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ORIGINAL ARTICLE

Risk of out-of-hospital cardiac arrest in patients with epilepsy and users of antiepileptic drugs

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Aims: A few studies suggested that epilepsy and antiepileptic drugs with sodium channel-blocking properties were independently associated with out-of-hospital cardiac arrest (OHCA). However, these findings have not yet been replicated.

Methods: Using Danish registries, we conducted a nested case–control study in a cohort of individuals between 1 June 2001 and 31 December 2015. Cases were defined as OHCA from presumed cardiac causes, and were matched with non-OHCA-controls based on sex, and age on the date of OHCA. Exposure of interest was epilepsy or antiepileptic drug use. To study the association between individual antiepileptic drug use and the rate of OHCA, we compared each antiepileptic drug with valproic acid. Cox regression with time-dependent covariates was conducted to calculate hazard ratio (HR) and 95% confidence interval (CI).

Results: We identified 35 195 OHCA-cases and 351 950 matched non-OHCA controls. Epilepsy (cases: 3.58%, controls: 1.60%) was associated with increased rate of OHCA compared with the general population (HR: 1.76, 95%CI: 1.64–1.88) when common OHCA risk factors were taken into account. When we studied antiepileptic drug use, we found that 2 antiepileptic drugs without sodium channel blockage, clonazepam (HR: 1.88, 95%CI: 1.45–2.44) and pregabalin (HR: 1.33, 95%CI: 1.05–1.69), were associated with OHCA, whereas none of the antiepileptic drugs with sodium channel blockage were associated with OHCA.

Conclusion: Epilepsy is associated with increased rate of OHCA. Our findings do not support a possible association between antiepileptic drugs with sodium channel-blocking properties and OHCA.

KEYWORDS
antiepileptic drugs, epilepsy, pharmacoepidemiology, registry studies, sudden cardiac arrest

The authors confirm that the PI for this paper is Gunnar H. Gislason.

1 | INTRODUCTION

Out-of-hospital cardiac arrest (OHCA) is a vast general health problem that causes up to 50% of all cardiovascular deaths in industrialized countries.[1] OHCA may occur from cardiac arrhythmias secondary to disruptions in cardiac electrophysiology.[2] Several drugs used for cardiac disease (e.g. sotalol), but also common drugs used for noncardiac disease (e.g., antibiotics, antidepressants, antipsychotics), may impact on cardiac electrophysiology and increase the risk of OHCA by interacting with cardiac ion channels.[3,4] The best-known risk drugs are those that impair cardiac repolarization by blocking **cardiac potassium channels**, thereby leading to QT-prolongation on the electrocardiogram.[4] However, studies have shown that drug-induced arrhythmia may also apply to drugs that impair cardiac depolarization by blocking **cardiac sodium channels**, thereby leading to QRS widening on the electrocardiogram.[5]

A few studies have suggested that antiepileptic drugs with sodium channel-blocking properties and epilepsy independently could increase the risk of OHCA.[6,7] Moreover, it has been suggested that the increased OHCA risk of epilepsy patients may be partly explained by antiepileptic drug use.[6] However, these studies have important limitations (e.g., inclusion of small number of cases and misclassification of the outcome) and have yet to be reproduced.

Accordingly, we sought to investigate in a nationwide cohort that was specifically designed to study OHCA in the general population whether: (i) epilepsy was associated with OHCA; or (ii) whether OHCA rate was more elevated in users of antiepileptic drugs with sodium channel-blocking properties than users of antiepileptic drugs without such properties.

What is already known about this subject

- A few studies have suggested that epilepsy and antiepileptic drugs with sodium channel-blocking properties may independently increase the risk of out-of-hospital cardiac arrest (OHCA), but the evidence from these studies is inconclusive because these studies were small and had other important limitations in their design.

