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ORIGINAL ARTICLE

Opioid use is associated with increased out-of-hospital cardiac arrest risk among 40 000-cases across two countries

Talip E. Eroglu[1,2,3] | Carlo A. Barcella[3] | Marieke T. Blom[1] | Patrick C. Souverein[2] | Grimur H. Mohr[3] | Christian Torp-Pedersen[3,4,5] | Fredrik Folke[3,6] | Mads Wissenberg[3,6] | Anthonius de Boer[2] | Gunnar H. Gislason[3,7,8] | Hanno L. Tan[1,9] | for the ESCAPE-NET Investigators

[1]Department of Cardiology, Heart Center, Academic Medical Center, University of Amsterdam, Amsterdam, The Netherlands

[2]Division of Pharmacoepidemiology and Clinical Pharmacology, Utrecht Institute for Pharmaceutical Sciences, Utrecht University, Utrecht, The Netherlands

[3]Department of Cardiology, Herlev and Gentofte Hospital, University of Copenhagen, Gentofte, Denmark

[4]Department of Cardiology, Aalborg University Hospital, Aalborg, Denmark

[5]Department of Clinical Investigation and Cardiology, Nordsjaellands Hospital, Hillerød, Denmark

[6]Copenhagen Emergency Medical Services, Denmark

[7]National Institute of Public Health, University of Southern Denmark, Copenhagen, Denmark

[8]The Danish Heart Foundation, Copenhagen, Denmark

[9]Netherlands Heart Institute, Utrecht, The Netherlands

Correspondence
Hanno L. Tan, MD, PhD, Department of Cardiology, Heart Center, Academic Medical Center, University of Amsterdam, Meibergdreef 9, 1105 AZ, Amsterdam, The Netherlands.
Email: h.l.tan@amc.uva.nl

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Aims: Opioid use has substantially increased in the last decade and is associated with overdose mortality, but also with increased mortality from cardiovascular causes. This finding may partly reflect an association between opioids and out-of-hospital cardiac arrest (OHCA). Therefore, we aimed to investigate OHCA-risk of opioids in the community.

Methods: We conducted 2 population-based case–control studies separately in the Netherlands (2009–2018) and Denmark (2001–2015). Cases were individuals who experienced OHCA of presumed cardiac cause. Each case was matched with up to 5 non-OHCA-controls according to age, sex and OHCA-date. Conditional logistic regression analysis was used to calculate odds ratios (ORs) and 95% confidence intervals (CIs).

Results: We included 5473 OHCA-cases matched with 21 866 non-OHCA-controls in the Netherlands, and 35 017 OHCA-cases matched with 175 085 non-OHCA-controls in Denmark. We found that use of opioids (the Netherlands: cases: 5.4%, controls: 1.8%; Denmark: cases: 11.9%, controls: 4.4%) was associated with increased OHCA-risk in both regions (the Netherlands: OR 2.1 [95% CI 1.8–2.5]; Denmark: OR 1.8 [95% CI 1.5–2.1]). The association was observed in both sexes, and in individuals

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

with cardiovascular disease (the Netherlands: OR 1.8 [95% CI 1.5–2.1]; Denmark: OR 1.6 [95% CI 1.5–1.7]) or without (the Netherlands: OR 3.4 [95% CI: 2.4–4.8], $P_{interaction}$ < .0001; Denmark: OR 2.3 [95% CI: 2.0–2.5], $P_{interaction}$ < .0001).

Conclusion: Use of opioids is associated with increased OHCA-risk in both sexes, independently of concomitant cardiovascular disease. These findings should be considered when evaluating the harms and benefits of treatment with opioids.

KEYWORDS

epidemiology, opioids, sudden cardiac arrest

1 | INTRODUCTION

Opioid use has drastically increased in the last decade in the USA.[1,2] The rise in opioid prescriptions is paralleled by an increase in overdose deaths.[2,3] In the USA, approximately 130 people died every day from an opioid overdose in 2016 and 2017.[4] In Europe, use of opioids has also substantially increased since 2009,[5] albeit to a lesser extent. In the Netherlands, 1 027 019 individuals (6.0% of the total population) received at least 1 opioid prescription in 2017.[6]

A previous study by Ray *et al.* demonstrated that opioids not only increase the risk of overdose mortality, but also may increase mortality from other causes.[7] In that study, it was shown that >2/3 of the excess deaths associated with opioids were due to causes other than overdose; of these, >1/2 were cardiovascular deaths.[7] An increased risk for cardiac arrhythmias has been proposed as a contributing factor to this association.[7]

Out-of-hospital cardiac arrest (OHCA) may result from cardiac arrhythmias (ventricular tachycardia,[8] ventricular fibrillation[8] or bradyarrhythmias [asystole][9]) secondary to disruptions in cardiac electrophysiology.[8] In vivo and in vitro studies indicated that opioids influence cardiac electrophysiology, resulting in QT-prolongation on the electrocardiogram (ECG).[10–14] Other mechanisms by which opioids might contribute to an increase in cardiac arrhythmia risk include: increased platelet aggregation; opioid withdrawal syndrome; myocardial fibrosis; increase in inflammatory markers such as C-reactive protein; and accelerated atherosclerosis with chronic opioid use.[15–19] Whether the use of opioids is associated with increased risk of OHCA is not established to our knowledge. Establishing whether or not use of opioids is associated with increased OHCA risk is of clear clinical importance in the face of the rising number of opioid users worldwide.[20,21] Therefore, we aimed to study whether opioids are associated with increased OHCA risk overall and in subgroups defined by age, sex and presence of cardiovascular disease. To address these questions, we conducted 2 case–control studies separately in the Netherlands and Denmark using data from 2 large ongoing population-based emergency medical services (EMS)-attended OHCA-registries that were specifically designed to study OHCA in the general population.

