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ORIGINAL ARTICLE

Out-of-hospital cardiac arrest and differential risk of cardiac and non-cardiac QT-prolonging drugs in 37 000 cases

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Aims: Drugs that prolong the QT interval, either by design (cardiac QT-prolonging drugs: anti-arrhythmics) or as off-target effect (non-cardiac QT-prolonging drugs), may increase the risk of ventricular arrhythmias and out-of-hospital cardiac arrest (OHCA). Risk mitigation measures were instituted, in particular, surrounding prescription of cardiac QT-prolonging drugs. We studied OHCA risk of both drug types in current clinical practice.

Methods: Using data from large population-based OHCA registries in the Netherlands and Denmark, we conducted two independent case–control studies. OHCA cases with presumed cardiac causes were matched on age/sex/index date with up to five non-OHCA controls. We calculated odds ratios (ORs) for the association of cardiac or non-cardiac QT-prolonging drugs with OHCA risk using conditional logistic regression analyses.

Results: We identified 2503 OHCA cases and 10 543 non-OHCA controls in the Netherlands, and 35 017 OHCA cases and 175 085 non-OHCA controls in Denmark. Compared to no use of QT-prolonging drugs, use of non-cardiac QT-prolonging drugs (Netherlands: cases: 3.0%, controls: 1.9%; Denmark: cases: 14.9%, controls: 7.5%)

The authors confirm that the PI for this paper is Hanno L. Tan.

was associated with increased OHCA risk (Netherlands: OR 1.37 [95% CI: 1.03–1.81]; Denmark: OR 1.63 [95% CI: 1.57–1.70]). The association between cardiac QT-prolonging drugs (Netherlands: cases: 4.0%, controls: 2.5%; Denmark: cases: 2.1%, controls: 0.9%) and OHCA was weaker (Netherlands: OR 1.17 [95% CI: 0.92–1.50]; Denmark: OR 1.21 [95% CI: 1.09–1.33]), although users of cardiac QT-prolonging drugs had more medication use and comorbidities associated with OHCA risk than users of non-cardiac QT-prolonging drugs.

Conclusion: In clinical practice, cardiac QT-prolonging drugs confer lower OHCA risk than non-cardiac QT-prolonging drugs, although users of the former have higher a priori risk. This is likely due to risk mitigation measures surrounding prescription of cardiac QT-prolonging drugs.

KEYWORDS

epidemiology, ESCAPE-NET, QT-prolonging drugs, sudden cardiac arrest

1 | INTRODUCTION

Out-of-hospital cardiac arrest (OHCA) is a leading cause of death, accounting for 50% of cardiovascular deaths in industrialized societies.[1] OHCA is usually caused by cardiac arrhythmias (ventricular tachycardia/ventricular fibrillation, VT/VF).[2] Numerous factors may increase the risk of VT/VF by impacting on cardiac electrophysiology, including drugs that block cardiac ion channels.[3] Serious concerns about the safety of such drugs have been raised.[4,5] Excess mortality was shown upon use of cardiac antiarrhythmic drugs that block the **cardiac potassium current** I_{Kr} and cause QT interval prolongation (Vaughan-Williams class III drugs including d-sotalol[5]), torsades de pointes (TdP), VT and VF. To minimize this proarrhythmic risk of cardiac antiarrhythmic drugs, various recommendations were issued over the last decades when prescription of such drugs to treat cardiac diseases is considered, in particular, to patients with elevated vulnerability to this adverse drug effect, e.g., patients with heart failure.[6]

Drugs that are prescribed for non-cardiac diseases (e.g., antidepressants, antipsychotics, antibiotics), but block I_{Kr} as an off-target effect, may also cause QT prolongation.[7–11] Accordingly, several studies found an increased OHCA risk upon use of these drugs.[12,13] Unlike antiarrhythmic drugs, which are generally prescribed by cardiologists who are aware of their OHCA risk and have the means to take risk-mitigating precautions,[14] non-cardiac QT-prolonging drugs are most often prescribed by non-cardiologists who may be less aware of this risk and/or have fewer means to monitor it (e.g., serial ECG); moreover, some drugs are available without prescription.[15,16] A recent study demonstrated that this may even result in prescription of QT-prolonging drugs to patients with a known diagnosis of congenital Long QT syndrome (LQTS) who have a clearly increased risk of TdP and from whom prescription of these drugs should be withheld (Class I recommendation).[17]

What is already known about this subject

- Drugs that prolong the QT interval, either by design (cardiac QT-prolonging drugs: anti-arrhythmics) or as off-target effect (non-cardiac QT-prolonging drugs), may increase the risk of ventricular arrhythmias and out-of-hospital cardiac arrest (OHCA).
- Education efforts have been invested to increase the awareness of this risk among cardiologists (in training), and to train them to take risk-mitigating actions. Whether this has resulted in risk reduction in the general population in current clinical practice is unknown.

