Antidepressant Use and Risk of Out-of-Hospital Cardiac Arrest: A Nationwide Case–Time–Control Study

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Treatment with some types of antidepressants has been associated with sudden cardiac death. It is unknown whether the increased risk is due to a class effect or related to specific antidepressants within drug classes. All patients in Denmark with an out-of-hospital cardiac arrest (OHCA) were identified (2001–2007). Association between treatment with specific antidepressants and OHCA was examined by conditional logistic regression in case–time–control models. We identified 19,110 patients with an OHCA; 2,913 (15.2%) were receiving antidepressant treatment at the time of OHCA, with citalopram being the most frequently used type of antidepressant (50.8%). Tricyclic antidepressants (TCAs; odds ratio (OR) = 1.69, confidence interval (CI): 1.14–2.50) and selective serotonin reuptake inhibitors (SSRIs; OR = 1.21, CI: 1.00–1.47) were both associated with comparable increases in risk of OHCA, whereas no association was found for serotonin–norepinephrine reuptake inhibitors/noradrenergic and specific serotonergic antidepressants (SNRIs/NaSSAs; OR = 1.06, CI: 0.81–1.39). The increased risks were primarily driven by: citalopram (OR = 1.29, CI: 1.02–1.63) and nortriptyline (OR = 5.14, CI: 2.17–12.2). An association between cardiac arrest and antidepressant use could be documented in both the SSRI and TCA classes of drugs.

INTRODUCTION

Depression is a widespread disease, especially among patients with coronary heart disease (CHD), and has been identified as an independent risk factor for sudden cardiac death (SCD) and CHD-related mortality.[1,2] The use of antidepressants doubled from 1996 to 2005 in the United States, and they are now among the most commonly prescribed classes of medication.[3] In Denmark, the use of antidepressants is also growing every year, with citalopram accounting for more than 53 million defined daily doses in 2009, which made it the ninth most frequently prescribed drug overall.[3,4] Tricyclic antidepressants (TCAs) have previously been associated with increased risk of SCD and myocardial infarction (MI) owing to possible cardiotoxic properties.[5,6] By contrast, the newer selective serotonin reuptake inhibitor (SSRI) antidepressants are considered relatively safe even in overdose, which is why TCAs have been largely replaced by SSRI antidepressants for treatment of depression.[7,8] However, the US Food and Drug Administration recently issued a warning about citalopram (>40 mg/daily) and the risk of prolonged QT interval and torsade de pointes as a consequence of the findings made in a thorough QT study and in postmarketing surveillance.[9] Notably, the warning issued by the agency about citalopram and the studies linking the use of SSRIs with SCD in patients with and without CHD have raised concerns about the safety of SSRI antidepressants.[10,11]

Substances in a given class, e.g., TCAs and SSRIs, are regarded as having a class effect; i.e., either there are no differences in therapeutic effects or the differences are clinically unimportant. Previous studies investigating the risk of SCD associated with antidepressants consequently looked mostly at the overall risk of SCD related to SSRIs and TCAs and not at specific antidepressants. Therefore, it is currently unclear whether there are

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important differences between specific antidepressants within drug classes and the risk of out-of-hospital cardiac arrest (OHCA). We therefore examined the relationship between treatment with specific antidepressants and risk of OHCA in a nationwide unselected cohort.

RESULTS

We identified 19,110 patients who experienced OHCA between 2001 and 2007 according to the Danish Cardiac Arrest Register and the Copenhagen Emergency Care unit and who on January 1, 1997 were ≥10 years old (overall median age of 70.5 years; interquartile range: 59.2–79.7).

Baseline characteristics of the OHCA population in treatment with an antidepressant are presented in Table 1. In total, 2,913 (15.2%) patients were in treatment with an antidepressant at the time of OHCA. Of these, 378 patients were in treatment with more than one antidepressant. We identified 1,696 (58.2%) patients who were in treatment with only SSRI antidepressants, 286 (9.8%) with only TCAs, 553 (19.0%) with only serotonin–norepinephrine reuptake inhibitors/noradrenergic and specific serotonergic antidepressants (SNRIs/NaSSAs), and 378 (13.0%) with more than one class of antidepressants (Table 1). Only nine patients were in treatment with drugs from all three classes. Overall, few statistically significant differences were identified