What this study adds

- The association between epilepsy and use of antiepileptic drugs is here studied in a large cohort specifically designed to study OHCA (total 35 195 patients with OHCA).
- Epilepsy was associated with increased rate of OHCA. The association persisted when common OHCA risk factors were taken into account. Furthermore, increased OHCA rate occurred in both sexes.
- Use of sodium blocking antiepileptic drugs was not associated with increased OHCA rate. Of the tested antiepileptic drugs, compared to valproic acid, significant associations are identified for nonsodium blocking antiepileptic drugs clonazepam and pregabalin.

2 | METHODS

2.1 | Data sources and definitions

Each resident in Denmark is assigned a unique civil registration number upon birth or immigration, which allows individual-level linkage of information across different nationwide clinical databases. Using this unique civil registration number, it is possible to follow all Danish citizens, allowing large-scale research with nationwide coverage.[8]

Patients with OHCA were identified from the Danish Cardiac Arrest Registry, which is an ongoing nationwide register that contains information on all OHCAs in Denmark since June 2001. OHCA was defined as a clinical condition of cardiac arrest where an ambulance has been summoned, and where cardiopulmonary resuscitation has been attempted, either by a bystander or emergency medical service personnel. Capture of OHCA is nearly complete as the Emergency Medical Services is obliged to fill out a case report for every attended OHCA providing information on important factors related to the OHCA. The presumed cause of OHCA was retrieved from discharge or death certificates by using diagnosis codes. OHCAs with diagnosis codes for cardiac disease, unknown disease, or unexpected collapse, were classified as being of presumed cardiac cause. OHCA with presumed noncardiac cause including trauma, attempted suicide, drug overdose, drowning, violent attack and other noncardiac diseases was excluded. The used register has been described in detail previously.[9] The Danish National Patient Register contains information on all hospital contacts coded with diagnostic codes according to the International Classification of Diseases (ICD) system and was used to obtain information on comorbidities.[10] The National Prescription Register contains complete drug-dispensing records classified according to the Anatomical Therapeutic Chemical (ATC) system and was used to obtain data on drug use.[11] Information on patients' age, sex and vital status was obtained from the Danish Civil Registration System.[8] Finally, data from the National Causes of Death Registry was used to determine the cause of death.[12]

2.2 | Study population

2.2.1 | Study design

We conducted a nested case–control study in a nationwide cohort of individuals between 1 June 2001 and 31 December 2015. Cases were individuals who suffered OHCA from presumed cardiac causes. Each case was matched with up to 10 non-OHCA controls from the

general population according to sex, and age on the date of OHCA (index-date).

2.2.2 | Exposure of interest and covariates

Patients with epilepsy were defined as any primary and secondary diagnoses registered in the Danish National Patient registry any time before the index date. Antiepileptic drug use was defined as having a drug-dispensing record within 90 days before the index-date. The included antiepileptic drugs and their ATC codes are listed in Table S1. Antiepileptic drugs were classified into 2 groups based on their potential to block the sodium channel (neural and/or cardiac),[13–16] as done in a previous study.[6] To minimize the risk of bias, we used an active comparator design in which the reference category consisted of the antiepileptic drug valproic acid. This drug was used as reference as it is considered not to have any effects on cardiac ion channels.[7]

Comorbidities were defined as any primary or secondary diagnoses registered up to 10 years before the index-date. We included the following risk factors for OHCA: ischaemic heart disease, congestive heart failure, atrial fibrillation, cerebrovascular disease, peripheral artery disease, diabetes mellitus, chronic kidney disease, severe psychiatric disorders and chronic obstructive pulmonary disease (see Table S2 for the ICD codes). Diabetes mellitus was defined as the use of antidiabetic drugs within 6 months before the index-date.

Concomitant pharmacotherapy was defined as having drug dispensing records for the drugs of interest up to 180 days before the index-date (see Table S2 for the ATC codes).