What this study adds

- Cardiac QT-prolonging drugs confer a lower OHCA risk than non-cardiac QT-prolonging drugs, although users of cardiac QT-prolonging drugs have a higher comorbidity burden than users of non-cardiac QT-prolonging drugs.
- This is likely due to risk mitigation measures surrounding prescription of cardiac QT-prolonging drugs.

We hypothesized that, in the face of implementation of risk mitigation actions during prescription of cardiac QT-prolonging drugs, the OHCA risk of these drugs is attenuated in contemporary clinical practice, while the risk of non-cardiac QT-prolonging drugs remains present. To test our hypothesis, we conducted two independent case–control studies using data from two large ongoing population-based emergency medical services (EMS)-attended OHCA registries.

2 | METHODS

2.1 | Study design and setting

We conducted two independent case–control studies among OHCA cases with presumed cardiac cause sourced from ongoing population-based EMS-attended OHCA registries in the Netherlands (AmsteRdam REsuscitation STudies, ARREST) and Denmark (Danish Cardiac Arrest Registry, DANCAR). We excluded persons with an obvious non-cardiac cause, a repeat OHCA, age <18 years, or incomplete drug dispensing records one year prior to OHCA. From ARREST, we included all OHCA cases with documented VT/VF (June 2005–December 2011), excluding OHCA patients with non-shockable rhythm (asystole, pulseless electrical activity), because their drug use was not systematically collected before 2009. From DANCAR, we studied all OHCA cases with or without shockable rhythm (2001–2015) in our main analysis, and all OHCA cases with VT/VF in our subanalysis. Both registries are part of the ESCAPE-NET consortium that studies OHCA across Europe.[18] For both registries, each OHCA case was matched with up to five non-OHCA controls who were alive on the index date (OHCA date) using risk set matching based on sex, age and index date.[19]

This study was conducted according to the principles outlined in the Declaration of Helsinki and was approved by the Institutional Review Boards of the Academic Medical Center Amsterdam and the Danish Data Protection Agency (Ref. no. 2007-58-0015, local ref. no. GEH-2014-017, I-Suite 0.2735). Information on the Danish study population was encrypted and rendered anonymous by Statistics Denmark. In Denmark, ethical approval is not required for observational, registry-based studies where patients remain anonymous.

2.2 | Data sources

2.2.1 | The Netherlands

The ARREST registry is an ongoing population-based observational registry of all EMS-attended OHCAs in one contiguous region of the Netherlands (2.4 million inhabitants, urban and rural areas) that prospectively collects all suspected OHCAs in cooperation with EMS and dispatch centres (who notify ARREST personnel of each suspected OHCA) according to the Utstein recommendations.[19] ECGs of all resuscitation attempts are obtained from the EMS defibrillators and, when used, automated external defibrillators (AEDs). Complete drug dispensing records one year before index date are obtained from community pharmacies. Non-OHCA controls were sampled from the PHARMO Database Network, which contains drug dispensing records from community pharmacies. In the Netherlands, nearly all individuals are registered at a single community pharmacy independent of prescriber; therefore, data on medication use for both cases and controls are considered complete.

2.2.2 | Denmark

DANCAR is an ongoing nationwide register including information on all OHCAs in Denmark (population 5.8 million).[20] A patient is included when a clinical condition of cardiac arrest results in a resuscitation attempt by bystanders or EMS. The registration of OHCA cases is complete as EMS is activated for all clinical emergencies in Denmark and EMS must complete a case report form for every OHCA. OHCAs of presumed cardiac cause were events with diagnosis codes, obtained from death certificates and discharge diagnoses, containing cardiac disease, unexpected collapse or unknown disease. Every resident in Denmark is assigned upon birth or immigration a unique and permanent personal civil registration number, which permits the identification of each person across the nationwide registries at an individual level. The Danish National Patient Registry holds information on all hospital contacts and surgical procedures since 1977. A primary and, when relevant, one or more secondary diagnoses are assigned to every contact. The diagnoses are classified according to the International Classification of Diseases. All dispensed drug prescriptions are recorded in the National Prescription Register, where the drugs are classified according to the Anatomical Therapeutic Chemical system. Age, sex and vital status were retrieved from the Danish Civil Registration System. Causes of death, including primary and contributing causes, were retrieved from the Danish Register of Causes of Death.