Table 1 Baseline characteristics of patients with an out-of-hospital cardiac arrest who received antidepressant therapy at the time of event

	Any antidepressant	SSRI	TCA	SNRI/NaSSA	Two classes of antidepressants[a]
n (%)	2,913	1,696 (58.2)	286 (9,8)	553 (19.0)	378 (13.0)
Overall age, years (IQR)	72.0 (60.1–80.8)	73.5 (61.3–81.4)	67.1 (58.2–75.4)	71.3 (59.0–80.7)	72.6 (58.5–80.9)
Men (%)	1,437 (49.3)	877 (51.7)	139 (48.6)	253 (45.8)	168 (44.4)
Age, years (IQR)	70.0 (58.6–79.4)	72.2 (60.0–80.3)	66.6 (58.9–72.9)	68.6 (56.6–79.4)	65.6 (46.1–78.8)
Women (%)	1,476 (50.7)	819 (48.3)	147 (51.4)	300 (54.3)	210 (55.6)
Age, years (IQR)	74.0 (62.3–82.0)	74.8 (62.8–82.8)	68.1 (58.1–78.7)	74.5 (62.9–82.2)	75.1 (63.4–81.7)
Income group (%)					
0 (lowest income quintile)	717 (24.6)	418 (24.7)	80 (28.0)	135 (24.4)	84 (22.2)
1	788 (27.1)	466 (27.5)	62 (21.7)	149 (26.9)	111 (29.4)
2	699 (24.0)	424 (24.4)	75 (26.2)	129 (23.3)	81 (21.4)
3	447 (15.4)	240 (14.2)	45 (15.7)	95 (17.2)	67 (17.7)
4 (highest income quintile)	262 (9.0)	158 (9.3)	24 (8.4)	45 (8.1)	35 (9.3)
Comorbidity (%)					
Diabetes	404 (13.9)	241 (14.2)	51 (17.8)	66 (11.9)	46 (12.2)
Peripheral vascular disease	181 (6.2)	111 (6.5)	25 (8.7)	31 (5.6)	14 (3.7)
Cerebral vascular disease	495 (17.0)	332 (19.6)	40 (14.0)	63 (11.4)	60 (15.9)
Ischemic heart disease	499 (17.1)	313 (18.5)	42 (14.7)	88 (15.9)	56 (14.8)
Myocardial infarction	297 (10.2)	183 (10.8)	30 (10.5)	48 (8.7)	36 (9.5)
Heart failure	473 (16.2)	297 (17.5)	40 (14.0)	87 (15.7)	49 (13.0)
COPD	493 (16.9)	294 (17.3)	43 (15.0)	91 (16.5)	65 (17.2)
Cancer	307 (10.5)	174 (10.3)	48 (16.8)	51 (9.2)	34 (9.0)
Dementia	188 (6.5)	119 (7.0)	3 (1.0)	32 (5.8)	34 (9.0)
Depression	269 (9.2)	106 (6.3)	23 (8.0)	75 (15.6)	65 (17.2)
Any psychiatric disease	753 (25.9)	367 (21.6)	60 (21.0)	183 (33.1)	143 (37.8)
Concomitant pharmacotherapy (%)					
ACEi	654 (22.5)	379 (22.4)	64 (22.4)	129 (23.3)	82 (21.7)
Loop diuretics	894 (30.6)	520 (30.7)	84 (29.4)	157 (28.4)	131 (36.7)
β-Blockers	519 (17.8)	315 (18.6)	36 (12.6)	100 (18.1)	68 (18.0)
Calcium-channel blockers	360 (12.4)	218 (12.9)	34 (11.9)	62 (11.2)	46 (12.2)
Antipsychotics	667 (22.9)	326 (19.2)	64 (22.4)	166 (30.0)	111 (29.4)
Anxiolytics/sedatives	1,420 (48.8)	767 (45.2)	129 (45.1)	294 (53.2)	230 (60.9)

ACEi, angiotensin-converting enzyme inhibitor; COPD, chronic obstructive pulmonary disease; IQR, interquartile range; SNRI/NaSSA, serotonin–norepinephrine reuptake inhibitor/noradrenergic and specific serotonergic antidepressant; SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant.

