pharmacoepidemiology

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Non-Cardiac Depolarization-Blocking Drugs Are Associated with Increased Risk of Out-of-Hospital Cardiac Arrest in the Community

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Abstract: Depolarization-blocking drugs (DB drugs) used for cardiac disease increase the risk of cardiac arrhythmia (ventricular tachycardia/ventricular fibrillation [VT/VF]) and out-of-hospital cardiac arrest (OHCA) in specific patient groups. However, it is unknown whether drugs for non-cardiac disease that block cardiac depolarization as the off-target effect increase the risk of OHCA on a population level. Therefore, we aimed to investigate OHCA risk of non-cardiac, DB drugs in the community. We conducted a population-based case-control study. We included OHCA cases from an emergency-medical-services-attended OHCA registry in the Netherlands (ARREST:2009–2018), and age/sex/OHCA-date matched non-OHCA controls. We calculated adjusted odds ratios (OR_{adj}) of use of non-cardiac DB drugs for OHCA using conditional logistic regression. Stratified analyses were performed according to first-registered rhythm (VT/VF or non-VT/VF), sex, and age (≤50, 50–70, or ≥70 years). We included 5473 OHCA cases of whom 427 (7.8%) used non-cardiac, DB drugs and 21,866 non-OHCA controls of whom 835 (3.8%) used non-cardiac, DB drugs and found that non-cardiac, DB-drug use was associated with increased OHCA-risk when compared to no use (OR_{adj}1.6[95%-CI:1.4–1.9]). Stratification by first-recorded rhythm revealed that this applied to OHCA with non-VT/VF (asystole) (OR_{adj}2.5[95%-CI:2.1–3.0]) but not with VT/VF (OR_{adj}1.0[95%-CI:0.8–1.2]; *p*-value interaction < 0.001). The risk was higher in women (OR_{adj}1.8[95%-CI:1.5–2.2] than in men (OR_{adj}1.5[95%-CI:1.2–1.8]; *p*-value interaction = 0.030) and at younger ages ($OR_{adj≥70yrs}$1.4[95%-CI:1.2–1.7]; $OR_{adj50–70yrs}$1.7[95%-CI:1.4–2.1]; $OR_{adj≤50yrs}$3.2[95%-CI:2.1–5.0]; *p*-value interaction < 0.001). Use of non-cardiac, DB drugs is associated with increased OHCA risk. This increased risk occurred in patients in whom non-VT/VF was the first-registered rhythm, and it occurred in both sexes but more prominently among women and more strongly in younger patients (≤50 years).

Keywords: non-cardiac depolarization-blocking drugs; out-of-hospital cardiac arrest; epidemiology; ESCAPE-NET

Citation: Eroglu, T.E.; Blom, M.T.; Souverein, P.C.; de Boer, A.; Tan, H.L. Non-Cardiac Depolarization-Blocking Drugs Are Associated with Increased Risk of Out-of-Hospital Cardiac Arrest in the Community. *Pharmacoepidemiology* **2022**, *1*, 64–75. https://doi.org/10.3390/pharma1020007

Academic Editor: Cristina Bosetti

Received: 29 April 2022
Accepted: 6 July 2022
Published: 1 August 2022

1. Introduction

Out-of-hospital cardiac arrest (OHCA) remains a major health problem that accounts for 50% of all deaths from cardiovascular causes in industrialized societies [1,2]. The majority of such deaths are caused by cardiac arrhythmias that result from disruptions in cardiac electrophysiology [3]. Such arrhythmias may be tachyarrhythmias (ventricular tachycardia [VT], ventricular fibrillation [VF]) [3], or bradyarrhythmias (asystole) [4]. Various drugs

may induce the causative electrophysiologic disruptions by impacting cardiac ion channels [5–12]. The best-known risk drugs are drugs that impair cardiac repolarization (QT prolongation on the ECG) by blocking cardiac potassium channels [5–12]. Drugs that impair cardiac depolarization (depolarization-blocking drugs [DB drugs]), typically blockers of cardiac sodium channels, may also increase the risk of OHCA [13–16]. Depolarization of the sarcolemma initiates the cardiac action potential, thereby triggering cardiac excitation. Accordingly, DB drugs may slow impulse conduction and facilitate re-entrant excitation and VT/VF, and/or they may evoke asystole (non-VT/VF). An increase in OHCA risk secondary to the use of DB drugs is well known in some clinical contexts, in particular, in myocardial ischemia/infarction [13,17] and in Brugada syndrome [16]. However, whether this risk extends beyond these specific contexts and also involves the general population is not established. We aimed to establish this by analyzing data from a registry that was specifically designed to study OHCA in the general population (AmsteRdam REsuscitation STudies, ARREST [18]). Moreover, we hypothesized that OHCA risk is also elevated for drugs which are prescribed for non-cardiac diseases yet impair cardiac depolarization as an off-target effect (non-cardiac DB drugs), e.g., antidepressants [14] and some anticonvulsants [15]. We reasoned that while cardiac DB-drugs (typically antiarrhythmic drugs) exert a strong depolarization block by design (deriving their therapeutic action from this property), their proarrhythmic risk and the determinants of this risk are well known [13], and measures to mitigate this risk have been included in clinical guidelines [19]. In contrast, such knowledge and appropriate risk-mitigating actions are lacking for non-cardiac DB drugs. Yet, this knowledge is dearly needed given the widespread use of these drugs (these drugs are used by 6% of the population in the Netherlands [20]. Furthermore, antidepressants are a large group within non-cardiac DB drugs; these are used by 7.2% on average in 27 European countries according to a previous study [21]).