What is already known about this subject

- Opioid use has substantially increased in the last decade and is associated with overdose mortality, but also with increased mortality from cardiovascular causes.
- Previous studies suggested that opioids may induce the fatal arrhythmias that underlie out-of-hospital cardiac arrest (OHCA), as in vivo and in vitro studies indicated that opioids impact on cardiac electrophysiology. Whether opioids increases OHCA-risk in the general population is unknown.

What this study adds

- We studied the risk of OHCA associated with opioid use in 40 000 OHCA cases from 2 registries in the Netherlands and Denmark.
- Use of opioids is associated with a ~2-fold increased risk of OHCA in both regions. This increased risk occurs in both sexes, and both in individuals with cardiovascular disease and those without. These findings should be considered when evaluating the harms and benefits of treatment with opioids.

2 | METHODS

2.1 | Design and setting

We conducted 2 population-based case–control studies separately in the Netherlands and Denmark. Cases were individuals who suffered OHCA from presumed cardiac causes sourced from ongoing population-based EMS-attended OHCA-registries in the Netherlands (AmsteRdam REsuscitation STudies, ARREST; 2009–2018) and Denmark (Danish Cardiac Arrest Registry, DANCAR; 2001–2015). Both registries are part of the ESCAPE-NET consortium that studies OHCA across Europe.[22] In both registries, OHCAs are recorded

according to Utstein criteria.[23] We excluded OHCAs with incomplete drug dispensing-records 1 year prior to OHCA-date (index-date) or those with obvious noncardiac cause according to Utstein recommendations, e.g., trauma, asphyxiation and drug intoxication.[23] Each case was matched on age, sex and index-date with up to 5 non-OHCA controls who were alive on the index-date, as described previously.[24]

This study was conducted based on the principles outlined in the Declaration of Helsinki, and was approved by the institutional review board of Academic Medical Center Amsterdam and the Danish Data Protection Agency (Ref.no. 2007-58-0015, local ref.no. GEH-2014-017, I-Suite 0.2735). In Denmark, ethical approval is not required for de-identified retrospective register-based studies.

2.2 | The Netherlands

A detailed description of the ARREST registry is provided elsewhere.[25] In short, ARREST is an ongoing population-based registry that enrols EMS-attended OHCAs in 1 large region of the Netherlands representative for the community at large (~2.6 million inhabitants and covering both urban and rural areas). OHCAs were registered in collaboration with all dispatch centres, ambulance personnel and hospitals in the study region. By doing so, a complete coverage of study region and inclusion of >95% all OHCAs is ensured. After each suspected OHCA, EMS personnel routinely send ECGs, dispatch forms and run sheets, and call the ARREST study center to provide information on location and circumstances of OHCA. Complete drug dispensing records in the year before OHCA is retrieved from the patient's pharmacy using standardized protocols.

Non-OHCA controls were sampled from the PHARMO Database Network, a population-based network of healthcare databases that combines different healthcare settings, including community pharmacies, and contains, among other things, drug dispensing records from community pharmacies.[26,27] We also retrieved complete drug dispensing records in the year before the index-date for the controls. In the Netherlands, virtually all patients are registered at a single pharmacy independent of prescriber; therefore, drug dispensing records are considered as complete.[28] A detailed description of the PHARMO Database Network is provided elsewhere.[26,27]

2.3 | Denmark

DANCAR is an ongoing population-based register including information on all OHCAs in Denmark (population 5.8 million).[29] A patient is included when a clinical condition of cardiac arrest results in resuscitation attempt either by bystanders or EMS. Capture of OHCA is nearly complete as the EMS is obliged to fill out a case report for every attended OHCA. Diagnosis codes from death certificates and discharge diagnoses were used to define the cause of OHCA. Cases including codes for cardiac disease, unknown disease, or unexpected collapse, were classified as being of presumed cardiac cause. Details of this registry are described elsewhere.[29] A unique and permanent civil registration number is assigned to all Danish citizens upon birth or immigration, which allows the identification of patients across the Danish nationwide registries at an individual's level. Information on hospital admission were obtained from the Danish National Patient registry and included data on discharge diagnosis codes which were recorded according to the International Classification of Diseases (ICD): until 1994 the ICD-8 and from 1994 the ICD-10. Information on dispensed prescriptions for drugs was obtained from the Danish National Prescription Registry, where the drugs are classified according to the Anatomical Therapeutic Chemical (ATC) system. Information about age, sex and vital status were retrieved from the Danish Civil Registration System. From the Danish Register of Causes of Death, we retrieved information about causes of death, including primary and contributing causes.