[a]Patients in treatment with two of the following: SSRI, TCA, or SNRI/NaSSA.

between patients receiving the different antidepressant drug classes (Table 1). Patients in treatment with SSRIs or TCAs had fewer hospitalizations for depression or any psychiatric diseases, and these patients were also less likely to be in concomitant treatment with antipsychotic agents ($P < 0.001$ for all; Table 1).

Figure 1 depicts the proportion of OHCA patients (Figure 1a) and the age- and gender-matched controls (Figure 1b) in treatment with an antidepressant at the time of OHCA from 2001 to 2007 according to the class of antidepressant. From 2001 to 2007, there was an increase in the overall use of antidepressants (Figure 1a,b, *P* value for trend <0.001), with SSRI being the most frequently used class. Figure 2 illustrates the proportion of specific antidepressants used among OHCA patients who were in treatment with antidepressants at the time of OHCA. Citalopram was found to be the most frequently used type of antidepressant among OHCA patients, although a decline in the frequency of use was seen for patients in treatment at the time of OHCA from 2001 to 2007 (*P* for trend = 0.004). A reverse (increasing) pattern was seen for escitalopram (Figure 2, *P* for trend <0.001). A similar pattern in the use of specific antidepressants was also seen for the age- and gender-matched control population (data not shown).

Overall, results from the case–time–control analysis showed that treatment with any antidepressant was significantly associated with OHCA (odds ratio (OR) = 1.23, 95% confidence interval (CI): 1.06–1.43). Similar results were obtained for use of SSRIs (OR = 1.21, CI: 1.00–1.49) and TCAs (OR = 1.69, CI: 1.14–2.50) but not for SNRIs/NaSSAs (OR = 1.06, CI: 0.81–1.39). We found no additional increase in the risk of OHCA following concomitant treatment with two different classes of antidepressants, although the statistical power is too low to exclude additive or synergistic risk detection (data not shown).

Figure 3 shows the main results from the case–time–control analysis for risk of OHCA associated with specific antidepressants; both citalopram and nortriptyline were found to be significantly associated with OHCA (OR = 1.29, CI: 1.02–1.63 and OR = 5.14, CI: 2.17–12.2, respectively). No statistically significant association between OHCA and treatment with escitalopram, paroxetine, sertraline, imipramine, amitriptyline, venlafaxine, mianserin, or mirtazapine was found (Figure 3).

Other analyses

The predefined exposure periods in relation to the time of OHCA was set to 30-day intervals for case and control periods, which are used in all of the analyses for this article. However, for sensitivity, we performed additional analyses in which we repeated the analyses using treatment intervals of 40 and 50 days. Our findings using 40- and 50-day intervals for the case and control periods yielded similar results for both citalopram (OR = 1.26, CI: 1.01–1.57 and OR = 1.33, CI: 1.08–1.64, respectively) and nortriptyline (OR = 3.23, CI: 1.51–6.90 and OR = 2.82, CI: 1.39–5.75, respectively). Finally, we also performed additional sensitivity analyses in which we excluded patients who died from suicide and patients with a hospital admission 60 days before OHCA, which yielded similar results for all types of investigated antidepressants, including citalopram (OR = 1.29, CI: 1.02–1.63 and OR = 1.26, CI: 1.00–1.60, respectively) and nortriptyline (OR = 5.14, CI: 2.17–12.2, identical results in both sensitivity analyses).

DISCUSSION

In this nationwide study, we were able to demonstrate how antidepressant therapy with SSRIs or TCAs is associated with OHCA. In particular, we considered the risks of OHCA associated with the use of citalopram or nortriptyline. By comparison, no risk was associated with the use of SNRIs/NaSSAs.

To appreciate the results of this study, it is important to acknowledge the strengths and weaknesses of the case–time–control study design. In this method, the medication received at the time of OHCA is compared with medication received at some chosen time periods before the cardiac arrest (in our study, 90–60 days and 120–90 days before OHCA) using conditional

