to be less elevated [OR_{adj} 1.4 (95% CI 1.2–1.6)]. The use of >1 non-cardiac QT-drug from either category was associated with an even higher risk (*Table 2*). Next, we studied whether patient characteristics were different between users of category 1 and 2 non-cardiac QT-drugs. We found higher prevalence of men and use of antiarrhythmic drugs Vaughan–Williams class 1 or 3 among users of category 2 drugs,

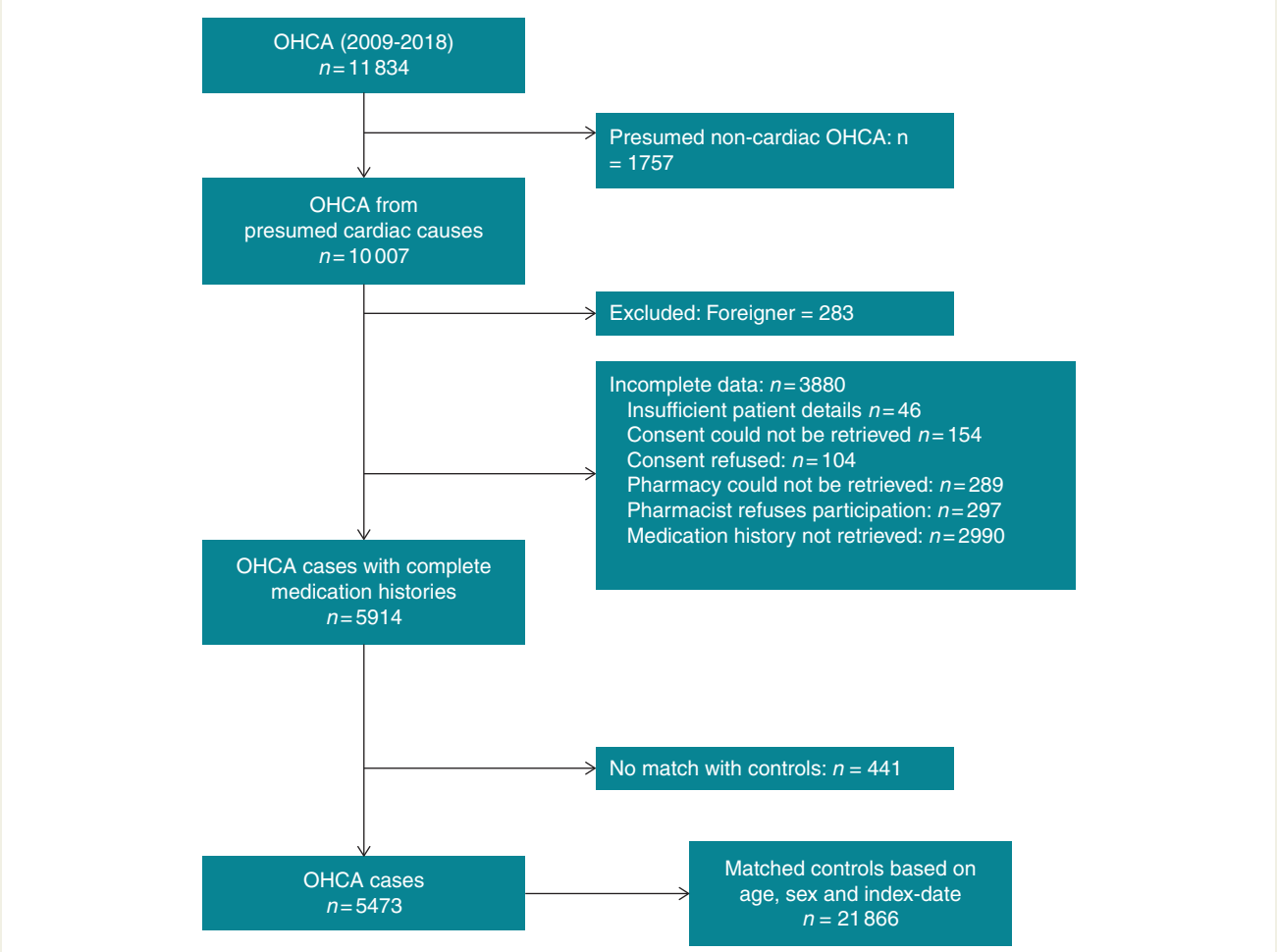

Figure 1 Flow chart of inclusion of out-of-hospital cardiac arrest (OHCA) cases and controls.

