2018

Algorithms used to identify ventricular arrhythmias and sudden cardiac death in retrospective studies: a systematic literature review

Yizhou Ye

E. Paul Larrat
University of Rhode Island, larrat@uri.edu

See next page for additional authors

Citation/Publisher Attribution
Ye Y, Larrat EP, Caffrey AR. Algorithms used to identify arrhythmias and sudden cardiac death in retrospective studies: a systematic literature review. Therapeutic Advances in Cardiovascular Disease 2018; 12(2):39-51. doi: 10.1177/1753944717745493
Available at: http://dx.doi.org/10.1177/1753944717745493

Algorithms used to identify ventricular arrhythmias and sudden cardiac death in retrospective studies: a systematic literature review

Yizhou Ye, PhD[1], E P. Larrat, PhD[1], and Aisling R. Caffrey, PhD, MS[1,2,3]

1. College of Pharmacy, Department of Pharmacy Practice, University of Rhode Island, Kingston, RI, United States
2. Veterans Affairs Medical Center, Infectious Diseases Research Program and Center of Innovation in Long Term Services and Supports, Providence, RI, United States
3. School of Public Health, Brown University, Providence, RI, United States

Corresponding author: Aisling R. Caffrey, PhD, MS, Assistant Professor, University of Rhode Island; 7 Greenhouse Road, Kingston, RI 02881; office: (401) 874-5320; e-mail: Aisling_Caffrey@uri.edu

Introduction

Sudden cardiac arrest is a severe condition in which the heart stops beating suddenly and unexpectedly and often leads to sudden cardiac death outside of the hospital or in the emergency room.[1] Unexpected sudden cardiac death is rare, with an estimated incidence ranging from 50 to 100 per 100,000 individuals per year in Europe and North America.[2,3] Acute ventricular arrhythmia may account for over 80% of sudden cardiac deaths.[4]

Retrospective pharmacoepidemiologic studies are used to assess risks attributed to drug exposures.[5,6] Even though the relationship between QT interval prolongation and sudden cardiac death and/or ventricular arrhythmias (SCD/VA) remains putative, drug-induced QT interval prolongation may increase the risk of SCD/VA and therefore affects the safety profile of medications, which can result in black box warnings and drug withdrawals.[7,8] Terfenadine and cisapride were withdrawn in the United States (US) in 1998 and 2000 respectively, due to their association with QT prolongation and ventricular arrhythmia.[9,10] More recently, in 2013, azithromycin received a black box warning for potential risk of QT prolongation and fatal cardiac arrhythmias based on the findings of a large retrospective pharmacoepidemiologic study.[11,12]

In this era of big data, particularly for studies of rare outcomes, such as SCD/VA, a valid operational definition of the outcome is needed. Physician review of an electrocardiogram (ECG) is the gold standard for identifying QT prolongation, however it has limited use in retrospective database studies.[13] First, ECG results are often not available in administrative databases. Further, a study identifying events by manual medical record review of ECGs and physician notes would likely be under-powered to quantify the exposure-outcome relationship. Lastly, ECG results are

not available for cardiac events which occurred outside of the hospital, and would result in underestimation of these events.

A number of retrospective pharmacoepidemiologic drug safety studies have sought to quantify the association between these rare outcomes and different medication exposures, however the algorithms identifying SCD/VA have varied between studies.[14-18] Further the performance of these varying algorithms has not been compared. The objective of this systematic literature review was to identify the operational definitions of ventricular arrhythmias and sudden cardiac death used in retrospective database studies and compare validation results between algorithms.

Methods

A systematic literature review in the PubMed electronic databases was conducted to identify retrospective studies from peer-reviewed journals. A pre-determined search strategy developed by researchers from the US Food and Drug Administration (FDA) Sentinel Initiative (Supplemental Table 1) was used to select qualifying studies published between January 1, 2000 and August 31, 2016.[19] The FDA Sentinel Initiative has sought to improve the surveillance of safety events related to marketed medications, through the creation of robust databases and improved monitoring methods.[20] This literature review was limited to studies in humans and published in English. Other inclusion criteria were: retrospective studies in administrative databases; studies that identified SCD/VA; studies that specified codes for SCD/VA. Titles and abstracts of studies identified by the search were screened against the inclusion criteria. Qualifying or uncertain studies from title and abstract review underwent further full-text review for selection. References of selected studies were also examined for inclusion. Data extracted included operational definitions and administrative codes used for identifying SCD/VA. Other aspects of

study design including publication year, study setting and population, and sample size, were also collected. Validation methods and results were also extracted where validation was conducted. This literature review was conducted according to the standards set forth in the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) statement.[21]

Results

The search strategy identified 1,237 studies. After title and abstract review, 57 studies were selected for full-text review, after which, 22 (39%) studies were selected for inclusion. Figure 1 shows the literature search, review, and selection process.