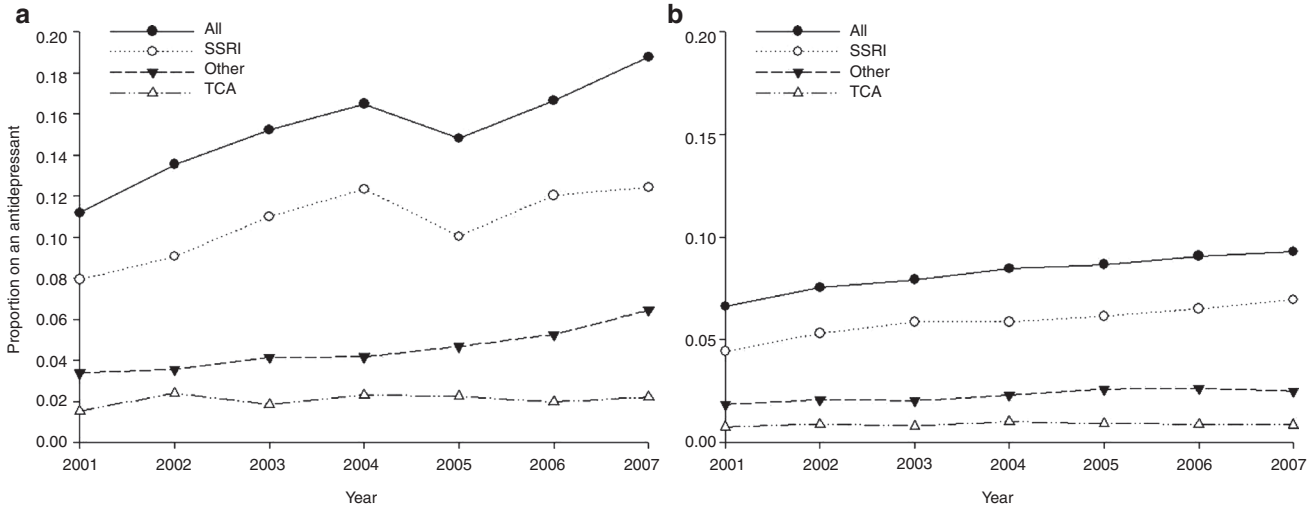

Figure 1 Proportion of patients with out-of-hospital cardiac arrest (OHCA) and controls in treatment at the time of event. (**a**) Patients with OHCA ($n = 2,913$); (**b**) control population. Controls were age- and gender-matched (1:4) from the entire Danish population. NaSSA, noradrenergic and specific serotonergic antidepressant; SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant.

logistic regression analyses. This method thereby estimates whether OHCA was associated with a recent initiation of the medications tested. Because each individual serves as his or her own control, the method provides good control for chronic conditions such as ischemic heart disease, hypertension, chronic obstructive pulmonary disease, smoking, overweight, and chronic depression. However, the method cannot distinguish between the risk of starting medication and the indication for the medication. Thus, if acute depression, worsening of depression, or some other reason that medication was started at just that time is a risk factor for OHCA, the risk could erroneously be attributed to the medication. Therefore, the case–time–control method for each drug tested cannot stand alone. Nevertheless, the fact that a range of drugs basically used for the same symptoms are associated with a range of risks is a strong indication that the medication is the factor associated with risk rather than the symptom being treated.

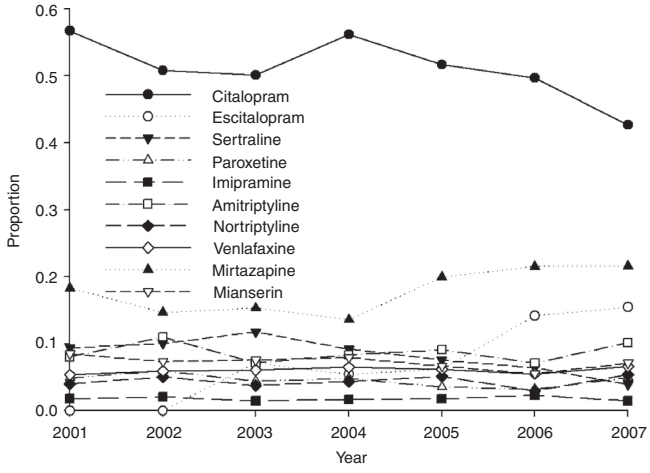

Figure 2 Proportion of claimed antidepressants by patients with out-of-hospital cardiac arrest (OHCA) according to year of event. Overall, 2,913 patients were in treatment with an antidepressant at the time of OHCA from 2001 to 2007.

