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Diagnostic Codes for Sudden Cardiac Death and Ventricular Arrhythmia Functioned Poorly to Identify Outpatient Events in EPIC's General Practice Research Database

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Abstract

Purpose—To examine the validity of OXMIS/Read diagnoses of hospitalization for sudden cardiac death and ventricular arrhythmia (SD/VA) for use in studies of arrhythmogenic effects of outpatient medications in the General Practice Research Database (GPRD).

Methods—We identified putative occurrences of hospitalization for SD/VA in patients receiving outpatient prescriptions for cisapride, domperidone, or metoclopramide. We then administered a questionnaire to general practitioners (GPs) caring for these patients, requested hospital discharge consult letters, and examined the positive predictive value (PPV) of diagnostic codes in identifying outpatient events precipitating hospitalization.

Results—We identified 84 putative events, 38 (45%) of which occurred in patients cared for by GPs participating in the follow-up scheme. Thirty of 38 questionnaires (79%) were completed. The PPV for the occurrence of any SD/VA was 93% (95% CI, 78%–99%). However, the PPV for SD/VA occurrence in an outpatient setting precipitating a hospitalization was only 23% (95% CI, 10%–42%). The majority of inpatient diagnostic codes reflected events occurring after hospital admission, not precipitating it.

Conclusions—While computerized codes for SD/VA agreed well with physician diagnosis, they operated poorly to identify events occurring in an outpatient setting. Studies of SD/VA in the GPRD should verify events on a case-by-case basis.

Keywords

Validation Studies; Data collection; Databases; Pharmacoepidemiology; General Practice Research Database; Questionnaires

Key Points

- Epidemiologic studies of drug-induced sudden cardiac death and ventricular arrhythmia (SD/VA) have been hampered by challenges in identifying cases that could have resulted from drugs prescribed to outpatients.

- In the General Practice Research Database (GPRD), the positive predictive value (using physician questionnaire as the gold standard) for diagnostic codes in identifying a SD/VA occurrence was 93%, yet only 23% for outpatient-occurring events precipitating a hospitalization.
- Studies of outpatient drug-induced SD/VA in the GPRD should verify events on a case-by-case basis.

Introduction

Drug-induced ventricular arrhythmia and sudden cardiac death have arisen as a major public health concern, resulting in the removal of more drugs from the market than any other adverse drug effect in the past ten years ¹. Because the baseline incidence of ventricular arrhythmia is only about 0.5 to 2 events per thousand person-years ^{2–6}, very large epidemiologic studies are needed to characterize risks associated with particular drugs. Although the use of cisapride has been tightly restricted because of this risk, published large epidemiologic studies have been unable to demonstrate an increased risk ^{5–7}. In addition to the low incidence of ventricular arrhythmia and sudden cardiac death, epidemiologic studies of this outcome are hampered by challenges in identifying cases of ventricular arrhythmia and sudden cardiac death that could have resulted from drugs prescribed to outpatients ⁷.

The General Practice Research Database (GPRD) is widely used for pharmacoepidemiologic research ⁸, and has been used to study ventricular arrhythmia associated with the use of cisapride ⁶, antipsychotic drugs ⁹, and non-sedating antihistamines ¹⁰. However, the validity of the study outcome has not been examined in the GPRD. Therefore, we sought to examine the positive predictive value (PPV) of diagnosis codes for ventricular arrhythmia and sudden cardiac death in the GPRD, particularly as it relates to cases occurring outside of the hospital, which is generally the focus of studies utilizing this database, since the drugs identified in the database are prescribed to community-dwelling patients.

Subjects & Methods

Study Overview and Database Description

We examined the PPV of a set of diagnostic codes, listed in Table 1, as a marker of sudden cardiac death and ventricular arrhythmia (SD/VA) occurring in outpatients within the GPRD. The GPRD, an anonymized primary care data source, contains outpatient electronic medical records from 755 practices in the United Kingdom (UK), with data on nearly 10 million persons. As virtually all patient care is coordinated by the general practitioner (GP) through the National Health Service ¹¹, GPRD provides a near-complete picture of care for registered individuals. The database is broadly representative of the UK population in terms of age, sex, and geography ¹². The GPRD records outpatient prescriptions and outpatient diagnoses, as well as hospital diagnoses that are entered in response to receipt of a consultant's letter (i.e., hospital discharge summary) ¹¹. Diagnoses are recorded using the Read and Oxford Medical Information System (OXMIS) coding systems. We used GPRD data entered from its establishment in 1987 through March 2002, as obtained from EPIC (London, UK, a part of the Cegedim Group), and included only data classified as "up-to-standard" ¹¹.