2.3 | Statistical analysis

The nested case–control design was applied to estimate the association between epilepsy and the rate of OHCA, and between antiepileptic drug use and the rate of OHCA, by calculating the hazard ratio (HR) and the associated 95% confidence interval using a time-dependent Cox proportional hazards regression model. We fitted Cox regression using a nested case–control design in which each OHCA case was matched with up to 10 controls based on sex and age on the date of OHCA. To study the association between individual antiepileptic drug use and the rate of OHCA, we compared each antiepileptic drug with valproic acid.[7] All models were adjusted for prespecified confounders: ischaemic heart disease including acute myocardial infarction, congestive heart failure, atrial fibrillation, cerebrovascular disease, peripheral artery disease, diabetes mellitus, chronic kidney disease, severe psychiatric disorders, chronic obstructive pulmonary disease, number of filled prescriptions for cardiovascular drugs and the use of QT-prolonging drugs. Furthermore, we studied the relation between epilepsy and OHCA stratified according to sex. Finally, to investigate a possible confounding effect by cerebrovascular disease, we studied the association between antiepileptic drugs and OHCA in patients without cerebrovascular disease. The study population was described as cases and controls using the χ^2 test for categorical variables and the Mann–Whitney test for continuous variables.

2.4 | Ethics

Ethical approval is not required for register-based studies with de-identified data and no active participation by study participants in Denmark. The use of register-based data has been approved by the Danish Data Protection Agency (Ref.no. 2007-58-0015, local ref.no. GEH-2014-017, I-Suite 0.2735).

3 | RESULTS

The study population consisted of 35 195 cases with OHCA and 351 950 matched controls without OHCA (Figure 1). The median age was 72 years and 66.82% were male (Table 1). The cases generally had much more comorbidities and concomitant pharmacotherapy than their matched controls (Table 1).

Epilepsy was diagnosed in 1260 (3.58%) cases and 5636 (1.60%) controls, and was associated with increased rate of OHCA (HR:1.76, 95% confidence interval [CI] 1.64–1.88, Figure 2). This increased OHCA-rate occurred in both men (HR: 1.75, 95%CI 1.61–1.89) and women (HR:1.81, 95%CI 1.61–2.04, Figure 2). When we studied individual antiepileptic drugs, we found that 2 antiepileptic drugs without sodium channel-blocking properties, **clonazepam** (cases 0.48%, controls 0.14%, HR 1.88, 95%CI 1.45–2.44) and **pregabalin** (cases 0.62%, controls 0.26%; HR 1.33, 95%CI 1.05–1.69), were associated with OHCA, whereas none of the sodium channel-blocking antiepileptic drugs were associated with significantly increased rate of OHCA

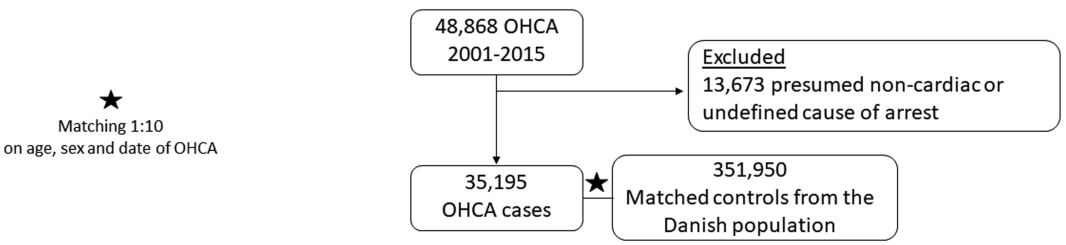

FIGURE 1 Flow chart of inclusion of out-of-hospital cardiac arrest (OHCA) cases and controls. OHCA, out-of-hospital cardiac arrest