[Insert Figure 1]

Table 1 describes the characteristics of the included studies. More than half of the included studies were published after 2012, which was the year a previous literature review of validated methods for identifying SCD/VA was published.[19] Twelve of the included studies (55%) were conducted in US populations, using Medicare or Medicaid data (n=10, 45%),[10,11,14,15,22-27] commercial health plan data (n=1, 5%),[18] or Veterans Health Administration data (n=1, 5%).[17] The other ten studies (45%) were conducted in: European databases (n=5, 23%) from the Netherlands,[28] France,[29] Italy,[30] Denmark,[31] and Sweden[32]; the Taiwanese National Health Insurance Research Database (n=3, 14%)[16,33,34]; and Canadian provincial databases (n=2, 9%).[35,36] International Classification of Diseases, Ninth Revision (ICD-9) codes were used in 17 studies (77%), while 4 studies (18%) used International Classification of Diseases, Tenth Revision (ICD-10) codes, and one study (5%) used both ICD-9 and ICD-10 codes. All studies used diagnosis codes for event definitions and no procedure codes were used.

[Insert Table 1.]

Algorithms applied to medical data

SCD/VA was identified from medical data in 15 studies (68.2%) using ICD-9 and 3 (14%) studies using ICD-10. Shared by six ICD-9 medical data studies, the most frequently adopted algorithm (Table 2) included diagnosis codes identified from inpatient discharges and emergency department (ED) visits.[10,15,23,24,27,30] Validation was conducted in 3 of these studies by confirmation of SCD/VA through medical record review. When principal inpatient discharge diagnosis and first-listed ED visit diagnosis were assessed together, the PPVs ranged from 73% to 100%.[10,15,30] Considering both principal and non-principal inpatient discharge diagnoses, the algorithm was found to have a 92% positive predictive value (PPV) for identifying SCD/VA in one study.[10] Another study identified a higher PPV with principal ED visit diagnosis (94%) than with principal discharge diagnosis (80%).[15]

[Insert Table 2.]

Variations of this algorithm have also been used in several studies. One variation of the algorithm (excluded ICD-9 code 798) was used in a Taiwanese study (National Health Insurance Research Database) and a Medicaid/HealthCore study but neither study evaluated the validation of the algorithm.[26,33] Another variation (only included ICD-9 codes 427.1, 427.4, and 427.5) of this algorithm identified ventricular arrhythmias from principal inpatient discharge diagnoses using Medicare data.[22] This study validated the reduced algorithm in a registry cohort of confirmed life-threatening ventricular arrhythmia cases, resulting in a sensitivity of 77% and specificity of 94%. This algorithm also demonstrated a PPV of 93% as validated by medical record review of 30 cases.[22] A third variation (with additional ICD-9 code 427.69) identified SCD/VA from inpatient hospitalizations in the Netherlands. Medical record review demonstrated a PPV of 82%. Addition of codes for unspecified cardiac arrhythmia codes lowered the PPV to 50%.[22,28]

The next most common algorithm for arrhythmias was utilized in two studies, one from the Netherlands and the other from Canada.[28,36] The algorithm identified ventricular arrhythmias and cardiac arrest from hospital stays with primary diagnoses of arrhythmias. Only the Dutch study validated the algorithm, where a review of medical records was used to verify the ICD-9 codes used for ventricular arrhythmia and cardiac arrest (PPV 82%) and ICD-9 codes for unspecified cardiac arrhythmias (PPV 10%).[28] The five other studies each used a different algorithm to identify SCD/VA. The Harvard community health plan study used select ICD-9 subcodes under 426, 427, 429, 780, and 785 from hospital stays and ED visits, with a low PPV of 4%.[18] The United Healthcare study included office visits and inpatient stays with diagnoses of arrhythmic events (ICD-9 codes 426.x, 427.x) but this approach also had low a PPV of 10% based on a review of medical records.[9] Three other algorithms were used in two of the Taiwanese studies and the Veterans Health Administration study and none of these studies validated their operational definition.[16,17,34]

ICD-10 diagnosis codes for acute ventricular arrhythmia were used in 3 studies (13.6%). A French study,[29] a Denmark-Sweden bi-national study,[32] and one of the Canadian studies[35] each used a different algorithm for identifying QT prolongation in hospital stays or ED visits. The Canadian study used ICD-10 codes I47.2 and I49.0 and a manual chart review was conducted in 202 charts resulting in a PPV of 92%.[35] The French study used ICD-10 codes I46.1, I47.2, and I49.0 from hospital discharge summaries. In comparison with ECG records, this algorithm had a PPV of 60%.[29] The bi-national study used ICD-10 codes I47.2, I49.0, I49.3, I46.0, I46.1, I46.9, R96.0, and R96.1 and no validation was conducted.[32]

Algorithms applied to death data

Five of the included studies (23%) utilized death certificate or death registry data to identify SCD (ICD-9, n=3; ICD-10, n=1; ICD-9 and ICD-10, n=1). Three of four ICD-9 death data studies (75%) implemented the same algorithm to define plausible SCD, which excluded deaths with terminal institutional stays or terminal procedures inconsistent with unresuscitated cardiac arrest (Table 3).[14] This algorithm was validated by medical record review in a general Medicaid population and in opioid users, and the PPV of this algorithm was 87% and 88%, respectively.[14,25]

[Insert Table 3.]