2.3 | Exposure definition

Drug use was defined as having a drug dispensing record within ≤90 days prior to index date (ARREST) or covering a period of maximally 90 days before index date (DANCAR), since, in both countries, the average repeat prescription length for drugs used for chronic diseases is 90 days. For antimicrobial agents, this period was ≤14 days prior to index date because these drugs are generally prescribed for short periods. QT-prolonging drugs were derived from www.CredibleMeds.org (accessed August 29, 2020), which classifies QT-prolonging drugs into four categories with varying risk of TdP (Supplemental Table S1). We studied the drugs listed in category 1 ("known risk of TdP, even when taken as recommended") that are often prescribed in the Netherlands or Denmark (Supplemental Table S2).

2.4 | Covariates

We took the use of cardiovascular drugs (Table 1) and antidiabetics up to 6 months prior to index date as proxies for comorbidities.[19] Additionally, we identified various comorbidities associated with OHCA (Table 1) using hospital diagnoses up to 5 years before index date in DANCAR, but not in ARREST, because these data were lacking controls.

TABLE 1 Baseline characteristics of cases and controls

	ARREST		DANCAR	
	Cases	Controls	Cases	Controls
Total	2503	10 543	35 017	175 085
Mean age, years (standard deviation)	65.8 (13.8)	65.8 (13.8)	70.7 (13.7)	70.7 (13.7)
Male sex	1938 (77.4)	8167 (77.5)	23 422 (66.9)	117 110 (66.9)
Concomitant drug use				
Beta-blockers	855 (34.2)	2338 (22.2)	8354 (23.9)	25 521 (14.6)
Renin-angiotensin system inhibitors	1007 (40.2)	2778 (26.3)	13 097 (37.4)	44 732 (25.6)
Diuretics	890 (35.6)	2356 (22.3)	17 485 (49.9)	53 641 (30.6)
Nitrates	358 (14.3)	574 (5.4)	3956 (11.3)	6997 (4.2)
Statins	831 (33.2)	2613 (24.8)	9605 (27.4)	34 898 (19.9)
Antithrombotics	1090 (43.5)	3004 (28.5)	16 059 (45.9)	50 583 (28.9)
Calcium blockers	390 (15.6)	1221 (11.6)	6970 (19.9)	27 630 (15.8)
Antidiabetics	399 (15.9)	1135 (10.8)	5326 (15.2)	13 472 (7.7)
Comorbidity				
Ischaemic heart disease[a]	n/a	n/a	7507 (21.4)	15 051 (8.6)
Congestive heart failure	n/a	n/a	6152 (17.6)	6672 (3.8)
Atrial fibrillation	n/a	n/a	5392 (15.4)	11 149 (6.4)
Chronic obstructive pulmonary disease	n/a	n/a	4643 (13.3)	7322 (4.2)
Cerebrovascular disease	n/a	n/a	3730 (10.7)	10 795 (6.2)
Peripheral arterial disease	n/a	n/a	3061 (8.7)	5634 (3.2)
Chronic kidney disease	n/a	n/a	2074 (5.9)	3298 (1.9)
Severe psychiatric disorder[b]	n/a	n/a	2065 (5.9)	4427 (2.5)
Substance abuse	n/a	n/a	2385 (6.8)	3600 (2.1)

Numbers are number (%) unless indicated otherwise. n/a, not available.
[a]Including acute myocardial infarction.
[b]Depression, bipolar disorder and/or schizophrenia.

2.5 | Statistical analyses

Conditional (multivariable) logistic regression analyses were conducted to evaluate the association between QT-prolonging drugs and OHCA risk. First, we examined the association between cardiac or non-cardiac QT-prolonging drugs and OHCA risk compared with no use of any category 1 QT-prolonging drug. We then examined the association between individual drugs or types of QT-prolonging drugs and OHCA risk compared with no use of any category 1 QT-prolonging drug. Next, we examined whether patient characteristics or concomitant medication use was different between cases who used cardiac QT-prolonging drugs and those who used non-cardiac QT-prolonging drugs using chi-square or independent *t*-tests. In the multivariable analysis, we excluded category 1 QT-prolonging drugs from the covariates for which we were adjusting, e.g., while sotalol is both a category 1 QT-prolonging drug and a beta-blocker, we excluded sotalol in the covariate beta-blocker. We also studied the association between QT-prolonging drugs and OHCA risk in three periods (2001–2005, 2006–2010 and 2011–2015) to investigate whether the risk of these drugs decreased over time in DANCAR, but not in ARREST, where the number of drug users was too low. We conducted stratified analysis according to sex (in both ARREST and DANCAR). Finally, we compared the relative magnitude of I_{Kr} blocking effects of cardiac and non-cardiac QT-prolonging drugs by determining the ratio of effective free therapeutic plasma concentration ($ETCP_{unbound}$) over the concentration that inhibits 50% of I_{Kr} channels (IC50)[21] of the most widely used drugs in our study. Results are presented both as unadjusted and adjusted odds ratios (OR_{adj}) with associated 95% confidence intervals (CIs). A two-sided *P*-value of <.05 was considered statistically significant.