TABLE 1 Study population characteristics

	Cases ($n = 35\,195$)	Controls ($n = 351\,950$)
Age (y), median [IQR]	72 [62–81]	72 [62–81]
Male sex, *n* (%)	23 519 (66.82)	235 190 (66.82)
Comorbidity, *n* (%)		
Ischaemic heart disease[a]	9316 (26.47)	41 992 (11.93)
Heart failure	7136 (20.28)	17 285 (4.91)
Atrial fibrillation	6102 (17.34)	26 850 (7.63)
Diabetes mellitus	5330 (15.14)	27 095 (7.70)
Cerebrovascular disease	4910 (13.95)	30 224 (8.59)
Peripheral artery disease	3914 (11.12)	15 798 (4.49)
Chronic kidney disease	2249 (6.39)	7557 (2.15)
Severe psychiatric disorders[b]	976 (2.77)	3262 (0.93)
Chronic obstructive pulmonary disease	5162 (14.67)	17 897 (5.09)
Concomitant pharmacotherapy, *n* (%)		
Beta blockers	8569 (24.35)	52 878 (15.02)
Calcium channel blockers	6978 (19.83)	55 877 (15.88)
Antithrombotics	16 075 (45.67)	102020 (28.99)
Diuretics	17 516 (49.77)	107869 (30.65)
Renin–angiotensin system inhibitors	13 105 (37.24)	89 481 (25.42)
Nitrates	3962 (11.26)	14 416 (4.10)
Antiarrhythmic drugs class 1 or 3	675 (1.92)	1887 (0.54)
QT-prolonging drugs	5857 (16.64)	28 932 (8.22)
Number of cardiovascular drugs (%)		
0	10208 (29.00)	168 881 (47.98)
1	5415 (15.39)	55 262 (15.70)
2	6416 (18.23)	54 600 (15.51)
> 2	13 156 (37.38)	73 207 (20.80)

IQR, interquartile range.
[a]Including acute myocardial infarction;
[b]depression, bipolar disorder and/or schizophrenia.

(Table 2). In our sensitivity analysis, the estimates for the association between individual antiepileptic drugs and OHCA-rate did not change significantly when we excluded patients with cerebrovascular disease (Table S3).

4 | DISCUSSION

In this nationwide nested case–control study, the main findings were: (i) epilepsy was associated with increased rate of OHCA. This increased rate occurred in both sexes; (ii) antiepileptic drugs with sodium channel-blocking properties were not associated with higher rates of OHCA than antiepileptic drugs without such properties in contrast with what has been reported elsewhere; and (iii) compared to valproic acid, significant increased rate of OHCA was identified for clonazepam and pregabalin.

Some AEDs act by blocking neuronal sodium channels.[13] As various neuronal and cardiac ion channel isoforms are highly homologous,[17] concerns regarding OHCA associated with sodium channel-blocking antiepileptic drugs has been raised in epidemiological studies.[6,7] Antiepileptic drugs that impair cardiac depolarization by blocking cardiac sodium channels may slow impulse conduction and facilitate re-entrant excitation and fatal arrhythmias that underlie OHCA, as shown for some class 1C antiarrhythmic drugs (e.g., flecainide, encainide).[18] Accordingly, Bardai *et al*. investigated in a longitudinal observational database whether sudden cardiac death was more likely in users of antiepileptic drugs with sodium channel-blocking properties than users of antiepileptic drugs without these properties, and found that antiepileptic drugs with sodium channel-blocking properties were significantly associated with increased sudden cardiac death, while antiepileptic drugs without such properties were not.[6] In that study, Bardai *et al*. reported that **carbamazepine** (odds ratio: 3.2) and **gabapentin** (odds ratio: 5.7) were the only individual antiepileptic drugs that were significantly associated with sudden cardiac death compared with no use of any antiepileptic drugs. Compared to our study findings, the findings by Bardai *et al*. may be