Another algorithm conducted with Taiwanese death registry data defined the study outcome as unspecific cardiovascular death (ICD-9 codes 401-449 and ICD-10 codes I10-I79).[16] The Danish death registry study identified death from cardiovascular causes using ICD-10 codes.[31] Codes used in the Danish study were I00-I99 (diseases of the circulatory system) and R96.x (other sudden death, cause unknown).[31] Neither study performed validation of their algorithms.

Discussion

We identified validated operational definitions for identifying ventricular arrhythmias and sudden cardiac death in retrospective database studies. The most frequently used algorithms in medical data (Table 2) and death registries (Table 3) had an average PPV of 85% and 88%, respectively. These two algorithms were validated in various patient populations, including Medicaid and Medicare, administrative claims databases, and several European and Canadian databases. For ICD-9 algorithms in medical data, the PPV was highest when limited to principal inpatient or ED discharge diagnoses, and addition of less specific subcodes decreased the PPV.[9,10] Though one ICD-10 algorithm in medical data was found to have a high PPV, this algorithm has not been used or validated in another database.[35] Less than a quarter of the included studies identified SCD from death certificates or death registries, however one algorithm using ICD-9

codes was found to have a high PPV for identifying sudden cardiac death among patients with a low risk of unexpected death.[14]

Our study has a few limitations. Firstly, the literature search terms might miss some other studies that also identified ventricular arrhythmias and sudden cardiac death in retrospective databases. We attempted to address this limitation by examining the references of reviewed studies for additional studies and found no additional eligible studies in the references. Secondly, the true incidence of ventricular arrhythmias and sudden cardiac death are unknown, since such events may originate in the outpatient setting and therefore the diagnosis may not be recorded in medical data or may be absent as a cause of death. Hence the incidence and prevalence are likely to be underestimated. As such, validation studies usually only calculate the PPV but not sensitivity or specificity. However, as a PPV is the proportion of true positive in tested positive, validated algorithms with high PPV may accurately identify cases captured in retrospective administrative databases.

Conclusions

Our study identified a validated algorithm for ventricular arrhythmias and sudden cardiac death in medical data, as well as a validated operational definition for sudden cardiac death in death data. Consistency between studies is necessary for establishing causal relationships between medications and rare adverse events, such as ventricular arrhythmias and sudden cardiac death. Further, transparency in the reporting of these algorithms is essential for understanding differences between studies and should include lists of codes and sufficient data source details (primary versus secondary diagnosis, hospitalizations versus ED visits). As such, to ensure comparability between new research and the existing literature, pharmacoepidemiologic research in this area should utilize

common, validated algorithms, such as the ones identified in our review, to operationally define these events.

Declaration of Conflicting Interests

The Authors declare that there is no conflict of interest.

Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Table 1 Characteristics of reviewed retrospective administrative database studies

	First author	Publish year	Population	Design and sample size	Outcome definition and codes utilized	Code version	Clinical setting from which events were assessed	Validation method and result
1	Hanrahan [18] (PMID: 7606309)	1995	US Harvard Community Health Plan claims, 1988-1990	Cohort study in antihistamine users (N=26,320). Number of events in hospitalization or ED not clarified. Validation: medical records review (N=1,749)	Study outcome included sudden death, torsades de pointes or other ventricular arrhythmias, syncope, and ventricular ectopy in the following settings: (i) Ambulatory events (no codes provided); (ii) Any hospitalization or ED discharge diagnoses of: ICD-9 codes 426.0-426.5 (except 426.2), 427.1, 427.4-427.6, 427.9, 429.2, 429.9, 780.2-780.4, 785.0, 785.1, 785.5; (iii) Fatal vital status (no codes provided); (iv) Electrocardiogram review	ICD-9	Inpatient and outpatient events, algorithm applied to inpatient events only	Medical records review confirmed 70 events, PPV 4% (70/1749)
2	McDonald [22] (PMID: 12228777)	2002	US Medicare claims, 1985-1995	Descriptive study among Medicare patients with ventricular arrhythmia in Seattle-area Myocardial Infarction and Triage Intervention (MITI) registry (N=4,073)	Principal hospitalization discharge diagnosis of ventricular tachycardia or ventricular fibrillation/cardiac arrest: ICD-9 codes 427.1, 427.4, 427.5	ICD-9	Inpatient events	MITI validation: sensitivity 77% and specificity 94% (no number provided) KPNC validation: PPV 93%

				Validation: medical records review: (i) Sensitivity and specificity calculated using MITI data as "gold standard" for life-threatening ventricular arrhythmias; (ii) Clinical chart review from Kaiser Permanente in Northern California (KPNC) hospitals on all patients meeting case definition (N=512)				
3	De Bruin[28] (PMID: 16291479)	2005	The Netherlands, PHARMO database, 1999-2000	PHARMO record linkage system of a defined population of 330,000 Dutch residents Validation: medical records review (N=111)	Principal hospitalization discharge diagnoses of: (i) ventricular arrhythmias: ICD-9 codes 427.1, 472.4, 427.41, 427.42, 427.5, 427.69; (ii) cases in (i) and unspecified cardiac arrhythmias: ICD-9 codes 427.2, 427.60, 427.8, 427.89, 427.9	ICD-9	Inpatient events	Medical records review definition (i): 50 cases out of 61 confirmed, PPV 82%; definition (ii): 55 cases out of 111confirmed, PPV 50%
4	Hennessy[10] (PMID: 18662288)	2008	US Medicaid claims, 1999-2000	Etiologic study of 7,395 users of cisapride, metoclopramide, or a proton pump inhibitor (N=145 cases, N=7250 controls)	Principal hospitalization discharge diagnosis of sudden cardiac death or ventricular arrhythmia ICD-9 codes 427.1, 427.4, 427.41, 427.42, 427.5, 798, 798.1, 798.2	ICD-9	Inpatient events	Validation definition (a witnessed sudden collapse with the person found unconscious or dead, with evidence that the person had