Overall, SSRIs are the most frequently used antidepressant drug class in Denmark, which is reflected in the proportion of prescriptions claimed among OHCA patients, with citalopram and escitalopram being the two most widely used SSRIs (**Figure 1**). Results from recent studies have demonstrated an increased risk of stroke and SCD associated with SSRI antidepressant therapy.[10,11] Furthermore, a study examining the use of SSRIs among patients with CHD found an increased risk of MI and cardiovascular death associated with SSRI antidepressants.[12]An important strength of the present study is the ability to evaluate risk differences within antidepressant drug classes, which revealed how the increased risk of OHCA related to SSRI therapy was driven primarily by citalopram (**Figure 3**). In support of the identified risk of OHCA associated with citalopram treatment in this study, the Food and Drug Administration recently issued a warning on high doses of citalopram (>40 mg/day) after a thorough QT study identified a dose-dependent relationship between citalopram dose (20, 40, and 60 mg/day) and prolongation of the QT interval: 8.5 ms, (90% CI: 6.2–10.8); 12.6 ms (90% CI: 10.9–14.3), and 18.5 ms (90% CI: 16.0–21.0), respectively.[9] However, although this thorough QT study provided evidence of proarrhythmic properties associated with citalopram, it is important to note that in our study we were not able to draw conclusions as to whether the increased association between OHCA and citalopram is attributable to a QT prolongation and the subsequent development of torsade de pointes ventricular tachycardia. Citalopram had also previously been linked with abnormal QTc prolongation and torsade de pointes before the thorough QT study, although controlled randomized studies on citalopram examining cardiac outcomes are scarce.[9,13,14] One small randomized study of 284 patients treated with citalopram or placebo found no increased cardiac risk related to treatment, but this study was powered only for the analysis of depression, not the risk of an adverse event such as SCD.[15] Subanalysis of 256 patients from an observational study that focused on the risk of overall mortality and suicide

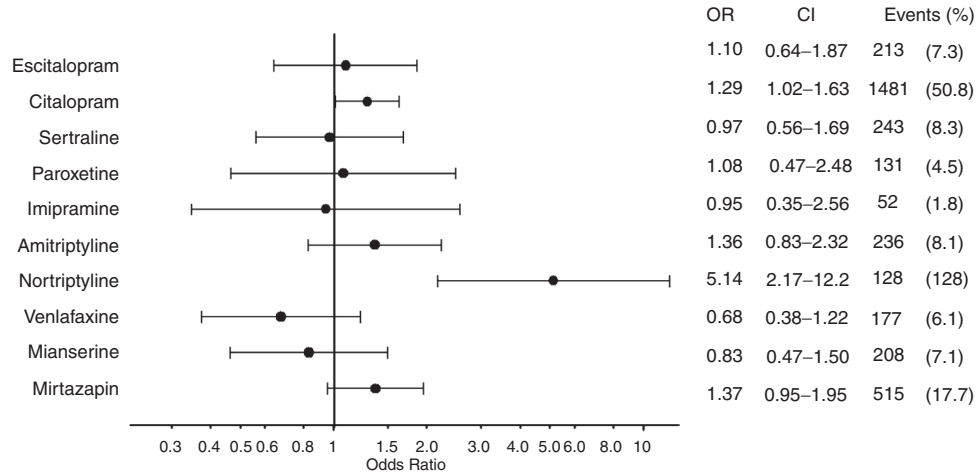

Figure 3 Risk of out-of-hospital cardiac arrest (OHCA) following treatment with specific antidepressants. Overall, 2,913 patients were in treatment with antidepressants on the day of OHCA. Of these, 378 patients received more than one antidepressant. In total, the 2,913 patients were in treatment with 3,384 antidepressants. No additional risk association to OHCA was found for patients in treatment with two antidepressants. ORs from the conditional logistic regression in case–time–control models are presented. CI, confidence interval; OR, odds ratio.

among patients on antidepressant treatment compared with no treatment found an increased cardiac risk among patients not in treatment with an SSRI, suggestive of a protective effect.[16] Finally, a recent observational study by Leonard *et al.*[17] found no risk of the composite end-point SCD/ventricular arrhythmia following use of citalopram. However, because the study relied on in-hospital diagnoses, it is possible that an association was masked because patients in an outpatient setting with a fatal outcome would not be likely to make it to the hospital.