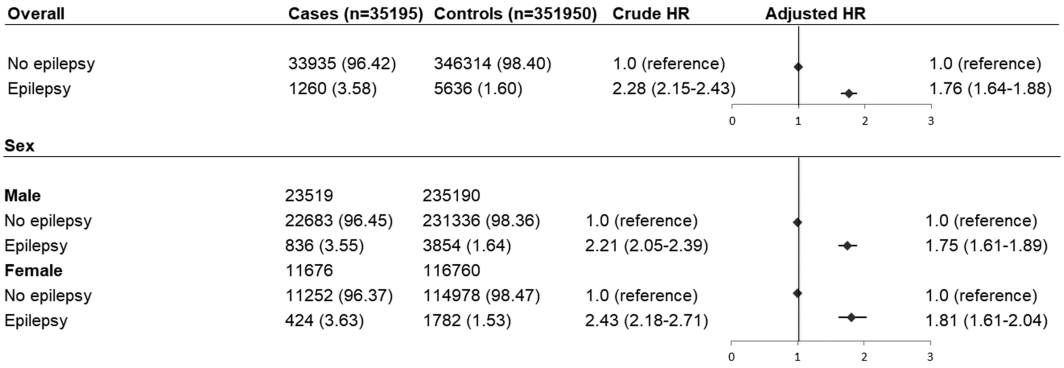

FIGURE 2 Hazard ratio of out-of-hospital cardiac arrest (OHCA) in patients with epilepsy in the overall population, and stratification according to sex. *P*-value interaction: sex*epilepsy = .07

TABLE 2 Hazard ratio of out-of-hospital cardiac arrest (OHCA) following treatment with specific antiepileptic drugs in overall population

	Cases (*n* = 35 195)	Controls (*n* = 351 950)	Crude HR	Adjusted HR[a]
Valproic acid	179 (0.51)	810 (0.23)	Reference	Reference
Sodium channel-blocking antiepileptic drugs				
Carbamazepine	166 (0.47)	885 (0.25)	0.85 (0.67–1.07)	1.00 (0.78–1.28)
Gabapentin	484 (1.38)	2035 (0.58)	1.08 (0.90–1.31)	1.20 (0.72–1.48)
Lamotrigine	196 (0.56)	1143 (0.32)	0.78 (0.62–0.97)	0.82 (0.65–1.04)
Oxcarbazepine	136 (0.39)	524 (0.15)	1.17 (0.91–1.50)	1.28 (0.98–1.67)
Phenytoin	28 (0.08)	191 (0.05)	0.66 (0.43–1.01)	0.90 (0.57–1.41)
Topiramate	10 (0.03)	76 (0.02)	0.59 (0.30–1.16)	0.76 (0.37–1.54)
Nonsodium channel-blocking antiepileptic drugs				
Clonazepam	168 (0.48)	481 (0.14)	1.58 (1.25–2.01)	1.88 (1.45–2.44)
Levetiracetam	53 (0.15)	199 (0.06)	1.21 (0.86–1.71)	1.33 (0.92–1.92)
Phenobarbital	75 (0.21)	328 (0.09)	1.03 (0.76–1.39)	1.20 (0.87–1.65)
Primidone	13 (0.04)	93 (0.03)	0.64 (0.35–1.17)	0.69 (0.36–1.32)
Pregabalin	219 (0.62)	917 (0.26)	1.09 (0.87–1.35)	1.33 (1.05–1.69)
Ethosuximide	<5	<5	NA	NA

Not included in the table: cases (%) and controls (%) of no users of antiepileptic drugs 90 days before case-index, users of > 2 antiepileptic drugs or users of other antiepileptic drugs: 33 219 (94.39%)/343 428 (97.58%), 244 (0.69%)/831 (0.24%), <5, 9 (<0.01%).

[a]Adjusted for ischaemic heart disease including acute myocardial infarction, congestive heart failure, atrial fibrillation, cerebrovascular disease, peripheral artery disease, diabetes mellitus, chronic kidney disease, severe psychiatric disorders, substance abuse, chronic obstructive pulmonary disease, number of filled prescriptions for cardiovascular drugs, use of QT-prolonging drugs and epilepsy.