Table 2 Use of non-cardiac QT drugs of categories 1 and/or 2 and the risk of out-of-hospital cardiac arrest (OHCA)

	OHCA-cases (*n* = 5473)	Non-OHCA-controls (*n* = 21 866)	Crude OR	Adjusted OR
No use of non-cardiac QT-drug	4836 (88.4)	20 624 (94.3)	1.0 (reference)	1.0 (reference)
Use of non-cardiac QT-drugs from category 1	175 (3.2)	301 (1.4)	2.5 (2.1–3.0)	1.7 (1.3–2.1)
1 QT-drug from category 1	166 (3.0)	298 (1.4)	2.4 (2.0–2.9)	1.6 (1.3–2.0)
>1 QT-drugs from category 1	9 (0.2)	3 (0.01)	12.7 (3.4–46.8)	9.7 (2.5–37.8)
Use of non-cardiac QT-drugs from category 2	401 (7.3)	868 (4.0)	2.0 (1.7–2.2)	1.4 (1.2–1.6)
1 QT-drug from category 2	347 (6.3)	785 (3.6)	1.9 (1.7–2.2)	1.4 (1.2–1.6)
>1 QT-drugs from category 2	54 (1.0)	83 (0.4)	2.7 (1.9–3.9)	2.0 (1.3–2.9)
Use of non-cardiac QT-drugs from both category 1 and category 2	61 (1.1)	73 (0.3)	3.5 (2.5–4.9)	2.2 (1.5–3.3)

OR, odds ratio.

while the prevalence of diuretics, antidepressants, and antipsychotic drugs was higher among users of category 1 drugs (*Table 3*). The OR_{adj} for OHCA for the most commonly used individual non-cardiac QT-drugs are provided in *Table 4*. Here, we found that increased OHCA-risk upon use of category 1 QT-drugs was mainly determined by domperidone and ciprofloxacin, i.e. these were the most widely used drugs with significantly increased OHCA-risk [OR_{adj} 3.9 (95% 2.0–7.8)], and OR_{adj} 2.0 (95% 1.05–3.7), respectively. Increased OHCA-risk of category 2 QT-drugs was mainly determined by mirtazapine [OR_{adj} 1.6 (95% 1.05–2.6), *Table 4*].

Table 3 Characteristics of users of non-cardiac QT-drugs from categories 1 and 2

	Category 1 QT-drugs	Category 2 QT-drugs	*P*-value
Total	476	1269	
Mean age, years (standard deviation)	71.4 (14.0)	71.0 (13.0)	0.62
Male sex	292 (61.3)	864 (68.1)	0.01
Cardiovascular drugs	345 (72.5)	904 (71.2)	0.61
Beta blockers	172 (36.1)	444 (35.0)	0.66
Calcium channel blockers	90 (18.9)	237 (18.7)	0.91
Antithrombotics	221 (46.4)	578 (45.6)	0.74
Diuretics	174 (36.6)	383 (30.2)	0.01
Renin–angiotensin system inhibitors	168 (35.3)	502 (40.0)	0.10
Nitrates	57 (12.0)	130 (10.2)	0.30
Statins	167 (35.1)	461 (36.3)	0.63
Antidiabetics	112 (23.5)	264 (20.8)	0.22
Antiarrhythmic drugs class 1 or 3	5 (1.1)	34 (2.7)	0.04
Anti-epileptic drugs	46 (9.7)	104 (8.2)	0.33
Antipsychotic drugs	125 (26.3)	193 (15.2)	<0.0001
Antidepressant drugs	224 (47.1)	441 (34.8)	<0.0001

Numbers are expressed as *n* (%) unless indicated otherwise.