2.6 | Nomenclature of targets and ligands

Key protein targets and ligands in this article are hyperlinked to corresponding entries in http://www.guidetopharmacology.org, and are permanently archived in the Concise Guide to PHARMACOLOGY 2019/20.[22]

3 | RESULTS

We included 2503 OHCA cases (mean age 65.8 years, 77.4% male, Table 1) and 10 543 matched non-OHCA controls in ARREST, and 35 017 OHCA cases (mean age 70.7 years, 66.9% male) and matched 175 085 non-OHCA controls in DANCAR (Figure 1). Compared to no use of QT-prolonging drugs, use of non-cardiac QT-prolonging drugs (ARREST: cases: 3.0%, controls: 1.9%; DANCAR: cases: 14.9%, controls: 7.5%, Figure 2) was associated with increased OHCA risk in both registries (ARREST: OR_{adj} 1.37 [95% CI: 1.03–1.81]; DANCAR: OR_{adj} 1.63 [95% CI: 1.57–1.70]). The association between use of cardiac QT-prolonging drugs and OHCA risk (ARREST: cases: 4.0%, controls: 2.5%; DANCAR: cases: 2.1%, controls: 0.9%) was weaker, and only significant in DANCAR (OR_{adj} 1.21 [95% CI: 1.09–1.33]), but not in ARREST (OR_{adj} 1.17 [95% CI: 0.92–1.50]). The association between individual drugs or types of non-cardiac QT-prolonging drugs and OHCA risk in both registries is depicted in Figure 3. When we stratified according to sex, we found that, in DANCAR, OHCA risk elevation was larger in women than in men (*P*-value for interaction: for cardiac QT-prolonging drugs = .0188; for non-cardiac QT-prolonging drugs = .0004, Supplemental Table S3). In ARREST, the difference in OHCA risk upon use of QT-prolonging drugs between the sexes was not statistically significant (*P*-value for interaction: cardiac QT-prolonging drugs = .071; non-cardiac QT-prolonging drugs = .143, Supplemental Table S4). We found no temporal trend in OHCA risk in DANCAR (Supplemental Figure S1), nor an increased OHCA risk for either cardiac or non-cardiac QT-prolonging drugs among patients with VT/VF as their first-registered heart rhythm (Supplemental Table S5).

To explore possible confounding, we studied whether concomitant medication use or comorbidities were different between cases who used cardiac QT-prolonging drugs and those who used non-cardiac QT-prolonging drugs (Table 2). In both registries, we found that users of cardiac QT-prolonging drugs more often used cardiovascular medication than users of non-cardiac QT-prolonging drugs. Similarly, in DANCAR, users of cardiac QT-prolonging drugs had a significantly higher burden of cardiovascular comorbidities than users of non-cardiac QT-prolonging drugs. Conversely, psychiatric disorders and substance abuse were more frequent among users of non-cardiac QT-prolonging drugs. Finally, when we compared the relative magnitude of I_{Kr} blocking effects of both categories, we found that cardiac QT-prolonging drugs have a higher $ETCP_{unbound}$/IC50 ratio than non-cardiac QT-prolonging drugs, i.e., higher I_{Kr} inhibition at therapeutic concentrations (Supplemental Table S6).

4 | DISCUSSION

Our main finding was that cardiac QT-prolonging drugs confer a lower OHCA risk than non-cardiac QT-prolonging drugs in current clinical practice, although users of cardiac QT-prolonging drugs have a higher comorbidity burden than users of non-cardiac QT-prolonging drugs. This finding was consistent across two independent cohorts from different European countries that were specifically designed to study OHCA in the general population and totalled more than 37 000 OHCA cases. The findings that women had higher OHCA risk than men (and that their risk was more elevated for non-cardiac QT-prolonging drugs than for cardiac QT-prolonging drugs), although this sex difference was not significant in ARREST, provided additional assurance for the validity and consistency of our data, fitting the observation that women have less repolarization reserve than men[22] and are more vulnerable to QT prolongation.