The aim of the present study is to study whether the use of non-cardiac DB drugs is associated with an increased risk of OHCA compared to no use of non-cardiac DB drugs. Secondly, we stratified according to first-recorded heart rhythm (VT/VF or non-VT/VF) to gain mechanistic insight and according to sex and age to identify vulnerable patient groups.

2. Results

The study population consisted of 5473 OHCA cases (mean age 68.8 years, 69.9% male, Table 1) and 21,866 matched non-OHCA controls (Figure 1). Non-cardiac, DB drugs were used by 427 (7.8%) cases and 835 (3.8%) controls and were associated with increased OHCA risk (OR_{adj}1.6[95%-CI:1.4–1.9], Figure 2). The OHCA risk of the most commonly used individual non-cardiac, DB drugs ranged from OR_{adj}1.1 (amitriptyline, Table 2) to OR_{adj}6.4 (metoclopramide). We found that OHCA risk was only elevated in patients with non-VT/VF ($OR_{non\text{-}VT/VF}$2.5[95%-CI:2.1–3.0]) but not in patients with VT/VF ($OR_{VT/VF}$1.0 [95%-CI:0.8–1.2], *p*-value interaction < 0.001, Figure 2). Furthermore, we found that OHCA risk was increased both in men (OR_{men}1.5[95%-CI:1.2–1.8]) and women (OR_{women}1.8[95%-CI:1.5–2.2]) and that this risk was more elevated in women than in men (*p*-value interaction < 0.030, Figure 2). Stratification according to age revealed that OHCA risk rose in consecutive groups of declining age, being largest in the youngest patient category ($OR_{\leq 50}$3.2[95%-CI:2.1–5.0], $OR_{50–70}$1.7[95%CI:1.4–2.1], $OR_{\geq 70}$1.4[95%-CI:1.2–1.7], *p*-value interaction < 0.001, Figure 2). Stratification according to cardiovascular drug use showed that OHCA risk was increased both in individuals with concomitant use of cardiovascular drugs (OR_{adj}1.3[95%-CI:1.2–1.5]) and those without (OR_{adj}2.8[95%-CI:2.2–3.6], Supplementary Table S2, *p*-value interaction < 0.001). Furthermore, when we compared resuscitation characteristics between cases that used non-cardiac, DB drugs and those that did not, we observed that users of non-cardiac, DB drugs suffered OHCA less often at a public location (14.3% vs. 26.0%, $p < 0.001$) and that OHCA was less often witnessed by bystanders or emergency medical services (68.1% vs. 74.0%, $p < 0.009$, Table 3). Additionally, the times from emergency medical services call to defibrillator connection were longer in users of non-cardiac, DB drugs (median 9.5 vs. 8.6 min, $p = 0.001$). There were no differences in

cardiopulmonary resuscitation status or proportion of automated external defibrillator deployment (Table 3). We found that OHCA risk was increased upon use of both non-cardiac, DB drugs that are also listed as QT-prolonging drugs (OR_{adj}1.6[95%-CI:1.4–1.8], Supplementary Table S3) and those that are not (OR_{adj}2.1[95%-CI:1.5-2.9]). Finally, our association between DB drugs and OHCA risk did not change (OR_{adj}1.6 [95% CI:1.4–1.8]) when we adjusted for the number of simultaneously dispensed drugs (see Supplementary Table S4 for the number of drugs being simultaneously dispensed).

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		
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 I or III	114 (2.1)	183 (0.8)

Numbers are number (%) unless indicated otherwise. Abbreviation: OHCA, out-of-hospital cardiac arrest. Use of cardiovascular drugs and/or antidiabetics was defined as use within six months before the index date (OHCA date). Use of Vaughan-Williams class I or III antiarrhythmic drugs was defined as use within 90 days before the index date.