Table 4 Risk for out-of-hospital cardiac arrest of the most commonly used non-cardiac QT-prolonging drugs from categories 1 or 2 compared with no use of non-cardiac QT-prolonging drugs

	Cases (*n* = 5473)	Controls (*n* = 21 866)	Crude OR (95% CI)	Adjusted OR (95% CI)
No use of non-cardiac QT-drugs	4836 (88.4)	20 624 (94.3)	1.0 (reference)	1.0 (reference)
Use of category 1 non-cardiac QT-drug				
Citalopram	37 (0.7)	115 (0.5)	1.4 (0.9–2.0)	0.9 (0.6–1.4)
Haloperidol	33 (0.6)	51 (0.2)	2.8 (1.8–4.3)	1.2 (0.7–2.2)
Ciprofloxacin	19 (0.4)	31 (0.1)	2.6 (1.5–4.7)	2.0 (1.05–3.7)
Domperidone	20 (0.4)	19 (0.1)	4.7 (2.5–8.8)	3.9 (2.0–7.8)
Escitalopram	10 (0.2)	26 (0.1)	1.6 (0.8–3.3)	1.3 (0.7–2.2)
Use of category 2 non-cardiac QT-drug				
Tramadol	82 (1.5)	161 (0.7)	2.2 (1.6–2.8)	1.4 (1.1–1.9)
Alfuzosin	46 (0.8)	163 (0.8)	1.2 (0.9–1.7)	0.9 (0.6–1.3)
Mirtazapine	37 (0.7)	81 (0.4)	2.0 (1.3–2.9)	1.6 (1.05–2.6)
Venlafaxine	26 (0.5)	68 (0.3)	1.6 (1.04–2.6)	1.4 (0.8–2.3)
Tolterodine	7 (0.1)	35 (0.2)	0.9 (0.4–1.9)	0.5 (0.2–1.2)

Numbers in table are expressed as number (%) unless indicated otherwise.
CI, confidence interval; OR, odds ratio.

Stratified analysis

Stratified analyses according to sex showed that the associations between both categories of non-cardiac QT-drugs and OHCA-risk were similar in men and women (*Table 5*). Stratification according to age revealed that OHCA-risk upon use of non-cardiac QT-drugs of either category was elevated across all age groups. However, this risk decreased with aging [Category 1: $OR_{\leq 50}$ 3.2 (95% CI 1.4–7.5); OR_{51-69} 1.8 (95% CI 1.3–2.8); $OR_{\geq 70}$ 1.5 (95% 1.1–2.1), *P*-value interaction <0.01; Category 2: $OR_{\leq 50}$ 3.1 (95% CI 1.7–5.9); OR_{50-70} 1.6 (95% CI 1.2–2.0); $OR_{\geq 70}$ 1.3 (95% 1.1–1.6), *P*-value interaction <0.01, *Table 6*]. Finally, when we stratified according to cardiovascular drug use, we found that OHCA-risk associated with use of non-cardiac QT-drugs of categories 1 and 2 was elevated regardless of use of cardiovascular drugs (*Table 7*).

Discussion

In this observational study with real-world data from a large population-based OHCA-registry, we found that non-cardiac QT-

Table 5 Risk for out-of-hospital cardiac arrest (OHCA) associated with use of non-cardiac QT-drugs of categories 1 and/or 2: stratification according to sex

	OHCA-cases ($n = 5473$)	Non-OHCA-controls ($n = 21\,866$)	Crude OR	Adjusted OR
Men	3823	15263		
No use of non-cardiac QT-drug	3422 (89.5)	14 431 (94.6)	1.0 (reference)	1.0 (reference)
Use of non-cardiac QT-drugs from category 1	103 (2.7)	189 (1.2)	2.3 (1.8–3.0)	1.7 (1.3–2.3)
Use of non-cardiac QT-drugs from category 2	264 (6.9)	600 (3.9)	1.9 (1.6–2.2)	1.4 (1.2–1.7)
Use of non-cardiac QT-drugs from both category 1 and category 2	34 (0.9)	43 (0.3)	3.2 (2.1–5.1)	2.2 (1.3–3.6)
Woman	1650	6603		
No use of non-cardiac QT-drug	1414 (85.7)	6193 (93.8)	1.0 (reference)	1.0 (reference)
Use of non-cardiac QT-drugs from category 1	72 (4.4)	112 (1.7)	2.8 (2.1–3.8)	1.6 (1.1–2.3)
Use of non-cardiac QT-drugs from category 2	137 (8.3)	268 (4.1)	2.2 (1.8–2.7)	1.4 (1.1–1.8)
Use of non-cardiac QT-drugs from both category 1 and category 2	27 (1.6)	30 (0.5)	3.9 (2.3–6.6)	2.3 (1.2–4.3)

P-value interaction: category 1: 0.5875, category 2: 0.3276, and categories 1 and 2 combined: 0.5519.