2.4 | Exposure of interest and covariates

We defined opioid use as having drug dispensing records of opioids (according to the ATC system) in the period 30 days before (ARREST) or covering a period of maximally 30 days before the index date (DANCAR).

In both registries, the use of cardiovascular pharmacotherapy and antidiabetic drugs was identified up to 6 months prior to index-date and were included in the analysis as proxies for cardiovascular disease and diabetes since these are well-known risk factors for OHCA, as we did previously (listed in Table 1).[19] Furthermore, in both registries we assessed the use of antidepressants, antipsychotics and antiepileptic drugs. We used a period of 90 days before index-date for antidepressants, antipsychotics and antiepileptic drugs in order to adjust for the direct cardiac electrophysiological effects of these drugs.[30–35] Moreover, use of these drugs could be considered as proxies for depression,[36] schizophrenia[37] and epilepsy,[35] which are risk factors for OHCA. To mitigate the limitations with the use of drug proxies, we also used information on comorbidities using in-patient and outpatient hospital discharge diagnoses and procedure codes up to 5 years prior to OHCA in our analysis using DANCAR-date, and calculated Charlson comorbidity index (CCI) scores based on these comorbidities. Furthermore, severe psychiatric disorders (i.e. depression, bipolar disorders and/or schizophrenia) were included in our analysis based on hospital discharge diagnosis using DANCAR-data. In ARREST, we could not perform direct adjustment for these variables since data regarding comorbidities were lacking in the controls.

2.5 | Statistical analyses

Conditional logistic regression analysis was used to estimate the association between use of opioids and OHCA risk by calculating adjusted odds ratios (OR_{adj}) and associated 95% confidence intervals (CI). Analyses were systematically adjusted for all comorbidities and medications listed in Table 1. To further investigate a possible confounding effect by the presence of cardiovascular disease, we studied the relationship between

TABLE 1 Baseline characteristics of cases and controls

	ARREST			DANCAR		
	Cases	Controls	*P*-value	Cases	Controls	P-value
Total	5473	21 866		35 017	175 085	
Mean age (y), mean (standard deviation)	68.8 (14.0)	68.8 (14.0)	n/a	70.7 (14.0)	70.7 (14.0)	n/a
Male sex	3823 (69.9)	15 263 (69.8)	n/a	23 422 (66.9)	117 110 (66.9)	n/a
Concomitant drug use						
Beta blockers[a]	1998 (36.5)	3839 (17.6)	<.001	8565 (24.5)	23 035 (13.2)	<.001
Calcium channel blockers[a]	902 (16.5)	2016 (9.2)	<.001	6970 (19.9)	24 370 (13.9)	<.001
Antithrombotics[a]	2299 (42.0)	4853 (22.2)	<.001	16 059 (45.9)	43 974 (25.1)	<.001
Diuretics[a]	1590 (29.1)	2712 (12.4)	<.001	17 485 (49.9)	46 831 (26.8)	<.001
Renin–angiotensin system inhibitors[a]	2073 (37.9)	4802 (22.0)	<.001	13 097 (37.4)	39 455 (22.5)	<.001
Nitrates[a]	574 (10.5)	841 (3.9)	<.001	3956 (11.3)	6027 (3.4)	<.001
Statins[a]	1843 (33.7)	4609 (21.1)	<.001	9605 (27.4)	31 025 (17.7)	<.001
Antidiabetics[a]	936 (17.1)	2145 (9.8)	<.001	5326 (15.2)	11 924 (6.8)	<.001
Antiarrhythmic drugs class 1 or 3[b]	114 (2.1)	183 (0.8)	<.001	675 (1.9)	822 (0.5)	<.001
Antiepileptics[b]	205 (3.8)	383 (1.8)	<.001	1959 (5.6)	3740 (2.1)	<.001
Antidepressants[b]	369 (6.7)	918 (4.2)	<.001	5595 (16.0)	14 097 (8.1)	<.001
Antipsychotics[b]	186 (3.4)	279 (1.3)	<.001	2380 (6.8)	3794 (2.2)	<.001
Comorbidity						
Ischemic heart disease[c]	n/a	n/a	n/a	7507 (21.4)	13 233 (7.6)	<.001
Congestive heart failure	n/a	n/a	n/a	6152 (17.6)	5589 (3.2)	<.001
Atrial fibrillation	n/a	n/a	n/a	5392 (15.4)	9290 (5.3)	<.001
Cerebrovascular disease	n/a	n/a	n/a	3730 (10.7)	9332 (5.3)	<.001
Peripheral artery disease	n/a	n/a	n/a	3069 (8.8)	5018 (2.9)	<.001
Malignancy	n/a	n/a	n/a	3245 (9.3)	11 203 (6.4)	<.001
Chronic obstructive pulmonary disease	n/a	n/a	n/a	4479 (12.8)	5961 (3.4)	<.001
Epilepsy	n/a	n/a	n/a	697 (2.0)	1209 (0.7)	<.001
Chronic kidney disease	n/a	n/a	n/a	2059 (5.9)	2780 (1.6)	<.001
Substance abuse	n/a	n/a	n/a	2507 (7.2)	3275 (1.9)	<.001
Severe psychiatric disorders[d]	n/a	n/a	n/a	797 (2.3)	1007 (0.6)	<.001