				The outcome validation component obtained and reviewed primary medical records for N=128 persons				been alive in the preceding 24 h, or evidenced cardiac arrest or ventricular arrhythmia in medical record) met in 118 of the 128 records, PPV 92%, 95% CI 86%-96%
5	Molokhia [29] (PMID: 18637888)	2008	France, Midi-Pyrenees hospital record, 1999-2004	Descriptive study for events identified from four hospitals in the administrative area of Midi-Pyrenees with a population coverage of 614,000 (N=861) Validation: medical records review (N=40)	Hospital discharge summaries with diagnosis of ventricular tachycardia, ventricular fibrillation, or sudden cardiac death (claim position unspecified): ICD-10 codes I47.2, I49.0, I46.1	ICD-10	Inpatient events	ECG confirmed 24 out of 40 identified cases, PPV 60%
6	Zambon[30] (PMID: 19236122)	2009	Italy, National Health Service Database, 1998-2003	Case-control study, 1,275 cases identified Validation: medical records review (N=11)	Principal hospitalization discharge diagnoses of ventricular arrhythmia or cardiac arrest: ICD-9 codes 427.1, 427.4, 427.41, 427.42, 427.5, 798, 798.1, 798.2	ICD-9	Inpatient events	Previous validated by medical record review in a different population (N=11). 8 of 11 identified cases confirmed: 1 out of 4 cases of ventricular arrhythmias and 7 out of 7 cases of cardiac arrest; PPV 73%

7	Chung[14] (PMID: 20029823)	2010	US Medicaid claims, 1990-1993	Validation study in events identified in TN Medicaid population (N=926) Validation: medical records review (N=174)	Sudden cardiac death in death certificate while having no evidence of a terminal institutional stay or no terminal procedures inconsistent with unresuscitated cardiac arrest: ICD-9 codes 401.9, 402.9, 410, 411, 414.0, 414.8, 414.9, 425.4, 427.1, 427.4, 427.5, 427.9, 429.2, 429.9, 440.9, 798.9 (ICD-10 codes not provided)	ICD-9	Inpatient and outpatient events	151 of 174 identified cases confirmed, PPV 87%; PPV for deaths occurring between 1994–1998 (ICD-9 coding): 85.1%; PPV for deaths between 1999–2005 (ICD-10 coding): 87.4%
8	Hennessy[15] (PMID: 19844945)	2010	US Medicaid and Medicare claims, 1999–2002	Validation study, events identified in inpatient settings (N=5,239) and ED visits (N=29,135) Validation: medical records review (N=116)	Primary hospitalization discharge diagnoses or first-listed ED visit diagnosis of sudden cardiac death or ventricular arrhythmia: ICD-9 codes 427.1, 427.4, 427.41, 427.42, 427.5, 798, 798.1, 798.2	ICD-9	Inpatient events	Medical record review of randomly selected patients in the cohort validated 99 out of 116 cases identified, PPV 85%, 95% CI 78%–91% Principal hospitalization discharge diagnosis: PPV 80%, 95% CI 68%-88%; First-listed ED visits diagnosis: PPV 94%, 95% CI 83%-98%
9	Johannes[36]	2010	Canada, Saskatchewan Health,	Nested case-control study in a cohort of domperidone or PPI users (N=83,212);	Primary hospitalization discharge diagnoses of ventricular arrhythmias:	ICD-9	Inpatient events	No independent validation conducted; case