Table 6 Risk for out-of-hospital cardiac arrest (OHCA) associated with use of non-cardiac QT-drugs of categories 1 and/or 2: stratification according to age

	OHCA-cases ($n = 5473$)	Non-OHCA-controls ($n = 21866$)	Crude OR	Adjusted OR
≤50 years	525	2100		
No use of non-cardiac QT-drug	463 (88.2)	2016 (96.0)	1.0 (reference)	1.0 (reference)
Use of non-cardiac QT-drugs from category 1	13 (2.5)	19 (0.9)	2.9 (1.4–5.6)	3.2 (1.4–7.5)
Use of non-cardiac QT-drugs from category 2	41 (7.8)	58 (2.8)	3.1 (2.1–4.8)	3.1 (1.7–5.9)
Use of non-cardiac QT-drugs from both category 1 and category 2	8 (1.5)	7 (0.3)	5.8 (1.9–17.8)	4.2 (1.1–16.2)
51–69 years	2138	8548		
No use of non-cardiac QT-drug	1897 (88.7)	8138 (95.2)	1.0 (reference)	1.0 (reference)
Use of non-cardiac QT-drugs from category 1	69 (3.2)	100 (1.2)	2.9 (2.2–4.0)	1.9 (1.3–2.8)
Use of non-cardiac QT-drugs from category 2	142 (6.6)	285 (3.3)	2.1 (1.7–2.6)	1.6 (1.2–2.0)
Use of non-cardiac QT-drugs from both category 1 and category 2	30 (1.4)	25 (0.3)	4.9 (2.9–8.4)	2.5 (1.3–4.6)
≥70 years	2810	11 218		
No use of non-cardiac QT-drug	2476 (88.1)	10 470 (93.3)	1.0 (reference)	1.0 (reference)
Use of non-cardiac QT-drugs from category 1	93 (3.3)	182 (1.6)	2.2 (1.7–2.8)	1.5 (1.1–2.1)
Use of non-cardiac QT-drugs from category 2	218 (7.8)	525 (4.7)	1.8 (1.5–2.1)	1.3 (1.1–1.6)
Use of non-cardiac QT-drugs from both category 1 and category 2	23 (0.8)	41 (0.4)	2.3 (1.4–3.8)	1.8 (0.99–3.2)

P-value interaction: category 1: 0.0095, category 2: 0.0012, and categories 1 and 2 combined: 0.0501.

drugs from both categories studied (categories 1 and 2) were associated with increased risks of OHCA. Thus, drugs classified as having a 'possible risk of TdP' (category 2) were associated with increased OHCA-risk, although their risk seemed to be smaller than that of drugs of category 1 ('known risk of TdP'). The OHCA-risk was increased in men and women, in all age categories (but highest at ages ≤50 years), and in the presence or absence of cardiovascular disease.

Previous studies have raised concerns about the risk of potentially fatal cardiac arrhythmias of drugs that impair cardiac repolarization by blocking cardiac potassium channels[4–7]; this applies both to drugs prescribed for cardiac disease[13] and drugs for non-cardiac disease (e.g. antipsychotics,[5] antidepressants,[6] and antibiotics[7]). To our knowledge, no prior study investigated OHCA-risk of non-cardiac QT-drugs from categories 1 and 2 separately. In general, we expected to find higher ORs of non-cardiac QT-drugs because of previous studies, e.g. the study of Straus *et al.*[4] In that study, Straus *et al.* investigated in a longitudinal observational database whether non-cardiac QT-drugs are associated with risk of sudden cardiac death, and found a three-fold increased risk upon use of non-cardiac QT-drugs compared with no use of non-cardiac QT-drugs.[4] Thus, that study reported somewhat higher risks than our study. These differences may be due to different designs. First, that study had limited sample size. Second, misclassification of outcome may have occurred, since that study was not based on a cohort that was specifically designed to study OHCA, while identifying and properly adjudicating OHCA victims is challenging. In contrast, our study was based on the