The inhibitory and pharmacological effects of citalopram are mediated mostly by the S(+)-enantiomer (escitalopram) and less by the R(+)-enantiomer (R-citalopram).[18] Thus, the pure enantiomer escitalopram is theoretically devoid of the adverse side effects related to racemic citalopram. Moreover, newer antidepressants such as escitalopram are thought of as having a more benign cardiovascular side-effect profile as compared with older antidepressants, despite data suggestive of lower efficacy.[19] Notably, the recent Food and Drug Administration warning about citalopram and abnormal QT prolongation did not indicate that there was a similar issue of abnormal QT prolongation following escitalopram treatment, which could suggest that the majority of the reported QT prolonging issues stem from the R-enantiomer.[9] In agreement with this notion, we did not find any statistically significant risk of OHCA associated with the use of escitalopram (**Figure 3**).

SADHART (the Sertraline Antidepressants Heart Attack Randomized Trial), the largest randomized safety trial of any SSRI, evaluated cardiovascular safety with sertraline treatment among depressed patients with post-MI or unstable angina.[20] The investigators were unable to detect a difference between sertraline and placebo on cardiovascular outcomes. Notably, the SADHART study included 369 patients and thus had insufficient power to examine end points such as SCD. However, the incidence of severe cardiovascular events was numerically lower among patients treated with sertraline as compared with placebo, possibly suggesting a protective effect. Sertraline was not associated with OHCA in our analyses (**Figure 3**).

Newer antidepressants, including SNRIs and NaSSAs, are considered safer in terms of cardiovascular risk profile than older antidepressants.[21] In this context, we did not find any association for the antidepressant class SNRIs/NaSSAs (OR = 1.06, CI: 0.81–1.39), nor were the specific antidepressants venfalaxine, mianserin, or mirtazapine associated with OHCA (**Figure 3**).

The cardiac side effects of TCAs include inhibition of cardiac ion channels, prolongation of the QT interval, and, subsequently, the risk of inducing torsade de pointes.[21] Therefore, caution is advised when prescribing TCAs because of the risk of possible cardiotoxicity.[22] Surprisingly, the only TCA associated with OHCA according to our analyses was nortriptyline; amitriptyline and imipramine were not (**Figure 3**). The neutral study finding regarding the risk of OHCA associated with amitriptyline is of particular interest considering that nortriptyline is the active metabolite of amitriptyline. However, it is possible that these findings were influenced by the fact that low doses of TCAs are often used for the treatment of neurological pain, with amitriptyline often being the TCA of choice, which could mask a possible association between amitriptyline use and OHCA.[23] Furthermore, we were able to identify only 52 patients who were in treatment with imipramine at the time of OHCA, which is also reflected in the wide confidence intervals (**Figure 3**).

Overall, we identified 2,913 patients who were being treated with antidepressants, but only 269 (9.2%) of these patients had been admitted to the hospital with depression within 5 years of the OHCA (**Table 1**). These findings suggest that the severity of the depressive state among most patients in this study population did not require hospital admission. Depression is the manifestation of a number of symptoms, including low self-esteem, depressed mood, diminished interest and pleasure from activities, and diminished appetite, and it has been identified as a risk factor associated with SCD and CHD-related mortality.[2,24,25] The potential mediators responsible for the increased association between depression and the adverse prognosis related to CHD and sudden death include abnormalities in heart rate variability following MI,[26] arrhythmic mechanisms,[25] decreased levels of ω3 fatty acids in red blood cell membranes,[27] levels of inflammatory markers,[28] behavioral risk factors (such as substance abuse), poor self-care, health-related behavior, and poor adherence to treatment.[29] Furthermore, there seems to be a dose-dependent relationship between the degree of depressive symptoms and the risk of sustaining cardiac events.[30] Results from the ENRICHD trial (Effects of Treating Depression and Low Perceived Social Support on Clinical Events after Myocardial Infarction) demonstrated that antidepressant treatment was associated with significant improvements in depression but also reduced risks of recurrent MI and death following antidepressant treatment.[31,32]

Strengths and limitations

The main strength of this study is the ability to combine the rare outcome OHCA on a national level with information from national registers on hospital admissions, concomitant pharmacotherapy, and comorbidity. The study population comprised OHCA patients both in and out of the labor market, independent of race, sex, socioeconomic status, and health insurance programs. The case–time–control method uses each individual as his or her own control while controlling for time trends in exposure, thereby reducing the risk of control selection bias. With this method, the risk of unmeasured confounders is minimized, but because this is an observational study, we acknowledge that we cannot fully exclude the effect of unmeasured confounders.