	(PMID: 20652862)		1990-2005	1,608 cases identified Validation: none	ICD-9 codes 427.1, 472.4, 427.41, 427.42, 427.5, 427.69;			definition cited to have PPV of 82%
10	Leonard[23] (PMID: 21796718)	2011	US Medicaid claims, 1999–2003	Cohort study in antidepressants users (N=3,397,470); 4,222 events identified Validation: none	Primary hospitalization discharge diagnoses or first-listed ED visit diagnosis of sudden cardiac death or ventricular arrhythmia: ICD-9: 427.1, 427.4, 427.41, 427.42, 427.5, 798, 798.1, 798.2	ICD-9	Inpatient events	No independent validation conducted; outcome definition cited to have PPV of 85%
11	Kawai[25] (PMID: 22938531)	2012	US Medicaid claims, 1992-2007	Validation study of 737 events identified in a cohort of propoxyphene or hydrocodone users (N=453,836) Validation: medical records review (N=81)	Sudden cardiac death in death certificate in a community setting while having no evidence of a terminal institutional stay or no terminal procedures inconsistent with unresuscitated cardiac arrest, ICD-9 codes 401.9, 402.9, 410, 411, 414.0, 414.8, 414.9, 425.4, 427.1, 427.4, 427.5, 427.9, 429.2, 429.9, 440.9, 798.9	ICD-9	Inpatient and outpatient events	Medical records review of the 81 sudden cardiac deaths identified confirmed 71 in the opioid user population, PPV=88%
12	Ray[11] (PMID: 22591294)	2012	US Medicaid claims, 1992-2006	Cohort study of azithromycin episodes (N=347,795); 29 cardiovascular deaths identified Validation: none	Cardiovascular death and sudden cardiac death in death certificate while having no evidence of a terminal institutional stay or no terminal procedures inconsistent with unresuscitated cardiac arrest, ICD-9 codes 401.9, 402.9, 410, 411, 414.0, 414.8, 414.9, 425.4, 427.1, 427.4, 427.5,	ICD-9	Inpatient and outpatient events	No independent validation conducted; outcomes definition cited to have PPV of 87%

					427.9, 429.2, 429.9, 440.9, 798.9			
13	Schellemann[26] (PMID: 22318795)	2012	US Medicaid claims, 1999-2003; HealthCore Database, 2001-2006	Cohort study of new methylphenidate users (N=43,999); 54 events identified Validation: none	Primary hospitalization discharge diagnoses or first-listed ED visit diagnosis of sudden cardiac death or ventricular arrhythmia: ICD-9 codes 427.1, 427.4, 427.41, 427.42, 427.5, 798.1, 798.2	ICD-9	Inpatient events	No independent validation conducted
14	Leonard[24] (PMID: 24027655)	2013	US Medicaid claims, 1999–2003	Cohort study of incident antipsychotic users (N=459,614); 747 events identified Validation: none	Primary hospitalization discharge diagnoses or first-listed ED visit diagnosis of sudden cardiac death or ventricular arrhythmia: ICD-9 codes 427.1, 427.4, 427.41, 427.42, 427.5, 798, 798.1, 798.2	ICD-9	Inpatient events	No independent validation study conducted; outcome definition cited to have PPV of 85%
15	Svanstrom[31] (PMID: 23635050)	2013	Denmark and Danish, Civil Registration System, 1997-2010	Cohort study of azithromycin episodes (N=1,102,419); 17 events identified Validation: none	Death from cardiovascular causes obtained from the Danish Register of Causes of Death: ICD-10 codes I00-99, R96.0, R96.1	ICD-10	Inpatient and outpatient events	No independent validation conducted
16	Leonard[27] (PMID: 25029519)	2014	US Medicaid claims, 1999–2007	Cohort study in loop diuretics users (N=654,060); 1,470 events identified Validation: none	Primary hospitalization discharge diagnoses or first-listed ED visit diagnosis of sudden cardiac death or ventricular arrhythmia:	ICD-9	Inpatient events	No independent validation conducted; outcome definition cited to have PPV of 85%

					ICD-9 codes 427.1, 427.4, 427.41, 427.42, 427.5, 798, 798.1, 798.2			
17	Rao[17] (PMID: 24615307)	2014	US Veterans Health Administration Database, 1999-2012	Cohort study of azithromycin episodes (N=594,792); number of events not specified Validation: none	Any hospitalization discharge diagnoses or first-listed ED visit diagnosis of serious cardiac arrhythmia: ICD-9 codes 426.82, 427.0, 427.1, 427.2, 427.41, 427.42, 427.5	ICD-9	Inpatient events	No independent validation conducted
18	Chen[34] (PMID: 26098410)	2015	Taiwan, National Health Insurance Research Database (NHIRD), 2000-2011	Case-crossover study in general population of NHIRD; 25,356 cases of arrhythmias identified Validation: none	Hospitalization or ER visit with a principal diagnosis of cardiac dysrhythmias: ICD-9 codes 427.x, 798.x	ICD-9	Inpatient events	No independent validation conducted
19	Chou[16] (PMID: 25409476)	2015	Taiwan, NHIRD, 2001-2011	Cohort study in azithromycin, clarithromycin, moxifloxacin, levofloxacin, ciprofloxacin, or amoxicillin-clavulanate users (N=10,684,100); 275 events of severe ventricular arrhythmia and 279 cardiovascular deaths identified Validation: none	Any inpatient or outpatient (including ED visit) diagnosis of severe ventricular arrhythmia (diagnosis type unspecified): ICD-9 codes 427.1, 427.4, 427.5, 798.1, 798.2, 798.9, V12.53; Cardiovascular death identified in death registry: ICD-9 codes 401–449 ICD-10 codes I10–I79	ICD-9 and ICD-10	Inpatient and outpatient events	No independent validation conducted