Numbers are *n* (%) unless indicated otherwise. n/a, not available.
[a]defined as use within 6 months before the index date
[b]defined as use within 90 days before the index date
[c]including acute myocardial infarction
[d]depression, bipolar disorder and/or schizophrenia.

opioid use and OHCA risk stratified according to presence of cardiovascular disease. By sub-selecting all individuals with or without cardiovascular disease from the original case–control data set, the original matching was lost. Therefore, in these unmatched subgroups, estimates were additionally adjusted for age and sex using multivariable logistic regression analyses. We also stratified our analyses according to sex and age (<70 or ≥70 years). The presence of interaction on a multiplicative scale between opioid use and OHCA, sex and age was estimated by consecutively including the cross-product of the 2 factors as a variable into the multivariate model. Moreover, a sensitivity analysis was performed to stratify our analyses by CCI score (0, 1 or ≥2) by using data from DANCAR. Finally, we performed supplementary analyses in subgroups only including patients with OHCA presenting with shockable rhythm (ventricular tachycardia/ventricular fibrillation ventricular tachycardia/ventricular fibrillation).

Continuous variables are presented as mean ± standard deviation, and categorical data are absolute numbers and proportions. Differences between cases and controls were tested using the χ^2 test or Student's *t* test, where appropriate. We considered a 2-sided *P*-value <.05 statistically significant.

2.6 | Nomenclature of targets and ligands

Key protein targets and ligands in this article are hyperlinked to corresponding entries in http://www.guidetopharmacology.org, and

are permanently archived in the Concise Guide to PHARMACOLOGY 2019/20 (Alexander *et al*., 2019 a,b).

3 | RESULTS

We identified 5473 OHCA cases (mean age 68.8 years, 69.9% male, Table 1) and matched them with 21 866 non-OHCA controls in the Netherlands, and 35 017 OHCA cases (mean age 70.7 years, 66.9% male) and matched them with 175 085 non-OHCA controls in Denmark (Figure 1). Compared to no use of opioids, current use of opioids (the Netherlands: cases: 5.4%, controls: 1.8%; Denmark: cases: 11.9%, controls: 4.4%, Figure 2) was associated with increased OHCA-risk in both registries (the Netherlands: OR_{adj} 2.1 [95% CI 1.8–2.5]; Denmark: OR_{adj} 1.7 [95% CI 1.6–1.8]). Current use of 2 or more opioids was associated with a further increased