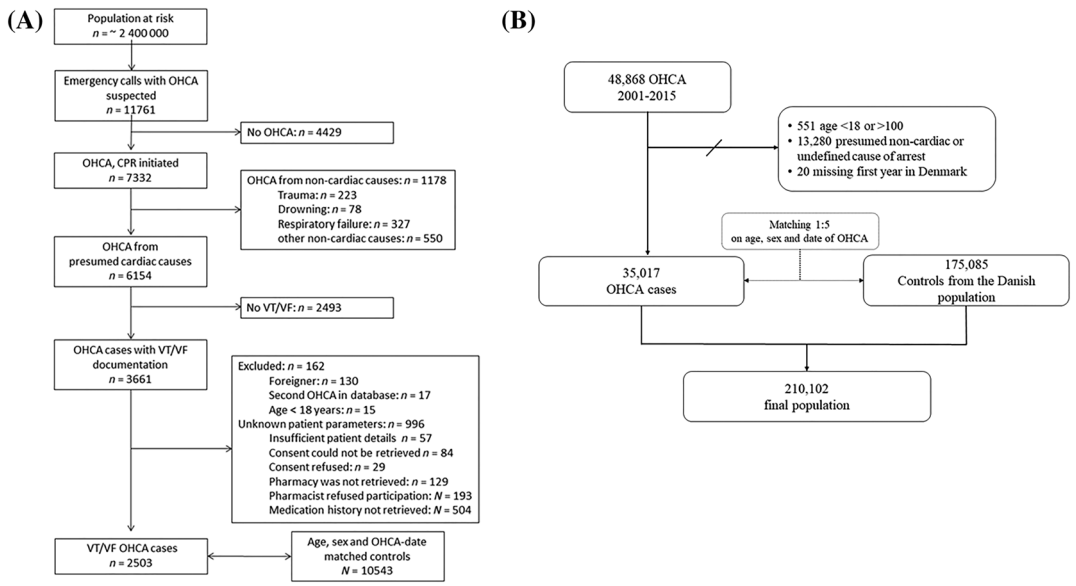

FIGURE 1 Flow chart of inclusion of out-of-hospital cardiac arrest cases in ARREST (A) and DANCAR (B) OHCA, out-of-hospital cardiac arrest; VT/VF, ventricular tachycardia/ventricular fibrillation

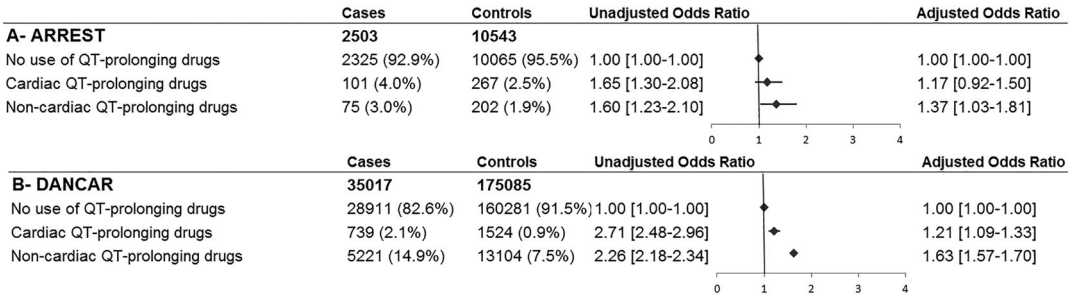

FIGURE 2 Risk of out-of-hospital arrest associated with use of cardiac or non-cardiac QT-prolonging drugs Not analysed: cases using both cardiac and non-cardiac QT-prolonging drugs in ARREST ($n = 2$) or DANCAR ($n = 146$). CI, confidence interval; OR, odds ratio. Numbers are number (%) unless indicated otherwise. In ARREST, effect estimates were adjusted for drug use, which served as proxies for comorbidities. In DANCAR we adjusted for both medication use and comorbidities. Error bars denote 95% confidence intervals