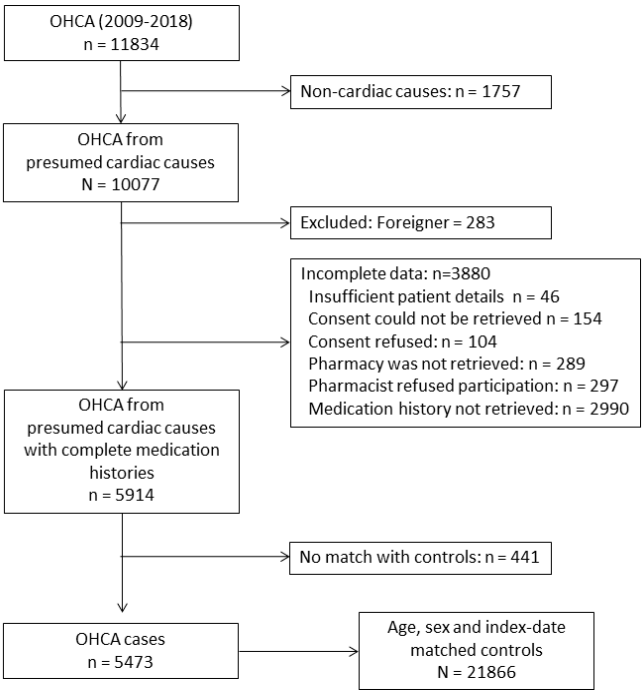

Figure 1. Flow chart of inclusion of out-of-hospital cardiac arrest (OHCA) cases and controls, OHCA, out-of-hospital cardiac arrest; VT/VF, ventricular tachycardia/ventricular fibrillation.

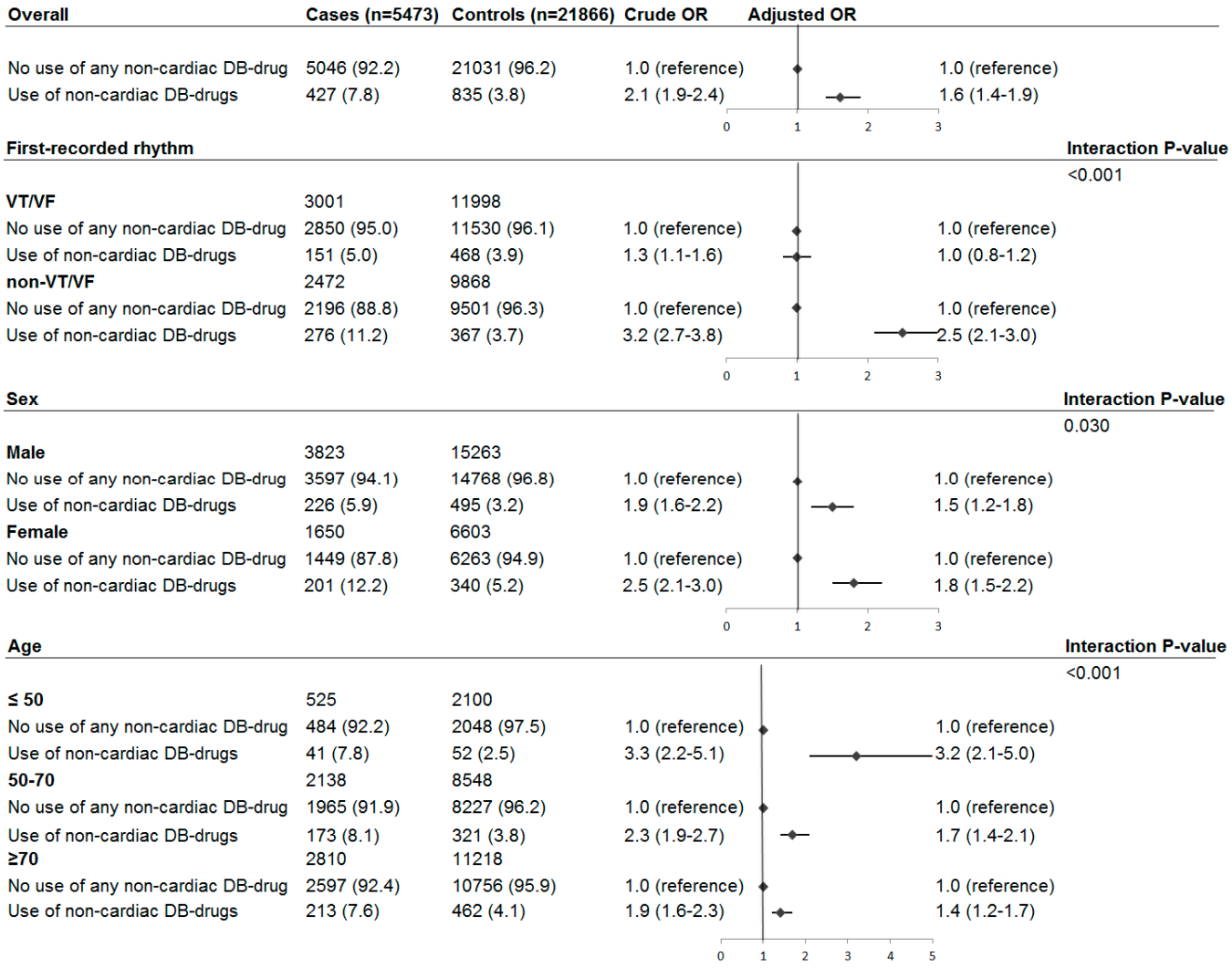

Figure 2. Risk for out-of-hospital cardiac arrest upon use of non-cardiac, depolarization-blocking drugs: overall and stratification according to first-recorded rhythm, sex, and age. Abbreviations: OR, odds ratio. Numbers in table are number (%) unless indicated otherwise. Error bars denote 95% confidence interval. Odds ratio adjusted for use of cardiovascular drugs, antidiabetics, and Vaughan-Williams class I or III antiarrhythmic drugs.