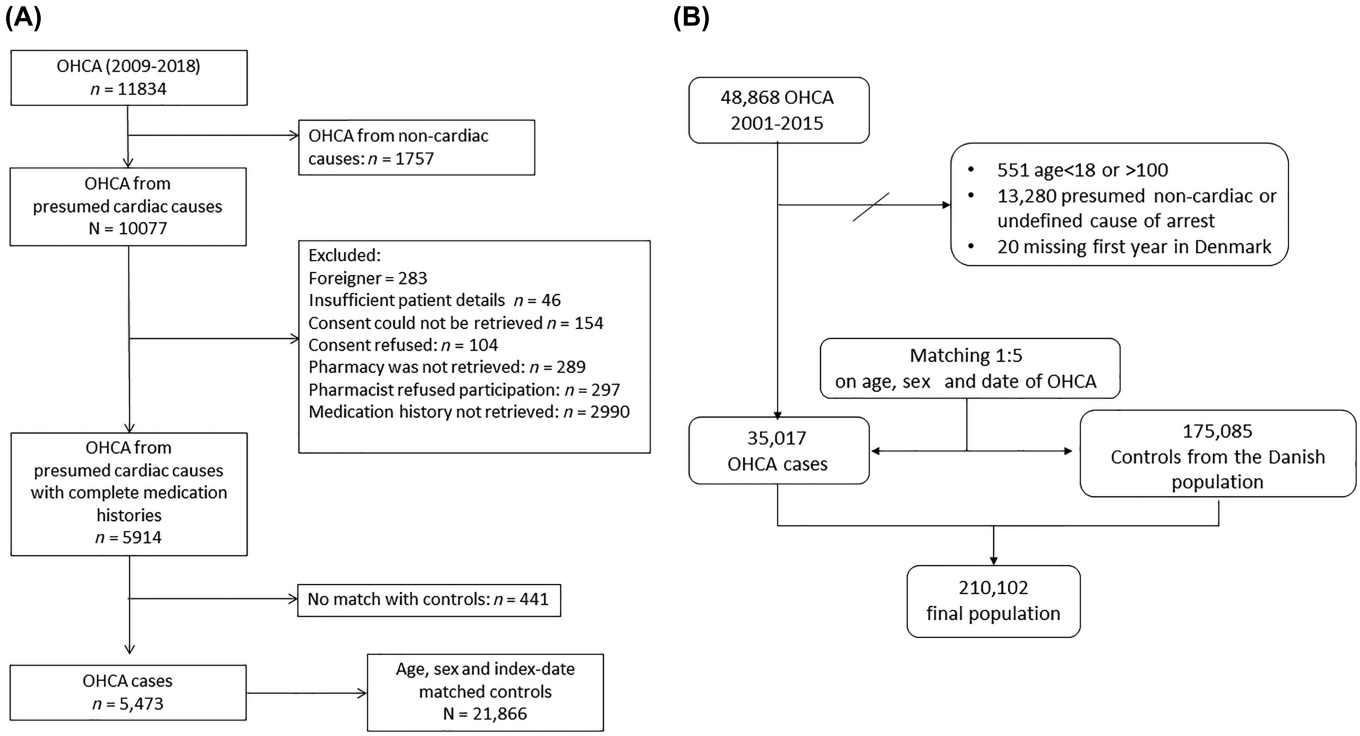

FIGURE 1 Flow chart of inclusion of out-of-hospital cardiac arrest (OHCA) cases in ARREST (A) and DANCAR (B). OHCA, out-of-hospital cardiac arrest; VT/VF, ventricular tachycardia/ventricular fibrillation

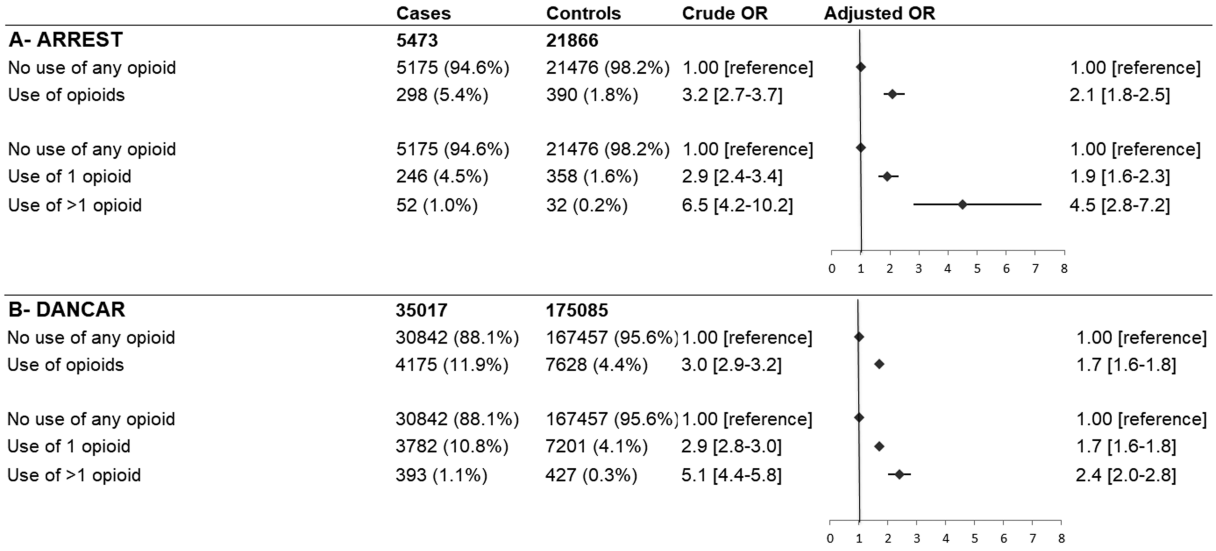

FIGURE 2 Risk of out-of-hospital cardiac arrest with use of opioids. CI, confidence interval; OR, odds ratio. Numbers are *n* (%) unless indicated otherwise. OR adjusted for use of all covariates listed in Table 1

TABLE 2 Risk for out-of-hospital cardiac arrest upon use of opioids: stratification according to cardiovascular disease, sex and age