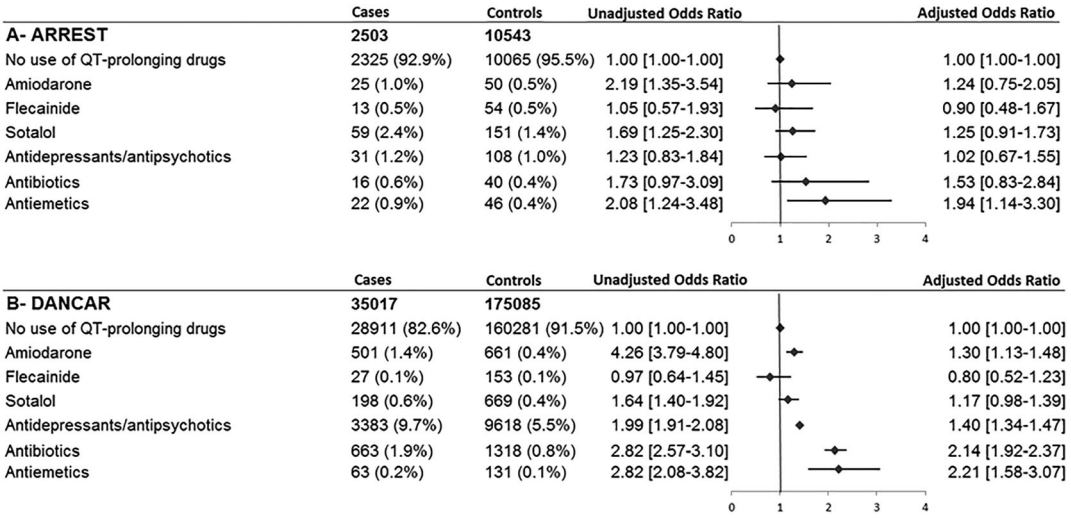

FIGURE 3 Risk of out-of-hospital cardiac arrest associated with use of individual drugs or types of QT-prolonging drugs Not analysed: cases using other cardiac QT-prolonging drugs or types of non-cardiac QT-prolonging drugs in ARREST ($n = 3$) or DANCAR ($n = 432$), and cases using more than one type of QT-prolonging drug in ARREST ($n = 9$) or DANCAR ($n = 839$). CI, confidence interval; OR, odds ratio. In ARREST, effect estimates were adjusted for drug use, which served as proxies for comorbidities. In DANCAR we adjusted for both medication use and comorbidities. Numbers are number (%) unless indicated otherwise. Error bars denote 95% confidence intervals

4.1 | The clinical problem of drug-induced QT prolongation

The recognition that several drugs may induce QT prolongation and sometimes life-threatening arrhythmias became widespread in the 1990s, when several publications pointed to the occurrence of QT prolongation and of episodes of TdP caused by drugs used by millions of patients, such as the antihistamine terfenadine,[7] the gastrointestinal drug cisapride,[9] and the antibiotic erythromycin.[10] This recognition was preceded by two events, both related to "quinidine syncope". One, represented by articles in the 1970s, linked quinidine therapy for atrial fibrillation to QT prolongation and TdP;[23] the other, was the suggestion in 1982 that "quinidine syncope" might represent a *forme fruste* of congenital LQTS,[24] thus implying that some patients might be predisposed to develop TdP when treated with drugs that share some pharmacological actions with quinidine. This was well before the genetic era and the realization that these drugs block the I_{Kr} current.[25] The evidence of a genetic predisposition to drug-induced LQTS was demonstrated in 2000[25] and more recently it was shown that almost 30% of individuals with drug-induced LQTS carry genetic variants related to LQTS.[26] The evolution of this knowledge, including risk factors such as hypokalaemia and female gender,[27] has been reviewed more than once, but more often in cardiology journals[11]; this may have favoured a different awareness of the problem between cardiologists and non-cardiologists.

4.2 | Possible causes for the differential risks of cardiac and non-cardiac QT-prolonging drugs

The finding that cardiac QT-prolonging drugs are associated with lower OHCA risk than non-cardiac QT-prolonging drugs in current

TABLE 2 Characteristics of OHCA cases who used cardiac or non-cardiac QT-prolonging drugs

	ARREST			DANCAR		
	Cardiac QT-prolonging drugs	Non-cardiac QT-prolonging drugs	*P*-value	Cardiac QT-prolonging drugs	Non-cardiac QT-prolonging drugs	*P*-value
Total	101	75		739	5221	
Mean age, years (SD)	70.5 (12.3)	66.7 (14.0)	.061	74.1 (10.8)	72.7 (13.4)	<.001
Male sex	72 (71.3)	49 (65.3)	.399	549 (74.3)	2835 (54.3)	<.001
Concomitant drug use						
Beta-blockers	83 (82.2)	34 (45.3)	<.001	257 (34.8)	1302 (24.9)	<.001
Renin-angiotensin system inhibitors	75 (74.3)	30 (40.0)	<.001	456 (61.7)	1811 (34.7)	<.001
Diuretics	66 (65.3)	38 (50.7)	.050	604 (81.7)	3051 (58.4)	<.001
Calcium channel blockers	29 (28.7)	9 (12.0)	.008	125 (16.9)	1070 (20.5)	.023
Nitrates	32 (31.7)	20 (26.7)	.471	194 (26.3)	666 (12.8)	<.001
Statins	49 (48.5)	27 (36.0)	.097	335 (45.3)	1508 (28.9)	<.001
Antithrombotics	81 (80.2)	38 (50.7)	<.001	620 (83.9)	2688 (51.5)	<.001
Antidiabetics	20 (19.8)	20 (26.7)	.283	165 (22.3)	959 (18.4)	.010
Comorbidity						
Ischaemic heart disease*	n/a	n/a	n/a	407 (55.1)	1228 (23.5)	<.001
Congestive heart failure	n/a	n/a	n/a	417 (56.4)	1077 (20.6)	<.001
Atrial fibrillation	n/a	n/a	n/a	441 (59.7)	906 (17.4)	<.001
Chronic obstructive pulmonary disease	n/a	n/a	n/a	136 (18.4)	1181 (22.6)	.009
Cerebrovascular disease	n/a	n/a	n/a	91 (12.3)	987 (18.9)	<.001
Peripheral arterial disease	n/a	n/a	n/a	118 (16.0)	582 (11.2)	<.001
Chronic kidney disease	n/a	n/a	n/a	108 (14.6)	437 (8.4)	<.001
Severe psychiatric disorder†	n/a	n/a	n/a	22 (3.0)	958 (18.4)	<.001
Substance abuse	n/a	n/a	n/a	25 (3.4)	670 (12.8)	<.001