Table 2. Risk of out-of-hospital cardiac arrest for the most commonly used non-cardiac, depolarization-blocking (DB) drugs.

	OHCA Cases (n = 5473)	Non-OHCA Controls (n = 21,866)	Crude OR (95% CI)	Adjusted OR * (95% CI)
No use of any non-cardiac, DB drugs	5046 (92.2)	21,031 (96.2)	1.0 (reference)	1.0 (reference)
Tramadol	103 (1.9)	172 (0.8)	2.5 (1.9–3.2)	1.7 (1.3–2.2)
Paroxetine	63 (1.2)	152 (0.7)	1.7 (1.3–2.4)	1.5 (1.1–2.1)
Amitriptyline	59 (1.1)	154 (0.7)	1.6 (1.2–2.2)	1.1 (0.8–1.6)
Metoclopramide	63 (1.2)	35 (0.2)	7.4 (4.9–11.1)	6.4 (4.2–10.0)
Carbamazepine	28 (0.5)	46 (0.2)	2.5 (1.5–4.0)	2.1 (1.3–3.4)
Nortryptiline	16 (0.3)	33 (0.2)	2.1 (1.1–3.8)	1.5 (0.8–2.8)

Table 2. *Cont.*

	OHCA Cases (n = 5473)	Non-OHCA Controls (n = 21,866)	Crude OR (95% CI)	Adjusted OR * (95% CI)
Clomipramine	9 (0.2)	33 (0.2)	1.1 (0.5–2.3)	0.8 (0.4–2.0)
Lithium	7 (0.1)	16 (0.1)	1.8 (0.7–4.4)	1.6 (0.7–4.1)
Fluoxetine	6 (0.1)	23 (0.1)	1.1 (0.5–2.8)	0.8 (0.3–2.0)
Fluvoxamine	10 (0.2)	18 (0.1)	2.3 (1.0–5.0)	1.6 (0.7–3.8)
Lamotrigine	5 (0.1)	10 (0.1)	2.1 (0.7–6.0)	2.1 (0.7–6.4)
Phenytoin	9 (0.2)	15 (0.1)	2.5 (1.1–5.8)	1.9 (0.8–4.6)

Abbreviation: OHCA, out-of-hospital cardiac arrest. * Odds ratio adjusted for use of cardiovascular drugs, antidiabetics, and Vaughan-Williams class I or III antiarrhythmic drugs. For other non-cardiac, DB drugs, the numbers were too low to calculate odds ratio.

Table 3. Resuscitation characteristics of out-of-hospital cardiac arrest cases that did or did not use non-cardiac, depolarization-blocking (DB) drugs.

	Use of Non-Cardiac DB Drugs (n = 427)	No Use of Any Non-Cardiac DB Drugs (n = 5046)	*p*-Value	Unknown
OHCA at public place	61 (14.3)	1310 (26.0)	<0.001	9 (0.2)
Witnessed status			0.009	47 (0.9)
Bystander-witnessed or emergency-medical-services-witnessed OHCA	286 (68.1)	3704 (74.0)		
Unwitnessed OHCA	134 (31.9)	1302 (26.0)		
Cardiopulmonary resuscitation status			0.384	66 (1.2)
Cardiopulmonary resuscitation before arrival of emergency medical services	297 (70.7)	3625 (72.7)		
No cardiopulmonary resuscitation performed	123 (29.3)	1362 (27.3)		
Automated external defibrillator used	200 (46.8)	2557 (50.7)	0.126	2 (<0.1)
Median call-to-defibrillator-connection time, min (IQR)	9.5 (7.4–12.4)	8.6 (6.6–11.2)	0.001	409 (7.5)

Abbreviations: IQR, interquartile range; OHCA, out-of-hospital cardiac arrest. Numbers are number (%) unless indicated otherwise. *p*-values are calculated using χ^2 statistics or Mann-Whitney.

3. Discussion

In this population-based observational study using real-world data, we found that use of non-cardiac DB drugs was associated with an increased OHCA risk. This increased risk occurred in patients in whom non-VT/VF (asystole) was the first-registered heart rhythm, and it occurred in both sexes but more prominently among women and more strongly in the youngest patients (≤50 years). Risk was increased both in subjects with cardiovascular disease and in those without and upon use of non-cardiac DB drugs with or without QT-prolonging properties.