Table 7 Risk for out-of-hospital cardiac arrest (OHCA) associated with use of non-cardiac QT-drugs of categories 1 and/or 2: stratification according to use of cardiovascular drugs

	OHCA-cases ($n = 5473$)	Non-OHCA-controls ($n = 21\,866$)	Crude OR	Adjusted OR
Use of cardiovascular drug	3516	8551		
No use of non-cardiac QT-drug	3041 (86.5)	7681 (89.8)	1.0 (reference)	1.0 (reference)
Use of non-cardiac QT-drugs from category 1	131 (3.7)	214 (2.5)	1.6 (1.2–1.9)	1.4 (1.1–1.8)
Use of non-cardiac QT-drugs from category 2	300 (8.5)	604 (7.1)	1.3 (1.1–1.5)	1.2 (1.02–1.4)
Use of non-cardiac QT-drugs from both category 1 and category 2	44 (1.3)	52 (0.6)	2.1 (1.4–3.1)	1.7 (1.1–2.7)
No use of cardiovascular drug	1957	13 315		
No use of any non-cardiac QT-drugs	1795 (91.7)	12 943 (97.2)	1.0 (reference)	1.0 (reference)
Use of non-cardiac QT-drugs from category 1	44 (2.3)	87 (0.7)	3.6 (2.5–5.2)	2.9 (1.9–4.3)
Use of non-cardiac QT-drugs from category 2	101 (5.2)	264 (2.0)	2.7 (2.1–3.4)	2.2 (1.6–2.9)
Use of non-cardiac QT-drugs from both category 1 and category 2	17 (0.9)	21 (0.2)	5.6 (3.0–10.7)	4.0 (2.0–8.2)

P-value interaction: categories 1: 0.4021, categories 2: 0.4575, and categories 1 and 2 combined: 0.1830.

ARREST registry which was specifically designed to study OHCA.[11] Third, the lower risk that we observed may be explained by increased awareness of this risk of QT-drugs over time. Prescribers may have become more prudent in prescribing QT-drugs as a result of growing attention for this risk in the past decades. Consequently, they may have taken more risk-mitigating precautions or refrained from prescribing these drugs altogether. Also, patients may have increased awareness and acted accordingly. Although we had no data to study these possibilities, a previous study highlighted the importance of the CredibleMeds list in promoting drug awareness among both prescribers and patients.[14] That study, based on an online survey of visitors to the CredibleMeds website, reported that this website is heavily used by both medical professionals (~41% of visitors) and patients (~56%).[14] That study reported that 79% of the patients refrained from, and 61% discontinued use of the drugs listed in the CredibleMeds website because of the information provided by the website.[14]

Our findings demonstrate that use of category 2 QT-drugs was also associated with increased OHCA-risk. Furthermore, the difference in OHCA-risk between category 1 and 2 QT-drugs was rather modest, although the prevalence of risk factors that increase OHCA-risk, in particular, cardiovascular comorbidity was not higher among users of category 2 QT-drugs compared with users of category 1 QT-drugs. In fact, the prevalence of drugs that prolong the QT-interval directly or indirectly (e.g. use of antidepressants and antipsychotics by blocking cardiac potassium channels or use of diuretics that may cause hypokalemia[3]) was higher among users of category 1 QT-drugs compared with users of category 2 QT-drugs. Given this, our findings indicate the notion that patient differences did not explain our association between category 2 QT-drugs and increased risk of OHCA-risk.

Our finding that category 2 QT-drugs classified as 'possible risk of TdP' also increases OHCA-risk has not previously been demonstrated, yet is of clinical significance, because it may indicate that the categorization of the drugs listed in CredibleMeds.org may have to be updated. Furthermore, our findings demonstrate that risk mitigation measures should also be applied to category 2 drugs.

Stratification analysis

We expected that OHCA-risk associated with use of non-cardiac QT-drugs would be larger in woman than in men. This expectation was based on the observation that women have less repolarization reserve than men and are more vulnerable to QT prolongation.[15] We found, however, a similarly increased OHCA-risk of QT-drugs from both categories in men and in women.