Numbers are number (%) unless indicated otherwise; n/a, not available or not applicable.
*Including acute myocardial infarction.
†Depression, bipolar disorder and/or schizophrenia.

clinical practice may be counter-intuitive. Aiming to understand this finding, we studied the two most plausible explanations: differences in patient properties or in drug properties that result in differences in a priori OHCA risk between users of both drug types. First, we studied the prevalences of risk factors that increase OHCA risk, in particular, cardiovascular comorbidity. Here, we confirmed the obvious expectation that users of cardiac QT-prolonging drugs had more registered cardiovascular comorbidities and prescriptions for cardiovascular drugs than users of non-cardiac QT-prolonging drugs (users of non-cardiac QT-prolonging drugs had more psychiatric comorbidities, but many non-cardiac QT-prolonging drugs are psychoactive drugs). We concluded that these patient differences did not explain why users of cardiac QT-prolonging drugs had lower OHCA risk (and would rather favour the opposite observation). Having found that the difference in OHCA risk of both drug types is not explained by differences in patient or drug properties, we next considered the possibility that it may be explained by differences in prescriber behaviour.

4.3 | Possible differences in prescriber behaviour

The first widespread awareness that antiarrhythmic drugs have proarrhythmic risk came when the Cardiac Arrhythmia Suppression Trial (CAST) of 1989 reported increased arrhythmic and non-arrhythmic mortality rates among post-myocardial infarction (MI) patients treated with Vaughan-Williams class IC antiarrhythmic drugs.[4] Similarly, in the SWORD trial of 1996, the Vaughan-Williams class III antiarrhythmic drug d-sotalol (which lacks the beta-blocking effects of sotalol, and acts by QT prolongation secondary to I_{Kr} block) showed increased mortality risk in patients with left ventricular dysfunction after MI.[5] As a consequence, d-sotalol use was advised against in patients with this disease profile.[6] These findings have impacted on the use of antiarrhythmic drugs in clinical practice. For instance, a study reported a significant decrease over time in the proportion of patients discharged after MI with at least one prescription of a Vaughan-Williams class I or III antiarrhythmic drug (from 11.9% in 1984–1985 to 5.8% in 1991–1994); this study concluded that negative results from

earlier trials (e.g., CAST) were rapidly implemented into routine clinical practice.[28] Similarly, sales of Vaughan-Williams class IC drugs plummeted by 75% in the wake of CAST.[29] These observations indicate that prescribers of antiarrhythmic drugs (almost exclusively cardiologists[14]) are acutely aware of the potential risk of these drugs, and that they utilize appropriate risk-mitigating actions when they consider prescription of these drugs. This is consistent with our finding that these drugs are associated with only mildly elevated OHCA risk in Denmark and non-elevated risk in the Netherlands.

In contrast, we found that non-cardiac QT-prolonging drugs are associated with significantly elevated OHCA risk in both cohorts studied, consistent with previous studies.[12,13] This drug group contains a broad range of widely used drugs[3] which, unlike antiarrhythmic drugs, are mostly prescribed by non-cardiologists. For example, 85% of prescriptions for antibiotics are made by general practitioners and 15% by medical specialists.[30] Non-cardiologists may have less awareness that non-cardiac QT-prolonging drugs increase the risk of life-threatening cardiac arrhythmia and/or they may lack easy access to methods for risk monitoring (e.g., ECG monitoring). Also, they are less aware of cardiac outcomes of clinical trials than cardiologists, resulting in differences in clinical management.[31] Furthermore, adherence rates to guidelines on antiarrhythmic drug treatment increase significantly with a higher level of specialization (ranging from primary care physicians and general cardiologists to cardiac electrophysiologists), while higher adherence rates result in better patient outcomes.[14]