The main limitation of this study is inherent in its observational nature. We have no precise indication for the initiation of treatment with antidepressants, the degree of depressive symptoms, coexisting psychiatric disease, or substance abuse that could influence outcome. Another limitation of this study is related to the large differences in sample size for the individual antidepressants. Within the class of SSRIs, we identified an increased risk associated with citalopram. But the substantially smaller sample sizes of the other SSRIs do not allow the conclusion that these are necessarily safer. Furthermore, we cannot fully determine whether patients actually took the claimed medication or whether patients discontinued antidepressant treatment, but because there is only a partial copayment of drug expenses in Denmark we assumed that patients who claimed a prescription

were likely to take the medication because they had an economic incentive. However, patients with depression may be more likely to display poor adherence to treatment as compared with other patients without depression, which could also influence our findings. The method used cannot distinguish between the risk of starting medication and the indication for the medication, and we acknowledge the possibility of confounding by indication—although we did find that a range of drugs used predominantly for the same indication yielded a range of risks, which suggests that the medication is the factor associated with risk rather than the indication. It is possible that the increased risk of OHCA associated with a specific antidepressant is caused by proarrhythmic capabilities as previously described in the literature. However, it is important to note that this is an observational study, which on its own cannot prove such causality.

In conclusion, this study shows that an association between OHCA and antidepressant use could be documented in both the SSRI and TCA drug classes. In particular, we found a risk of OHCA associated with use of citalopram and nortriptyline. Further studies on the cardiovascular risk of specific antidepressant drugs are warranted.

METHODS

Study population. OHCAs were identified from the Danish Cardiac Arrest Register and the Copenhagen Emergency Care unit in the period 2001–2007. We included all OHCA patients who on January 1, 1997 were ≥10 years old, as was done previously.[33] The Danish Cardiac Arrest Register contains information on date, time, and occurrence of all OHCAs for which an ambulance was dispatched.[34] The Copenhagen Emergency Care unit covers the central part of Copenhagen with physician-staffed ambulances that systematically record all data from OHCAs. Detailed information on the emergency care unit has been provided elsewhere.[35,36] Patients with obvious signs of death (i.e., trauma, rigor mortis, rigor livores), patients who were not classified by the treating physician as having an OHCA, or patients who did not receive cardiopulmonary resuscitation or defibrillation (by bystanders or ambulance personnel) were not recorded as OHCAs.

Databases. All residents in Denmark are assigned a unique and permanent personal civil registration number that enables individual-level linkage of information between nationwide registers. The Danish Register of Medicinal Product Statistics (National Prescription Register) holds information from Danish pharmacies on all dispensed drug prescriptions since 1995, classified according to the Anatomical Therapeutic Chemical (ATC) system, including dispensed strength, quantity, and date of dispensing. All pharmacies in Denmark are obliged to register all dispensed prescriptions because of the partial reimbursement of drug expenses by the government-financed health-care system. This ensures high validity and accuracy of the register.[37]

Information on comorbidity was obtained from the Danish National Patient Register, which has detailed information on all admissions to Danish hospitals since 1978.[38] Every hospital admission is registered with one primary diagnosis and, if appropriate, two or more secondary diagnoses according to the International Classification of Diseases (ICD)—before 1994, the 8th revision (ICD-8), and since 1994, the 10th revision (ICD-10). Causes of death, including primary cause, contributing causes, and underlying causes of death, were obtained from the National Causes of Death Register, registered according to the ICD-10. The Database for the Danish Labour Market holds information on average gross income for all Danish citizens.

We defined socioeconomic status by the individual's average annual gross income during the 5-year period before OHCA with information from the Database for the Danish Labour Market. Patients with suicide registered as the primary cause of death were identified in the National Causes of Death Register (ICD-10: X60-X84).