20	Wu[33] (PMID: 25713294)	2015	Taiwan, NHIRD, 2000-2009	Case-crossover study in general population of NHIRD; 17,718 incident cases identified Validation: none	Primary hospitalization discharge diagnoses or first-listed ED visit diagnosis of sudden cardiac death or ventricular arrhythmia: ICD-9 codes 427.1, 427.4, 427.41, 427.42, 427.5, 798.1, 798.2	ICD-9	Inpatient events	No independent validation conducted
21	Inghammar[32] (PMID: 26920666)	2016	Denmark and Sweden, National healthcare registry, Denmark: 1997-2011; Sweden: 2006-2013	Cohort study of fluoroquinolone episodes (N=909,656); 66 events identified Validation: none	Primary hospitalization discharge diagnoses or first-listed ED visit diagnosis of fatal or non-fatal serious arrhythmia: ICD-10 codes I47.2, I49.0, I49.3, I46.0, I46.1, I46.9, R96.0, R96.1	ICD-10	Inpatient events	No independent validation conducted
22	Trac[35] (PMID: 26903359)	2016	Canada, Ontario Health Insurance Plan, 2002-2013	Cohort study in macrolide users (N= 616,359) with 260 events Validation: medical records review (N=202)	Any hospitalization discharge diagnoses or ED visit diagnosis of ventricular arrhythmia: ICD-10 codes I47.2, I49.0	ICD-10	Inpatient events	PPV 92%, 95% CI 87%–95%

CI = confidence interval; ED = emergency department; ICD = International Classification of Diseases; NDI = National Death Index; NPV = negative predictive value; PPV = positive predictive value; SCA = sudden cardiac arrest; SCD = sudden cardiac death; TNR = true negative rate; TPR = true positive rate; US = United States; VA = ventricular arrhythmias

Table 2. Algorithm for identifying ventricular arrhythmia and sudden cardiac death in medical data*

ICD-9 code+	Code description
427.1	Paroxysmal ventricular tachycardia
427.4	Ventricular fibrillation and flutter
427.41	Ventricular fibrillation
427.42	Ventricular flutter
427.5	Cardiac arrest
427.9	Cardiac dysrhythmia, not otherwise specified
798	Sudden death, cause unknown
798.1	Instantaneous death
798.2	Death occurring in less than 24 hours from onset of symptoms, not otherwise explained

ED = Emergency Department; ICD = International Classification of Diseases

* Algorithm used by 6 of the included studies[10,15,23,24,27,30]

+ Variations of this algorithm were used in 4 other studies[22,26,28,33]

Table 3.
Algorithm for identifying ventricular arrhythmia and sudden cardiac death in death data *

ICD-9 code	Code description
401.9	Essential hypertension, not otherwise specified
402.9	Hypertensive heart disease, not otherwise specified
410	Myocardial infarction
411	Other acute/subacute ischemic heart disease
414.0	Coronary atherosclerosis
414.8	Chronic ischemic heart disease, other
414.9	Chronic ischemic heart disease, unspecified
425.4	Primary cardiomyopathy, not otherwise specified
427.1	Paroxysmal ventricular tachycardia
427.4	Ventricular fibrillation and flutter
427.5	Cardiac arrest
427.9	Cardiac dysrhythmia, not otherwise specified
429.2	Cardiovascular arteriosclerosis
429.9	Cardiovascular disease, not otherwise specified
440.9	Atherosclerosis, generalized and unspecified
798.9	Unattended death

ICD = International Classification of Diseases

* Algorithm used by 3 of the included studies[11,14,25]