3.1. Previous Studies

Previous studies have raised concerns about the risk of potentially lethal cardiac arrhythmias of drugs that impact cardiac electrophysiology [5–12]. The cardiac arrhythmia suppression trial (CAST) was the first randomized controlled trial to show evidence that drugs which block cardiac depolarization (Vaughan-Williams class IC cardiac antiarrhythmic drugs) also increase arrhythmic and non-arrhythmic mortality risk in vulnerable patients (e.g., those with acute myocardial ischemia/infarction) [13,17]. Subsequently, other studies by us [14,15] and others [16,22] reported on non-cardiac DB-drugs, and some evidence was found that these drugs may also increase the risk of OHCA in the general population. One study focused on the antidepressant nortriptyline and found

that nortriptyline was associated with increased OHCA risk [14]. Another study focused on anticonvulsants [15] and found that anticonvulsants with sodium-channel-blocking properties were associated with increased OHCA risk, while anticonvulsants without such properties were not. Both studies, however, had limited sample sizes. In addition, anecdotal findings (often case reports, compiled in [16]) have reported on the risk of OHCA associated with the use of various cardiac or non-cardiac DB drugs, but these studies were not conducted systematically. Finally, a systematic study focused on drug use among young (aged 1–49 years) OHCA victims in the general population and found that 9% of these patients had used a DB drug (either cardiac or non-cardiac) within 90 days before OHCA and that they had significantly more often unexplained (autopsy-negative) sudden arrhythmic deaths than explained sudden cardiac deaths [23]. That study, however, did not report whether DB-drug use occurred more often in these OHCA patients than in non-OHCA controls; moreover, it did not distinguish between cardiac and non-cardiac DB drugs. The present study is, to the best of our knowledge, the first to systematically investigate the magnitude of OHCA risk associated with use of non-cardiac DB drugs and extends previous studies by demonstrating an increased risk of OHCA in the community in a large, unselected population.

3.2. Stratified Analyses

Stratification according to first-registered rhythm revealed that increased OHCA risk upon use of non-cardiac DB drugs occurred when non-VT/VF but not VT/VF was the first-registered rhythm. This finding is consistent with the known effects of these drugs on cardiac cellular electrophysiology. Blocking of the cardiac sodium current by these drugs impedes the generation (upstroke) of the cardiac action potential, a process that is required to initiate cardiac excitation and subsequent propagation of the electrical impulse to surrounding cells (which must, in turn, generate an action potential to sustain further impulse propagation). Disruption of this process by DB drugs will lead to failure of impulse conduction resulting in asystole. Our findings are in line with previous studies [24–26]. Granfeldt et al. studied factors associated with non-shockable rhythm as first-recorded heart rhythm in OHCA and reported that antidepressants were associated with non-shockable rhythm (non-VT/VF). Since the majority of non-cardiac DB drugs included in our study are antidepressants, that study may provide indirect evidence that non-cardiac DB- drugs are associated with non-VT/VF [24]. Furthermore, previous studies have shown that asystole episodes also occur in patients with a mutation in *SCN5A* (the gene that encodes the major subunit of the cardiac sodium channel) [25,26]. We acknowledge that more study is needed to confirm our findings; our study may provide the basis for future research. Theoretically, DB drugs may also increase OHCA risk by raising the risk of VT/VF. This, however, was not found. This finding may be consistent with the observation that increased OHCA risk associated with these drugs was largest in the youngest age group studied. Slowing of impulse transmission facilitates the occurrence of re-entrant excitation and, thereby, VT/VF but is not sufficient in itself. Heterogeneities in the myocardial tissue are also needed to sustain re-entrant excitation. Such heterogeneities most often relate to tissue architecture, in particular, the presence of scar tissue or other inexcitable areas. Young individuals are likely to lack scar tissue because acquired diseases that cause such scar tissue, most notably myocardial ischemia/infarction and hypertension, have had no time or a shorter time to exert these effects. In addition to a biological mechanism, an alternative explanation for our observations might be the observed differences in resuscitation characteristics between cases that used non-cardiac, DB drugs and those that did not. The quickness of the prehospital resuscitation response influences the likelihood of the presence of VT/VF upon connection of a defibrillator. Accordingly, the presence of VT/VF is strongly influenced by these resuscitation characteristics. We observed that time from emergency medical services call to defibrillator connection was longer and that OHCA occurred less often at a public location in OHCA cases who used non-cardiac DB drugs than in those who did not. Hence, VT/VF in OHCA cases who used non-cardiac DB-drugs may have already

dissolved into asystole. This may explain, at least in part, why we observed increased OHCA risk upon use of non-cardiac DB-drugs when non-VT/VF but not VT/VF was the first-registered rhythm.