Together, these studies point to the relevance of prescriber behaviour and differences therein. We assumed, based on existing literature,[14] that the cardiac QT-prolonging drugs in our study were mostly prescribed by cardiologists, and the non-cardiac QT-prolonging drugs by other physicians, but we had no proof because prescriber information was lacking. To obtain indirect evidence for the role of prescriber behaviour, we studied whether the gap in OHCA risk between cardiac and non-cardiac QT-prolonging drugs widened in the later years of the study period. Such a widening could reflect a declining OHCA risk of cardiac QT-prolonging drugs (with an unchanged risk of non-cardiac QT-prolonging drugs) and could be consistent with increasing awareness and implementation of risk-mitigating actions by their prescribers over this period. A widening, however, was not found, possibly because the study period started in 2001, while this awareness may have already been fully present among cardiologists, and risk-mitigating actions implemented at that time, following the CAST trial of 1989 and the SWORD trial of 1996. Of interest, in the DANCAR registry, an increased OHCA risk was not found for either cardiac or non-cardiac QT-prolonging drugs among patients with VT/VF as their first-registered heart rhythm in OHCA (Supplemental Table S5). This discrepancy with outcomes from the ARREST registry may be due to differences between registries. The proportion of shockable first-registered heart rhythm is significantly lower in DANCAR than in ARREST (in 2015: 23% *vs* 47% shockable first-registered rhythm).[32] Also, while ECG documentation of VT/VF during OHCA is required in ARREST, it is not in DANCAR; this leads to higher risk of misclassification by erroneous inclusion of OHCAs with non-cardiac causes in DANCAR compared to ARREST.

Crucially, our findings and previous reports support the notion that prescriber behaviour can be sufficiently improved to significantly mitigate the OHCA risk of QT-prolonging drugs, and emphasize the importance of education efforts targeted at drug prescribers. These efforts were apparently effective among prescribers of cardiac QT-prolonging drugs. This offers the hope that, by investing in similar education efforts among prescribers of non-cardiac QT-prolonging drugs, OHCA risk mitigation can also be achieved for these drugs. This is clearly desirable given their widespread use. Also, OHCA should not occur in these individuals, because they typically do not suffer from cardiac disease, and they receive these drugs for conditions that are usually not (immediately) life-threatening, while similarly effective alternative drugs which do not put them at OHCA risk can also be prescribed. Education efforts may be supported by solutions that are already in existence or under development. For instance, automatic alerting systems integrated into an electronically-based drug prescription environment may alert the physician when prescription of a QT-prolonging drug is considered. This may help to increase the physician's awareness, and result in safer use of drugs through better personalization, e.g., avoidance of QT-prolonging drugs in patients with increased risk of hazardous QT prolongation.[33,34] Estimation of this risk may be aided by a pharmacogenetic passport that holds information on the presence or absence of genetic variants that may cause hazardous QT prolongation during drug use.[35]

4.4 | Strengths and limitations

A major strength of our study is its population-based design in which a very large number of OHCA cases were included prospectively, thereby minimizing the risk of selection bias. The 14 times larger number of studied cases included in Denmark than in the Netherlands does not contradict this, as it is explained by a 2.3 times longer inclusion period (15 *vs* 6.5 years) and a 2.4 times larger source population (5.8 *vs* 2.4 million) in Denmark. Moreover, in the Netherlands, 3589 OHCA cases were excluded from analysis for reasons that were unlikely to be related to OHCA risk of QT-prolonging drugs (drug information lacking in OHCA cases who had no shockable rhythm or in whom it could not be retrieved), while these exclusion criteria were absent in Denmark thanks to the presence of a National Prescription Register.This study has several limitations. First, misclassification in the use of QT-prolonging drugs may have occurred, as we defined drug use as presence of medication records ≤90 days prior to index date. Second, we could only perform direct adjustments for comorbidities in DANCAR, but not in ARREST. Lastly, residual confounding may remain from factors unavailable for analysis.

5 | CONCLUSION

Use of cardiac QT-prolonging drugs is associated with a lower risk of OHCA in the general population than use of non-cardiac

QT-prolonging drugs. This disparity exists despite higher disease severity in users of cardiac QT-prolonging drugs and stronger QT-prolonging effects of these drugs. We posit that this difference likely depends on successful implementation of risk-mitigating measures among prescribers of cardiac QT-prolonging drugs, but an insufficient degree of awareness of the life-threatening potential of QT-prolonging drugs among prescribers of non-cardiac QT-prolonging drugs. We advocate that the latter physicians are better alerted to the potential arrhythmogenic dangers of several non-cardiac drugs, because appropriate education efforts may significantly mitigate this clinical risk.

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COMPETING INTERESTS

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CONTRIBUTORS

T.E.E. and H.L.T. conceived the study idea. T.E.E. designed the research, collected data for the Dutch registry, performed the statistical analyses for the Dutch registry and wrote the manuscript. C.A.B. performed the statistical analyses for the Danish registry and reviewed the manuscript. P.C.S. worked up the original data from the Dutch registry to a data matrix ready for statistical analyses and reviewed the manuscript. All authors critically revised and approved the manuscript.

DATA AVAILABILITY STATEMENT

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

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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