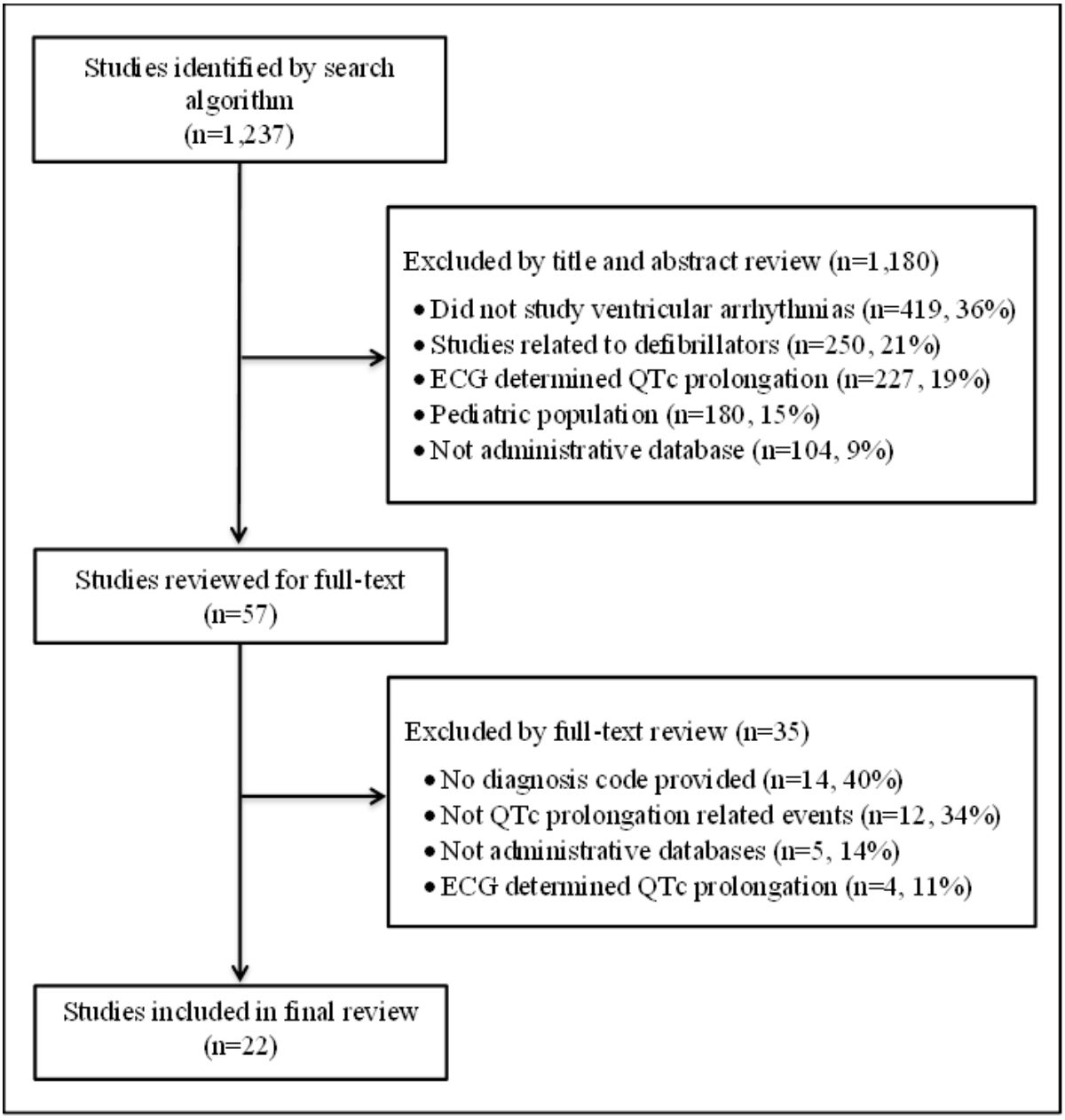

Figure1.
Flow chart of literature search and selection process
ECG = electrocardiogram, QTc = corrected QT interval

Reference

1. Hayashi M, Shimizu W, Albert CM. The spectrum of epidemiology underlying sudden cardiac death. *Circ Res.* 2015;116(12):1887-1906.
2. Fishman GI, Chugh SS, Dimarco JP, et al. Sudden cardiac death prediction and prevention: report from a National Heart, Lung, and Blood Institute and Heart Rhythm Society Workshop. *Circulation.* 2010;122(22):2335-2348.
3. Goldberger JJ, Buxton AE, Cain M, et al. Risk stratification for arrhythmic sudden cardiac death: identifying the roadblocks. *Circulation.* 2011;123(21):2423-2430.
4. Josephson M, Wellens HJ. Implantable defibrillators and sudden cardiac death. *Circulation.* 2004;109(22):2685-2691.
5. European Medicines Agency. Guideline on good pharmacovigilance practices (GVP) Module VIII – Post-authorisation safety studies (Rev 2) 2016; http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2012/06/WC500129137.pdf. Accessed September 20, 2016.
6. U.S. Department of Health and Human Services USFDA. Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment. 2005; http://www.fda.gov/downloads/regulatoryinformation/guidances/ucm126834.pdf. Accessed September 20, 2016.
7. Chiang CE. Congenital and acquired long QT syndrome. Current concepts and management. *Cardiology in review.* 2004;12(4):222-234.
8. Yap YG, Camm AJ. Drug induced QT prolongation and torsades de pointes. *Heart.* 2003;89(11):1363-1372.
9. Enger C, Cali C, Walker AM. Serious ventricular arrhythmias among users of cisapride and other QT-prolonging agents in the United States. *Pharmacoepidemiology and drug safety.* 2002;11(6):477-486.
10. Hennessy S, Leonard CE, Newcomb C, Kimmel SE, Bilker WB. Cisapride and ventricular arrhythmia. *British journal of clinical pharmacology.* 2008;66(3):375-385.
11. Ray WA, Murray KT, Hall K, Arbogast PG, Stein CM. Azithromycin and the risk of cardiovascular death. *The New England journal of medicine.* 2012;366(20):1881-1890.
12. U.S. Department of Health and Human Services USFDA. FDA Drug Safety Communication: Azithromycin (Zithromax or Zmax) and the risk of potentially fatal heart rhythms. 2013; http://www.fda.gov/Drugs/DrugSafety/ucm341822.htm. Accessed September 20, 2016.
13. Denny JC, Miller RA, Waitman LR, Arrieta MA, Peterson JF. Identifying QT prolongation from ECG impressions using a general-purpose Natural Language Processor. *Int J Med Inform.* 2009;78 Suppl 1:S34-42.
14. Chung CP, Murray KT, Stein CM, Hall K, Ray WA. A computer case definition for sudden cardiac death. *Pharmacoepidemiology and drug safety.* 2010;19(6):563-572.
15. Hennessy S, Leonard CE, Freeman CP, et al. Validation of diagnostic codes for outpatient-originating sudden cardiac death and ventricular arrhythmia in Medicaid and Medicare claims data. *Pharmacoepidemiology and drug safety.* 2010;19(6):555-562.
16. Chou HW, Wang JL, Chang CH, Lai CL, Lai MS, Chan KA. Risks of Cardiac Arrhythmia and Mortality Among Patients Using New-Generation Macrolides, Fluoroquinolones, and beta-Lactam/beta-Lactamase Inhibitors: A Taiwanese Nationwide