We also stratified our analysis according to sex, expecting that OHCA risk associated with use of non-cardiac DB drugs was larger in men than in women. This expectation was based on the observation that Brugada Syndrome for which the proarrhythmic risk of DB drugs is well-established and is accordingly linked to loss-of-function mutations in SCN5A the gene that encodes the major subunit of the cardiac sodium channel [27] increases risk of arrhythmias and OHCA significantly more in men than in women [28,29], although carriership of this disease is equally distributed between the sexes. The basis of this observation is unresolved but may be related to smaller depolarization reserves in men than in woman due to lower expressions of depolarizing cardiac ion channels [30,31]. We found, however, that increased OHCA risk upon use of non-cardiac, DB drugs occurred both in men and in women and that this effect was even larger in women. This observation cannot be explained at present. Hence, future studies are needed to replicate our findings and to discover the underlying mechanisms.

Our stratification according to age revealed a robust increase of OHCA risk with decreasing age with the largest risk in the youngest age group studied ($\leq$50 years). This observation suggests that increased OHCA risk upon use of non-cardiac DB drugs is more determined by factors that are relevant at a young age than by factors that are relevant at an older age. Older age is related to the development of co-morbidities that impact arrhythmia risk related to reduced depolarization, e.g., ischemic heart disease [32] and the development of scar tissue in the heart. In contrast, at a young age, given that such co-morbidities have often not yet developed, the role of genetic factors is relatively larger. For instance, variants in genes which encode proteins that play a role in the functional properties or regulate intracellular trafficking of cardiac sodium channels may render individuals more sensitive to the depolarization-blocking effects of DB drugs and more vulnerable to the occurrence of OHCA upon use of these risk drugs [14]. Such gene variants may be either rare [14] or common. A recent study showed that a polygenic risk score composed of common genetic variants was significantly associated with the magnitude of increase in PR and QRS duration upon infusion of the cardiac DB drug, ajmaline [33]. Of interest, in that study, female sex but not male sex was also associated with the magnitude of PR increase. Our stratification according to the presence of cardiovascular drug use revealed a stronger increase of OHCA risk in subjects without cardiovascular disease. This indicates that cardiovascular disease does not account for the association between non-cardiac DB-drugs and OHCA. Given that it is likely that in individuals without the presence of cardiovascular drug use, no (severe) cardiac disease was known since these individuals did not have drug-dispensing records for cardiovascular drugs; our findings support the notion that the increased OHCA risk may be due to a drug effect. Finally, our findings of non-cardiac, DB drugs that are not listed as QT-prolonging drugs [24] excludes the possibility that cardiac potassium-channel-blocking properties of some non-cardiac DB drugs are responsible for our observation. When we studied the individual non-cardiac, DB drugs, we found that tramadol was associated with increased OHCA risk. While tramadol is listed as a QT-prolonging drug, available evidence indicates that tramadol produces only minor QT-interval prolongation [34,35]. Hence, it is less likely that the increased OHCA risk upon tramadol use is explained by tramadol's cardiac potassium-channel-blocking properties [34,35]. It cannot, however, be ruled out that respiratory arrest contributed, to some extent, to OHCA risk upon tramadol use since tramadol is not only a cardiac sodium-channel-blocker [36] but also an opioid analgesic [37].

3.3. Strengths and Limitations

A major strength is that the ARREST registry was specifically set up to investigate the causes of OHCA in the general population and has a population-based real-world design in which each OHCA case is prospectively registered, thus minimizing the risk for selection

bias or inclusion bias. Nevertheless, our study also has limitations. A limitation is the lack of data regarding comorbidity in the majority of our cases and in all controls. Therefore, we could not perform direct adjustments for relevant comorbidities. To deal with this, we used proxies for diseases using drug-dispensing records. Although we have no direct evidence on how well our drug proxies replace the presence of relevant comorbidities, we may provide indirect evidence based on our previous study [38]. In that study, the association between nifedipine and OHCA risk was studied using two registries from the Netherlands (ARREST) and Denmark (Denmark). We calculated the odds ratio for each registry separately. In ARREST we used drug proxies, while in DANCAR we used information regarding comorbidities in the multivariable analyses to calculate the odds ratio. This approach resulted in similar findings. Therefore, we feel confident in using drug proxies in the present study as well. However, as with any observational study, a residual confounding remains possible. Another limitation is the lack of completeness of data from the OHCA cohort since almost half of the OHCA cases were not included, primarily due to lack of medication history (Figure 1). Patients were excluded if data on drug use was incomplete or could not be obtained (e.g., due to unknown pharmacy or the pharmacist's refusal to participate). However, we expect that such incomplete data were distributed randomly between users and non-users of non-cardiac, DB drugs. Therefore, we presume that this may only have a small impact on our findings. In addition, when we compared patient characteristics, such as age, sex, and first-registered heart rhythm between included cases and cases who were excluded due to incomplete data (n = 3880) or lack of controls (n = 441), we observed no major differences between these groups (included cases: 68.8 years mean age, 69.9% male, and 54.8% VT/VF; excluded cases: 65.6 years mean age, 70.8% male, 51.1% VT/VF). Another limitation is that we had no information regarding compliance to drug use, which may have resulted in misclassification of the exposure. Furthermore, given that >90% of cases and controls were not using non-cardiac, DB drugs and the associations described in the study were derived from a relatively small number of patients, we cannot rule out that our findings may have been affected by variable compliance. Therefore, we suggest future studies in large-scale OHCA databases with cases and controls that are well phenotyped in a uniform manner to validate our findings. Finally, misclassification of the first-registered heart rhythm may have occurred since we could only determine the heart rhythm at the moment when the manual defibrillators and/or automated external defibrillators were used. However, it is very hard—if not practically impossible—to obtain data about the heart rhythm at the exact moment when OHCA starts, considering the sudden and unexpected nature of OHCA.