Also, we found that this risk occurred in all age groups. Still, the risk was highest in the youngest group (<50 years). While this observation cannot be explained at present, it may suggest that a genetic component is relevant. A genetic predisposition to drug-induced LQTS has previously been demonstrated.[16] Moreover, a recent study showed that almost 30% of individuals with drug-induced LQTS carry genetic variants related to LQTS.[17] Hence, future studies are needed to search for genetic predictors of OHCA occurring upon use of QT-drugs.

Finally, we found that the elevated OHCA-risk of QT-drugs from both categories occurred both in subjects who used cardiovascular drugs (taken as proxy for the presence of cardiovascular disease) and those who did not. This observation provides additional support for the notion that this association was due to a drug effect.

Strengths and limitations

A major strength of the present study is its population-based real-world design in which each OHCA-case was obtained prospectively; these efforts reduce the risk for selection bias and increase the likelihood that our findings are applicable to the community at large. Nevertheless, our study has also some limitations. A limitation is the lack of information on comorbidities. To deal with this, we used drug proxies for comorbidities. Although we have no direct evidence that this approach captures the most relevant comorbidities sufficiently accurately, we derive assurance that it did from our previous study in which had similar findings when we used drug proxies or direct information regarding comorbidities.[18] Also, misclassification in comorbidities or in its severity by using drug proxies could occur. For instance, patients may receive renin–angiotensin system inhibitors for the treatment of heart failure

and present a normalized left ventricular function at the time of OHCA, while some patients suffer from severe heart failure at the time of OHCA and being treated with the same medication. Therefore, drug proxies may not be very sufficient to determine the severity of different comorbidities. This might result in bias, since it is known that diseases associated with potassium channel down-regulation, e.g. heart failure, are an important risk factor for OHCA during use of QT-drugs.[3] However, our stratification according to cardiovascular drug use revealed an increase in OHCA-risk in individuals without presence of cardiovascular drug use as well. Because, it is likely that OHCA-cases that did not use cardiovascular drugs at the time of OHCA do not suffer from cardiovascular disease associated with OHCA (e.g. ischaemic heart disease, heart failure), it indicates that cardiovascular disease does not account for the association between QT-drugs and OHCA; this supports the notion that increased OHCA-risk may be due to a drug effect. Moreover, possible misclassification by using drug proxies was probably similarly distributed between cases and controls.

Next, we lacked information about other important clinical features besides cardiovascular diseases, such as electrolyte abnormalities (e.g. hypokalemia) and kidney or liver disease, which can further prolong the QT interval and predispose to cardiac arrhythmia in the presence of QT-drugs.[19] Therefore, we cannot exclude that factors besides cardiovascular disease have driven our results, particularly since we cannot exclude that these confounder are unequally distributed between cases and controls. Moreover, given the unexpected, and therefore unpredictable nature of OHCA, it is very hard—if not practically impossible—to obtain data on QT interval just prior to OHCA occurrence. Hence, such information is not systematically available. In the ARREST registry, 12-lead ECGs from OHCA-cases which were witnessed by the ambulance personnel are sometimes available. However, this is a select group of patients, mostly with cardiac acute ischaemia. The QT duration on these ECGs is likely to be strongly influenced by the changes in cardiac repolarization caused by myocardial ischaemia, and not fully representative of possible changes in the duration of repolarization caused by the use of QT prolonging drugs. Furthermore, for a select group of OHCA patients, an ECG that was made during a visit to their cardiologist prior to OHCA may be obtained. However, these ECGs were made on indication. Studying these ECGs may result in selection bias, because patients who visit the cardiologist may suffer from conditions that may influence the QT duration. Moreover, these ECGs were not obtained just prior to OHCA, and therefore, may not be very suitable to evaluate the effects of QT-prolonging drugs on QT interval close to the event. Finally, it is also possible that unmeasured residual confounders might have affected our observed associations.

Conclusion

Use of non-cardiac QT-drugs from both category 1 ('known risk of TdP') and category 2 ('possible risk of TdP') was associated with increased OHCA-risk. This applied to both men and women, across all ages (with the highest risk in patients aged <50 years), and in patients taking or not taking cardiovascular drugs.

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Data availability

The data underlying this article cannot be shared publicly due to ethical/privacy reasons.

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