Study. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America.* 2015;60(4):566-577.
17. Rao GA, Mann JR, Shoaibi A, et al. Azithromycin and levofloxacin use and increased risk of cardiac arrhythmia and death. *Annals of family medicine.* 2014;12(2):121-127.
18. Hanrahan JP, Choo PW, Carlson W, Greineder D, Faich GA, Platt R. Terfenadine-associated ventricular arrhythmias and QTc interval prolongation. A retrospective cohort comparison with other antihistamines among members of a health maintenance organization. *Annals of epidemiology.* 1995;5(3):201-209.
19. Tamariz L, Harkins T, Nair V. A systematic review of validated methods for identifying ventricular arrhythmias using administrative and claims data. *Pharmacoepidemiology and drug safety.* 2012;21 Suppl 1:148-153.
20. U.S. Department of Health and Human Services USFDA. FDA's Sentinel Initiative - Background. 2016; https://www.fda.gov/safety/fdassentinelinitiative/ucm149340.htm. Accessed August 5, 2017.
21. Moher D, Liberati A, Tetzlaff J, Altman DG, Group P. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Med.* 2009;6(7):e1000097.
22. McDonald KM, Hlatky MA, Saynina O, Geppert J, Garber AM, McClellan MB. Trends in hospital treatment of ventricular arrhythmias among Medicare beneficiaries, 1985 to 1995. *American heart journal.* 2002;144(3):413-421.
23. Leonard CE, Bilker WB, Newcomb C, Kimmel SE, Hennessy S. Antidepressants and the risk of sudden cardiac death and ventricular arrhythmia. *Pharmacoepidemiology and drug safety.* 2011;20(9):903-913.
24. Leonard CE, Freeman CP, Newcomb CW, et al. Antipsychotics and the Risks of Sudden Cardiac Death and All-Cause Death: Cohort Studies in Medicaid and Dually-Eligible Medicaid-Medicare Beneficiaries of Five States. *Journal of clinical & experimental cardiology.* 2013;Suppl 10(6):1-9.
25. Kawai VK, Murray KT, Stein CM, et al. Validation of a computer case definition for sudden cardiac death in opioid users. *BMC Res Notes.* 2012;5:473.
26. Schelleman H, Bilker WB, Kimmel SE, et al. Methylphenidate and risk of serious cardiovascular events in adults. *Am J Psychiatry.* 2012;169(2):178-185.
27. Leonard CE, Razzaghi H, Freeman CP, Roy JA, Newcomb CW, Hennessy S. Empiric potassium supplementation and increased survival in users of loop diuretics. *PLoS One.* 2014;9(7):e102279.
28. De Bruin ML, van Hemel NM, Leufkens HG, Hoes AW. Hospital discharge diagnoses of ventricular arrhythmias and cardiac arrest were useful for epidemiologic research. *Journal of clinical epidemiology.* 2005;58(12):1325-1329.
29. Molokhia M, Pathak A, Lapeyre-Mestre M, et al. Case ascertainment and estimated incidence of drug-induced long-QT syndrome: study in Southwest France. *British journal of clinical pharmacology.* 2008;66(3):386-395.
30. Zambon A, Polo Friz H, Contiero P, Corrao G. Effect of macrolide and fluoroquinolone antibacterials on the risk of ventricular arrhythmia and cardiac arrest: an observational study in Italy using case-control, case-crossover and case-time-control designs. *Drug Saf.* 2009;32(2):159-167.
31. Svanstrom H, Pasternak B, Hviid A. Use of azithromycin and death from cardiovascular causes. *The New England journal of medicine.* 2013;368(18):1704-1712.

32. Inghammar M, Svanstrom H, Melbye M, Pasternak B, Hviid A. Oral fluoroquinolone use and serious arrhythmia: bi-national cohort study. *BMJ.* 2016;352:i843.
33. Wu CS, Tsai YT, Tsai HJ. Antipsychotic drugs and the risk of ventricular arrhythmia and/or sudden cardiac death: a nation-wide case-crossover study. *J Am Heart Assoc.* 2015;4(2).
34. Chen HL, Hsiao FY. Domperidone, cytochrome P450 3A4 isoenzyme inhibitors and ventricular arrhythmia: a nationwide case-crossover study. *Pharmacoepidemiology and drug safety.* 2015;24(8):841-848.
35. Trac MH, McArthur E, Jandoc R, et al. Macrolide antibiotics and the risk of ventricular arrhythmia in older adults. *CMAJ.* 2016;188(7):E120-129.
36. Johannes CB, Varas-Lorenzo C, McQuay LJ, Midkiff KD, Fife D. Risk of serious ventricular arrhythmia and sudden cardiac death in a cohort of users of domperidone: a nested case-control study. *Pharmacoepidemiology and drug safety.* 2010;19(9):881-888.