4. Materials and Methods

4.1. Study Design and Setting

We conducted a population-based case-control study. Cases were all of individuals who were included in the ARREST registry [18] in the study period 2009–2018. We included all emergency-medical-services-attended OHCAs from presumed cardiac causes excluding OHCAs with obvious non-cardiac causes (e.g., trauma, drowning, asphyxiation, drug intoxication/overdose) or those with incomplete drug-dispensing records one year prior to OHCA dates (index dates). Each OHCA case was matched using exact matching based on sex, age, and index date with up to five non-OHCA controls who were alive on the index date. This study was conducted based on the principles outlined in the Declaration of Helsinki. Written informed consent was obtained from all participants who survived OHCA. The Medical Ethics Committee of Academic Medical Center Amsterdam approved the use of data from patients who did not survive OHCA and approved this study(Ref.no.2017_260).

4.2. Data Collection

A detailed description of the ARREST registry is provided elsewhere [18]. In short, AR-REST is an ongoing population-based registry that enrolls all emergency-medical-services-

attended OHCAs prospectively in one contiguous region of the Netherlands using a mandatory notification system (consisting of all dispatch centers, ambulance personnel, and hospitals in the study region). By doing so, complete coverage of the study region and inclusion of >95% all OHCAs are ensured. After each suspected OHCA, ARREST personnel collect ECGs from all automated external defibrillators that have been deployed. The ECGs obtained from the emergency medical services (manual defibrillators) and automated external defibrillators were used to determine whether the first-registered rhythm was VT/VF or non-VT/VF. Emergency-medical-services-witnessed OHCAs were deemed to have cardiac causes unless an unequivocal non-cardiac cause existed. Controls were sampled from the PHARMO Database Network. The PHARMO Database Network is a network of electronic healthcare databases where anonymous data from different healthcare settings (e.g., general practitioners, pharmacies, hospitals, and clinical laboratories) in the Netherlands are combined [39]. In our study, individuals from this database that also contains drug-dispensing records were matched with the ARREST registry based on age, sex, and index year (OHCA year) [39]. For both cases and controls, we obtained drug-dispensing records one year prior to the index dates. In the Netherlands, virtually all individuals are registered at a single pharmacy independent of prescriber; therefore, medication records for both included cases and controls are considered as complete [40].

4.3. Exposure of Interest and Covariates

We defined non-cardiac DB-drug use as having a drug-dispensing record within 90 days prior to index date using the Anatomical Therapeutic Chemical Classification System since in the Netherlands, the average repeat prescription length for drugs used for chronic diseases is 90 days. For drugs usually prescribed for shorter periods, we adjusted the time window: $\leq$7 days for metoclopramide, $\leq$14 days for fexofenadine, and $\leq$30 days for tramadol. DB drugs were defined as drugs listed on the www.brugadadrugs.org website (accessed 1 November 2019) as class 1 DB drugs ('drugs to avoid by Brugada syndrome patients') or class 2 DB drugs ('drugs to preferably avoid') [16]. We studied all non-cardiac, DB drugs registered in the Netherlands that were used by at least one person in our dataset (see Supplementary Table S1 for the included drugs). We included cardiovascular disease and diabetes mellitus as covariates in our analyses because these are known risk factors for OHCA by using drug proxies as we did previously (Table 1) [14].