	ARREST				DANCAR			
	Cases ($n = 5473$)	Controls ($n = 21\,866$)	Crude OR (95% CI)	Adjusted OR (95% CI)	Cases ($n = 35\,017$)	Controls ($n = 175\,085$)	Crude OR (95% CI)	Adjusted OR (95% CI)
Sex								
Men	3823	15 263			23 422	117 110		
No use of any opioid	3659 (95.7)	15 048 (98.6)	1.0 (reference)	1.0 (reference)	21 221 (90.6)	113 341 (96.8)	1.0 (reference)	1.0 (reference)
Use of opioids	164 (4.3)	215 (1.4)	3.1 (2.5–3.9)	2.3 (1.8–2.8)	2201 (9.4)	3769 (3.2)	3.1 (3.0–3.3)	1.7 (1.6–1.8)
Women	1650	6603			11 595	57 975		
No use of any opioid	1516 (91.9)	6428 (97.4)	1.0 (reference)	1.0 (reference)	9621 (83.0)	54 116 (93.3)	1.0 (reference)	1.0 (reference)
Use of opioids	134 (8.1)	175 (2.7)	3.2 (2.5–4.1)	2.0 (1.6–2.6)	1974 (17.0)	3859 (6.7)	2.9 (2.7–3.1)	1.7 (1.6–1.8)
Age								
< 70 y	2663	10 648			14 940	75 435		
No use of any opioid	2529 (95.0)	10 508 (98.7)	1.0 (reference)	1.0 (reference)	13 376 (89.5)	73 508 (97.4)	1.0 (reference)	1.0 (reference)
Use of opioids	134 (5.0)	140 (1.3)	3.9 (3.1–5.0)	2.7 (2.0–3.5)	1564 (10.5)	1927 (2.6)	4.6 (4.2–4.9)	2.1 (2.0–2.3)
≥ 70 y	2810	11 218			20 077	99 650		
No use of any opioid	2646 (94.2)	10 968 (97.8)	1.0 (reference)	1.0 (reference)	174,66 (87.0)	93 949 (94.3)	1.0 (reference)	1.0 (reference)
Use of opioids	164 (5.8)	250 (2.2)	2.8 (2.2–3.4)	1.8 (1.5–2.3)	2611 (13.0)	5701 (5.7)	2.5 (2.4–2.6)	1.5 (1.5–1.6)
Cardiovascular disease								
Present[b]	3516	8551			26 036	85 147		
No use of any opioid	3277 (93.2)	8254 (96.5)	1.0 (reference)	1.0 (reference)	22 412 (86.1)	79 186 (93.0)	1.0 (reference)	1.0 (reference)
Use of opioids	239 (6.8)	297 (3.5)	2.0 (1.7–2.4)	1.8 (1.5–2.1)	3624 (13.9)	5961 (7.0)	2.3 (2.2–2.4)	1.6 (1.5–1.7)
Absent[a]	1957	13 315			8981	89 938		
No use of any opioid	1898 (96.7)	13 222 (99.3)	1.0 (reference)	1.0 (reference)	8430 (93.9)	88 271 (98.1)	1.0 (reference)	1.0 (reference)
Use of opioids	59 (3.0)	93 (0.7)	4.3 (3.1–6.1)	3.4 (2.4–4.8)	551 (6.1)	1667 (1.9)	3.6 (3.3–4.0)	2.3 (2.0–2.5)

CI, confidence interval; OR, odds ratio. Numbers are *n* (%) unless indicated otherwise. ARREST: *P*-value interaction stratification according to: sex .8895; age, .0026; cardiovascular disease <.0001. DANCAR: *P*-value interaction: sex, .0866; age, <.0001; cardiovascular disease, <.001.

In DANCAR: presence of cardiovascular diseases was defined as the presence of at least 1 cardiovascular disease (ischaemic heart disease, congestive heart failure, atrial fibrillation, periphery artery disease or cerebrovascular disease) or the use of at least 1 cardiovascular drug (defined as in ARREST).

[a]In ARREST: absence of cardiovascular disease was defined as not being in treatment with cardiovascular drugs.

In DANCAR: absence of cardiovascular disease was defined as the absence of cardiovascular diseases and not being in treatment with cardiovascular drugs.

[b]In ARREST: presence of cardiovascular disease was defined as the use of at least 1 cardiovascular drug (beta-blockers, calcium channel blockers, antithrombotics, diuretics, renin-angiotensin system inhibitors, nitrates, statins and/or Vaughan Williams class 1 or 3 antiarrhythmic drugs).

OHCA-risk (the Netherlands: OR_{adj} 4.5 [95% CI:2.8–7.2]; Denmark: OR_{adj} 2.4 [95% CI 2.0–2.8], Figure 2) compared to no use of opioids. Our primary findings were confirmed in our subanalyses in which we stratified for presence of cardiovascular disease: increased OHCA-risk was observed both among individuals with cardiovascular disease (the Netherlands: OR_{adj} 1.8 [95% CI: 1.5–2.1]; Denmark: OR_{adj} 1.6 [95% CI: 1.5–1.7]) Table 2) and among individuals without cardiovascular disease (the Netherlands: OR_{adj} 3.4 [95% CI: 2.4–4.8], $P_{interaction}$ < .0001; Denmark: OR: 2.3 [95% CI: 2.0–2.5], $P_{interaction}$ < .0001). Furthermore, the association between opioids and OHCA was observed and of equal magnitude in both sexes (the Netherlands: men: OR_{adj} 2.3 [95% CI: 1.8–2.8], women OR_{adj} 2.0 [95% CI 1.6–2.6], $P_{interaction}$ = .8895; Denmark: men: OR_{adj} 1.7 [95% CI 1.6–1.8], women OR_{adj} 1.7 [95% CI 1.6–1.8], $P_{interaction}$ = .0866, Table 2). Stratification according to age revealed that opioids were associated with increased OHCA-risk in both age categories and that this association was stronger in individuals aged younger than 70 years (the Netherlands: <70 y OR_{adj} 2.7 [95% CI 2.0–3.5], ≥70 y OR_{adj} 1.8 [95% CI 1.5–2.3], $P_{interaction}$ = .0026; Denmark <70 y OR_{adj} 2.1 [95% CI 2.0–2.3], ≥70 y OR_{adj} 1.5 [95% CI 1.5–1.6], $P_{interaction}$ < .0001, Table 2). We found an increased OHCA-risk for almost all individual opioids; only **fentanyl** was not significantly associated with increased OHCA-risk in ARREST (Table 3). Our sensitivity analyses in which we stratified by severity of comorbidities (CCI score) revealed that the OHCA-risk associated with opioid use was present and of similar magnitude in all strata, thereby confirming our main findings (Supplemental Table S1). Finally, opioid use persisted associated with increased OHCA risk in subanalysis only including OHCA patients with shockable rhythm (Table 4).