HR, hazard ratio.

due to different designs. First, that study had small number of patients exposed to antiepileptic drugs (carbamazepine: 10 cases; gabapentin: 3 cases). Moreover, all reported odds ratios for the individual antiepileptic drugs were greater than the null value, which may indicate that the increased risk associated with sodium channel-blocking antiepileptic drugs but not for nonsodium channel antiepileptic drugs may reflect limited sample size rather than actual difference.[6,19] Second, misclassification of the outcome may have occurred, since that study was not based on a cohort that was specifically designed to study OHCA. Third, as some antiepileptic drugs could have been prescribed for other indications than epilepsy, such as chronic neuropathic pain, it is conceivable that the observed sudden cardiac death risk may be caused by the underlying cardiovascular disease rather than the sodium channel-blocking properties of antiepileptic drugs.[19] Also, data on important risk factor of OHCA, such as myocardial infarction and diabetes mellitus, were not included in the analyses. Hence, no direct adjustments for important risk factors of OHCA were performed. Another study by Hookana *et al*. found that antiepileptic drugs were more commonly used by sudden cardiac death victims than the controls.[7] However, that study had limited sample size (192 users of any antiepileptic drugs among the cases). Moreover, data on important risk factors of sudden cardiac death, such as heart failure and atrial fibrillation, were not included in the analyses. Also, bias in the medical history between the cases and controls may have occurred, since the information of the cases was obtained from their families. In both studies, confounding by indication may play an important role since

each individual antiepileptic drug was compared with no use of any antiepileptic drugs.[6,7] In our study, we tried to minimize confounding by indication by using valproic acid as the comparator drug. Conclusively, despite previous studies of increased risk of OHCA associated with sodium channel-blocking antiepileptic drugs, using a nationwide registry that was specifically designed to study OHCA, we were not able to reproduce this finding.

We found that epilepsy was associated with higher rate of OHCA compared with the general population. Patients with epilepsy are at higher risk of cardiovascular disorders compared to subjects without epilepsy,[20] which may predispose these patients to develop OHCA. Nevertheless, the association persisted when common OHCA risk factors were taken into account, thus implying that the higher OHCA rate among epilepsy patients can only be partly explained by increased incidence of cardiovascular morbidities. Several pathophysiological mechanisms in patients with epilepsy that may contribute to the higher OHCA-rate observed in these patients includes autonomic dysfunction, cardiac repolarization disorders (e.g., shortening or prolongation of the QT-interval) and genetic predisposition.[6,21,22]

4.1 | Strength and limitations

A major strength of our study is the use of complete nationwide databases, which minimized the risk for selection and inclusion bias by including very large number of OHCA cases, rendering our findings for the community at large.

A limitation is that, as this is an observational study and our data are not randomized, we could only detect associations without proving causality as residual confounding might influence our findings. Another limitation is that misclassification bias may occur since some of the diagnostic and procedural codes used to identify our covariates have not been validated. However, the majority of codes used to identify our covariates have undergone scrutiny for data quality with high positive predictive value.[23] Another limitation is that we had no information about the indication for the antiepileptic drug prescription, which may result in indication bias. Considering that the types of seizures affect the choice for antiepileptic drug therapy, the underlying disease for which they are prescribed may have affected the association with OHCA. To try to address this, we conducted a subgroup analyses in patients without cerebrovascular disease. Our main results were confirmed in this subgroup analyses. Also, as the information on drug use was based on drug-dispensing records, we had no direct information on drug adherence and actual drug intake. However, drug-dispensing records are already 1 important step closer to actual intake than drug prescription records. Furthermore, we have no reason to assume that drug intake would differ between the cases and controls. Finally, we cannot exclude the possibility of misclassification of our outcome, since information regarding the exact cause of OHCA was not available because autopsy was not performed. Therefore, it cannot be ruled out that for example respiratory arrest contributed, to some extent, to OHCA-risk in patient with epilepsy.

5 | CONCLUSION

Epilepsy is associated with increased rate of OHCA. Our findings do not support an association between antiepileptic drugs with sodium channels blocking properties and OHCA.

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COMPETING INTERESTS

None declared.

CONTRIBUTORS

T.E.E. conceived the study idea, performed the analyses and wrote the manuscript. All authors critically revised and approved the manuscript.

DATA AVAILABILITY STATEMENT

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

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SUPPORTING INFORMATION

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