4.4. Statistical Analysis

We used conditional (multivariable) logistic regression analysis to assess the association between non-cardiac, DB drugs and OHCA risk by calculating the odds ratio (OR) and 95% confidence interval (CI). We calculated both crude estimates (unadjusted analysis) and multivariable analysis adjusted for all medications listed in Table 1. We adjusted for each individual class of drugs, as listed in Table 1, in the logistic regression model. First, we examined the association between non-cardiac DB drugs and OHCA risk compared with no use of any non-cardiac DB drug. Next, we stratified according to first-registered rhythm (VT/VF or non-VT/VF), sex, and age (age groups $\leq$50, 50–70, or $\geq$70 years). We conducted a stratified analysis according to use of cardiovascular drugs to determine whether effects modification was present. The presence of interaction on a multiplicative scale between non-cardiac, DB drugs and first-registered rhythm, sex, cardiovascular drug use, and age groups was estimated by consecutively including the cross-product of the two factors as a variable in the model. Furthermore, we compared resuscitation characteristics (location of OHCA, witnessed status OHCA, presence/absence of cardiopulmonary resuscitation, automated external defibrillator deployment, time from emergency call to defibrillator connection) between cases that used non-cardiac, DB drugs and those that did not since first-registered rhythm is strongly influenced by these resuscitation characteristics. Finally, some non-cardiac, DB drugs could block both cardiac sodium and potassium channels. An increase in OHCA-risk secondary to use of drugs that impair cardiac repolarization by blocking cardiac potassium channels is well-established [7]. Therefore, to exclude the

possibility that cardiac potassium-channel-blocking properties of some non-cardiac DB drugs is responsible for our observations, we separately studied the association on OHCA risk of non-cardiac, DB blocking drugs that are listed as QT-prolonging drugs according to www.CredibleMeds.org (Accessed on 16 July 2020) [41] and those that are not. Lastly, as a sensitivity analysis, we identified and adjusted for the number of drugs from Table 1 being dispensed simultaneously.

5. Conclusions

Use of non-cardiac, DB drugs is associated with increased risk of OHCA risk in the general population. This increased risk occurs in patients in whom non-VT/VF (asystole) is the first-registered heart rhythm, and it occurs in both sexes but more prominently among women and more strongly in the youngest patients ($\leq$50 years).

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/pharma1020007/s1, Table S1. Non-cardiac DB-drugs included in this study were defined as drugs listed on the www.brugadadrugs.org website; Table S2. Risk for out-of-hospital cardiac arrest upon use of non-cardiac depolarization blocking drugs: stratification according to cardiovascular drugs use; Table S3. Risk for out-of-hospital cardiac arrest upon use of non-cardiac depolarization blocking drugs with or without QT-prolonging potential; Table S4. Number of drugs being simultaneously dispensed.

Author Contributions: Conceptualization, T.E.E.; methodology, T.E.E., M.T.B. and P.C.S.; software T.E.E.; validation, M.T.B. and P.C.S.; formal analysis, T.E.E.; investigation, T.E.E.; resources, H.L.T.; data curation, T.E.E. and P.C.S.; writing—original draft preparation, T.E.E.; writing—review and editing, All authors; visualization, T.E.E.; supervision, M.T.B., P.C.S. and A.d.B.; project administration, T.E.E. and P.C.S.; funding acquisition, H.L.T. All authors have read and agreed to the published version of the manuscript.

Funding: This project has received funding from the European Union's Horizon 2020 research and innovation programme under acronym ESCAPE-NET, registered under grant agreement No 733381 (T.E.E., M.T.B., H.L.T.), the COST Action PARQ (grant agreement No CA19137) supported by COST (European Cooperation in Science and Technology), and the Dutch Heart Foundation (CVON2017-15 RESCUED and CVON2018-30 Predict-2; M.T.B., H.L.T.). The ARREST registry is supported by an unconditional grant of Stryker Emergency Care, Redmond, WA, USA. The funders were not involved in designing the study, collecting and analyzing the data, preparing the manuscript, or in the decision to publish.

Institutional Review Board Statement: The study was conducted according to the guidelines of the Declaration of Helsinki, and approved by the medical ethics committee of the Amsterdam UMC, location AMC in Amsterdam (Ref.no.2017_260).

Informed Consent Statement: Written informed consent was obtained from all surviving patients. The medical ethics committee of the Amsterdam UMC, location AMC in Amsterdam approved the use of data from patients who did not survive out-of-hospital cardiac arrest.

Data Availability Statement: The data underlying this article cannot be shared publicly due to ethical/privacy reasons. The data contain potentially identifying and sensitive patient information. The medical ethics committee of the Amsterdam UMC, location AMC had evaluated and approved the ARREST research protocol, including the requirement to store the study data in the hospital's high security environment. If need be the study data can be accessed by contacting ARREST's study coordinator Remy Stieglis (r.stieglis@amsterdamumc.nl). However, the study data cannot leave the high security data environment of the Amsterdam UMC and the PHARMO PD-group, due to their sensitive nature.

Acknowledgments: The authors greatly appreciate the contributions of Paulien Homma, Remy Stieglis, and Sandra de Haas for data management of the ARREST registry and are greatly indebted to all participating emergency medical services dispatch centers (Amsterdam, Haarlem, and Alkmaar), regional ambulance services (Ambulance Amsterdam, GGD Kennemerland, Witte Kruis, and Veiligheidsregio Noord-Holland Noord Ambulancezorg), fire brigades, and police departments in the study region for their contributions and support.

Conflicts of Interest: The authors declare no conflict of interest.

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