4 | DISCUSSION

In this population-based multi-country study using real-world data from 2 independent population-based OHCA-registries, we found that use of opioids was associated with an increased OHCA risk. The increased risk was also observed in subanalyses stratified by sex, age and presence of cardiovascular disease or comorbidities.

Previously, serious concerns about the cardiovascular safety of opioids have been raised.[7,38,39] A retrospective study by Ray *et al.* used register data from patients with chronic noncancer pain and no evidence of palliative or end-of-life care, and was designed to examine all-cause mortality and cardiovascular mortality for patients who were prescribed long-acting opioids versus control medication (analgesic anticonvulsants or low-cyclic antidepressants).[7] That study showed increased risk of all-cause mortality and cardiovascular mortality associated with long-acting opioids.[7] One suggested mechanism for the observed cardiovascular mortality were adverse respiratory effects of long-acting opioids[7] such as central sleep apneoa,[40] which has been associated with increased risk of arrhythmias, myocardial ischaemia and sudden death.[41] Similarly, Solomon *et al.* found an increased risk of out-of-hospital cardiac

TABLE 3 Use of individual opioids and out-of-hospital cardiac arrest risk compared with no use of any opioid in the general population

	ARREST				DANCAR			
	Cases (n = 5473)	Controls (n = 21 866)	Crude OR (95% CI)	Adjusted OR (95% CI)	Cases (n = 35 017)	Controls (n = 175 085)	Crude OR (95% CI)	Adjusted OR (95% CI)
No use of any opioid	5175 (94.6)	21 476 (98.2)	1.0 (reference)	1.0 (reference)	30 842 (88.1)	167 457 (95.6)	1.0 (reference)	1.0 (reference)
Individual opioids								
Tramadol	90 (1.6)	186 (0.9)	2.0 (1.6–2.6)	1.3 (1.02–1.8)	1724 (4.9)	3636 (2.1)	2.6 (2.5–2.8)	1.6 (1.5–1.7)
Codeine	24 (0.4)	26 (0.1)	3.6 (2.0–6.2)	2.9 (1.6–5.3)	239 (0.7)	544 (0.3)	2.4 (2.1–2.8)	1.6 (1.4–1.9)
Oxycodone	60 (1.1)	63 (0.3)	3.9 (2.7–5.6)	2.5 (1.7–3.6)	411 (1.2)	687 (0.4)	3.3 (2.9–3.8)	1.7 (1.5–2.0)
Fentanyl	26 (0.5)	45 (0.2)	2.5 (1.5–4.1)	1.7 (0.998–2.8)	206 (0.6)	343 (0.2)	3.4 (2.8–4.0)	1.7 (1.4–2.1)
Morphine	24 (0.4)	15 (0.1)	6.6 (3.5–12.3)	4.4 (2.2–8.8)	646 (1.8)	831 (0.5)	4.3 (3.9–4.8)	2.3 (2.0–2.6)
Methadone	n/a	n/a	n/a	n/a	96 (0.3)	111 (0.1)	4.7 (3.6–6.2)	1.4 (1.04–1.9)

Not analysed: cases using other opioids in ARREST (n = 22) or DANCAR (n = 460), and cases using more than 1 type of opioid in ARREST (n = 52) or DANCAR (n = 393). CI, confidence interval; OR, odds ratio. Numbers are n (%) unless indicated otherwise. OR adjusted for use of all the covariates listed in Table 1.

TABLE 4 Use of opioids and the risk of out-of-hospital cardiac arrest in patients with ventricular tachycardia/ventricular fibrillation as first-registered heart rhythm

ARREST				
	Cases $n = 3001$	Controls $n = 11\,998$	Crude OR	Adjusted OR
No use of any opioid	2907 (96.9)	11 791 (98.3)	1.0 (reference)	1.0 (reference)
Use of opioids	94 (3.1)	207 (1.7)	1.9 (1.4–2.4)	1.4 (1.1–1.8)
DANCAR				
	Cases $n = 9714$	Controls $n = 48\,570$	Crude OR	Adjusted OR
No use of any opioid	9048 (93.1)	46 835 (96.4)	1.0 (reference)	1.0 (reference)
Use of opioids	666 (6.9)	1735 (3.6)	2.0 (1.8–2.2)	1.3 (1.1–1.4)

OR, odds ratio. OR adjusted for use of all covariates listed in Table 1.

death among adults with arthritis who used opioids compared with those who used nonsteroidal anti-inflammatory drugs).[39] That study, however, had some limitations as health care claims were used to define the endpoint, thus raising the possibility of misclassification of the outcome. To overcome this limitation, and to comprehensively study risk factors associated with OHCA, we used 2 large EMS-attended population-based OHCA registries (ARREST, DANCAR) with more accurate and specific OHCA data. Also, misclassification of exposures could have occurred in previous studies as some nonsteroidal anti-inflammatory drugs may have been used as over-the-counter drugs and were not captured.[39] Although the biological mechanisms linking opioids to an increase in cardiovascular events are unclear, our results add to the accumulating evidence that opioid use is associated with increased cardiovascular risk.