Comorbidity and pharmacotherapy. From the Danish National Patient Register, we obtained information on patient comorbidity by identifying hospital admissions up to 5 years before the date of OHCA. Primary or secondary discharge diagnoses of the following diseases specified in the Charlson comorbidity index[39] modified for use with ICD-10 (refs. 40,41) were used to define patient comorbidity: cerebral vascular disease, peripheral vascular disease, ischemic heart disease, MI, heart failure, malignancy, and chronic obstructive pulmonary disease.

We identified patients with diabetes as individuals who claimed at least one prescription for glucose-lowering medications (ATC: A10; oral or insulin) 180 days before the time of OHCA. A history of depression was identified by discharge diagnosis codes 296.09, 296.29, 298.09 (ICD-8) or F31.3-5, F32, F33 (ICD-10), and any psychiatric illness (including substance abuse) was identified by 290–301 (ICD-8) or F00–F99 (ICD-10).

From the National Prescription Register, we identified the use of antidepressants: SSRIs (ATC code): citalopram (N06AB04), paroxetine (N06AB05), sertraline (N06AB06), and escitalopram (N06AB10); TCAs (ATC code): imipramine (N06AA02), amitriptyline (N06AA09), and nortriptyline (N06AA10); and ***NaSSAs and SNRIs*** (ATC code): mianserin (N06AX03), mirtazapine (N06AX11), and venlafaxine (N06AG02).

Duration of treatment and treatment periods. We estimated daily dosage by calculating the average dosage from up to five consecutive prescriptions before the actual prescription, which constitutes a treatment interval. An advantage of this method is that it allows for dosages to change as described in detail previously.[42] For each prescription claimed, the number of pills was divided by the estimated daily dosage. Thus, we estimated the treatment duration for each individual who claimed at least one prescription, as was done before.[43] Patients in treatment with antidepressants up to 30 days before their OHCA were in treatment during the case period. Two control periods were selected. Therefore, patients in antidepressant treatment 120–90 days or 90–60 days before OHCA were in treatment during the respective control periods.

Statistics. Comparison of categorical variables was done with the χ^2 test, and differences between continuous variables were tested with the Kruskal–Wallis test. We used the Cochran–Armitage test for trend to evaluate trends in drug exposure over time. The risk of OHCA in relation to use of antidepressants was estimated using conditional logistic regression analyses in case–time–control models. Importantly, time trends in drug exposure can introduce bias into traditional case-crossover studies as opposed to the current case–time–control analysis.[42,43] The control group for the case–time–control analyses was identified from the entire Danish population and matched (1:4) on age and sex using the "Greedy match algorithm."[44] The case–time–control method is based on the crossover paradigm in which the individual appears as his or her own control in other periods of time before the time of the event.[45] The use of this method minimizes the effect of unmeasured and unidentified confounders. The case period was defined as 30–0 days before the event; to enhance the strength of the analyses, we selected two control periods: 120–90 and 90–60 days before the event.

For all analyses, a two-sided $P < 0.05$ was considered statistically significant. All analyses were carried out using SAS, version 9.2 (SAS Institute, Cary, NC), and R: A Language and Environment for Statistical Computing (Vienna, Austria).

Sensitivity analyses. For sensitivity, we made additional case–time–control analyses with different time windows of exposure. We also performed additional sensitivity analyses in which we excluded 98 patients who died from suicide according to the National Causes of Death Register; to evaluate the effect of a recent hospital admission on our results, we repeated the analyses for patients with and without a hospital admission 60 days before OHCA. Finally, the results were tested against the violation of the conditional independence assumption for exposures at different time points.[42,43] The results obtained for parameter settings were similar to those presented here, which indicates an insignificant bias of the

case–time–control design, even when this assumption is violated (data not shown).

Ethics. This study was approved by the Danish Data Protection Agency (2008-41-2685). In Denmark, retrospective register-based studies in which individual patients cannot be identified do not require ethical approval.

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AUTHOR CONTRIBUTIONS

P.W. wrote the manuscript, designed research, performed research, and analyzed data; A.J., F.F., J.B.O., C.A., E.L.F., J.K.L., F.K.L., S.L.N., T.G., P.K.A., J.K.K., H.E.P., S.P., and L.K. analyzed data; and G.H.G. and C.T.-P. designed research and analyzed data.

CONFLICT OF INTEREST

The authors declared no conflict of interest.

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