The risk of OHCA caused by drugs has usually been linked to their potential to disrupt cardiac electrophysiology by impacting cardiac ion channels.[42] Besides antiarrhythmic drugs, these effects have also been linked to drugs to treat *noncardiac* diseases, such as antipsychotics and antidepressants.[30–35] On a cellular level, such drugs cause inhibition of **cardiac potassium channels**[30–33] or **cardiac sodium channels**.[34,35] Several clinical studies, mainly case reports, have reported ECG changes consistent with these cellular effects.[10–14] **Methadone**[10,11] and, to a lesser extent, **oxycodone**[12] and **tramadol**[13] may cause QT prolongation on the ECG consistent with block of cardiac potassium channels. Moreover, tramadol has been linked to ECG effects consistent with block of cardiac sodium channels.[14] Currently, there are data on the electrophysiological effects of opioids, and future research is needed to explore them.

Due to our study design, we cannot fully exclude that unmeasured confounders have driven our results, as we do not have information about possibly confounding clinical covariables, such as left ventricular ejection fraction or blood samples to detect drug (over)dose of opioids. To address the matter of possible confounding, we conducted subgroup analyses in subjects with or without cardiovascular disease. The results in the latter population minimized the possibility that cardiovascular disease accounts for the association between opioids and OHCA. In addition, subgroup analyses in subjects with different CCI scores confirmed our main findings. Furthermore, although we excluded all OHCAs due to obvious drug overdose, we cannot completely rule out that some included cases did have drug overdose, since we had no autopsy information or blood samples to detect drug overdose. This may have influenced our findings, since drug intoxication is common among victims of sudden death, even when a cardiac cause is suspected.[43] For instance, a study reported that 13.5% of sudden cardiac deaths, as defined by the World Health Organization, were attributable to occult overdose; of these 61% were attributable to opioid overdose.[43]

Regardless of the underlying mechanisms of our epidemiologic findings, our results are of clinical importance given the sharp rise in opioid use.[15,16] Therefore, a potential relationship between opioids and OHCA and mechanisms involved warrants future replication studies in other settings. These findings should be considered when evaluating harms and benefit of treatment with opioids.

4.1 | Strengths and limitations

A major strength of our study is that both registries were specifically set up to investigate OHCA in the general population in which each OHCA case is prospectively registered, thus minimizing the risk for selection bias or inclusion bias, and rendering our findings representative for the community at large. Nevertheless, our study has also some limitations. As discussed previously, confounding may have driven our results, as important covariables were lacking, such as indication for opioid therapy, left ventricular ejection fraction and blood samples to measure opioid serum levels. Furthermore, misclassification of exposure may have occurred, as opioid use was defined by having drug-dispensing records 30 days before OHCA. For instance, patients may use opioids for only a short period and not at the index-date. It is likely, however, that such misclassification is random and equally distributed between cases and controls. Another limitation is that we could not perform direct adjustments for comorbidities in ARREST, since data regarding comorbidity were lacking in the non-OHCA controls in the Netherlands. To deal with the lack of comorbidities in ARREST registry, we used drug proxies as we did previously.[24] However, using drug proxies may result in misclassification of the disease since cardiovascular drugs have a wide range of indications. For

instance, renin–angiotensin–aldosterone system inhibitor may be used to treat patients with heart failure and/or hypertension. Also, patients using statins may not necessarily have a cardiovascular disease. To mitigate the limitations associated with the use of drug proxies, we included comorbidities using diagnostic codes from the Danish registries in our multivariate analyses. The association between use of opioids and OHCA persisted, also after adjustments for malignancy. The majority of the used codes to define comorbidities in our study have undergone scrutiny for data quality with high positive predictive value.[44] Furthermore, although we excluded OHCA patients with obvious opioid overdose based on information from case reports filled out by ambulance personnel, some misclassification may still have occurred. We could not exclude OHCA patients without obvious overdoses because autopsy is rarely performed and blood samples to detect drug overdose are not routinely taken. Also, we could not exclude patients on opioid substitution therapy, since no such information was available to us. However, we presume that possible misclassification arising from this was similarly distributed between cases and controls. Finally, including patients receiving palliative care shortly before an expected death would affect the studied association. However, in both registries, only EMS-attended OHCAs were included. Patients receiving palliative care, shortly before an expected death are not expected to be resuscitated by the EMS. Therefore, these patients are not likely included in the used registries and contributed to the our association between opioids and increased OHCA-risk.

5 | CONCLUSION

Use of opioids is associated with increased OHCA-risk in the general population independently of cardiovascular disease. These findings should be considered when evaluating the harms and benefits of treatment with opioids.

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CONTRIBUTORS

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

COMPETING INTERESTS

The authors have nothing to disclose.

DATA AVAILABILITY STATEMENT

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

ORCID

Talip E. Eroglu https://orcid.org/0000-0002-4381-0068
Carlo A. Barcella https://orcid.org/0000-0002-0760-8372
Patrick C. Souverein https://orcid.org/0000-0002-7452-0477
Anthonius de Boer https://orcid.org/0000-0002-9485-8037
Hanno L. Tan https://orcid.org/0000-0002-7905-5818

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