Eligible study population

We identified putative outcomes occurring within a cohort of persons receiving cisapride, domperidone, or metoclopramide who had at least six months of follow-up prior to their first prescription for one of these agents. As most chronically-administered prescriptions in the

UK are issued in one-month supplies, we assumed that each prescription lasted 28 days. We confirmed this assumption by examining the frequency distribution of the number of days between subsequent prescriptions in the same individual.

Identification of putative outcomes

Putative outcomes of SD/VA were identified by the presence of a record for a hospitalization in association with one of the diagnostic codes listed in Table 1. We did not include codes for unexplained or unattended death because we previously found that only 26% of deaths occurring within two days of such a diagnosis appeared to be of cardiac origin ⁹.

Outcome validation

In collaboration with the Health Improvement Network Additional Information Service (THIN-AIS), we administered a mailed questionnaire to GPs about putative cases of SD/VA and requested a copy of the relevant hospital consultant letter and any electrocardiography strips or reports obtained in association with this putative event. We reviewed the resulting information using a structured abstraction form to elucidate a) the occurrence of physician confirmation of the outcome, b) the location of the onset of the event (inpatient versus outpatient), c) non-cardiac precipitating causes, and d) the GP's basis for his or her responses/determinations (i.e., memory or records). The validation definition, adapted from one used by Ray et al. ¹³ was a witnessed sudden collapse, or individual found unconscious or dead with evidence that the person has been alive in the past 24 hours, excluding events with an immediately-precipitating non-cardiac cause (e.g., blunt trauma, motor vehicle accident). Events that originated after hospital admission did not meet the outcome definition. Responding GPs were paid £70 (for questionnaire only) or £100 (for questionnaire plus consult letter, electrocardiography strips, or other supplemental information).

This study was approved by the GPRD's Scientific and Ethical Advisory Group and by the University of Pennsylvania's Committee on Studies Involving Human Beings. The funding sources had no role in the study's design, conduct, or interpretation.

Data Analysis

Questionnaire responses and supplemental information were abstracted and corresponding data were entered into a database. PPVs were calculated as the proportion of individuals with a physician-confirmed outcome. Binomial exact 95% confidence intervals (CIs) were calculated using Stata 9.0 (StataCorp LP, College Station, Texas: 2005).

Results

The study cohort consisted of 350,573 users of prokinetic agents of interest who contributed 48,183 person-years of observation. Among 10,888 person-years of exposure to cisapride, 25,199 person-years of exposure to metoclopramide, and 12,096 person-years of exposure to domperidone, we identified 17, 26, and 41 putative SD/VA outcomes in each of these groups, respectively. Of the 84 outcomes identified, 38 (45%) occurred in patients whose GP participated in the AIS follow-up scheme. Therefore, THIN-AIS requested questionnaires and consult letters for 38 outcomes, and received 30 (79%) usable responses. We were unable to obtain information on the remaining eight putative outcomes because of practices' inability to locate the patient's computerized record (N = 7) or GP refusal (N = 1). Thirty of 30 responses (100%) included a completed questionnaire, four (13%) also included a consult letter, and none contained an electrocardiography strip. Ninety percent of GPs

relied on their review of the medical record when completing the questionnaire, while 10% indicated a reliance on memory only. These results are presented in Figure 1.

Of the 30 evaluable responses, SD/VA was not confirmed by the GP in two. Therefore, the positive predictive value (PPV) for the occurrence of SD/VA was 93% (95% CI, 78% to 99%). However, of the 28 putative outcomes in which an event was confirmed, 13 (46%) originated in the hospital, the GP did not know the setting in eight (29%), and seven (25%) originated in the outpatient setting. Because none of the outpatient events was attributed by the GP to an immediately-precipitating cause, each met our *a priori* outcome definition. Thus, of the 30 responses evaluated, seven outpatient events led to a PPV of 23% (95% CI, 10% to 42%). Even if all eight events identified by the GP as occurring in an unknown setting were actually outpatient events, the corresponding PPV would only be 50% (95% CI, 31% to 69%). Table 2 presents PPVs stratified by diagnosis code.

Discussion

Epidemiologic studies using electronic records depend critically on the validity of the outcomes identified in research databases. Outcome validity can be described in two levels¹⁴. The first is whether the electronic record accurately reflects the diagnosis assigned by the physician. The second is whether the physician's diagnosis is correct. Validation studies such as this typically focus on the first level, as it is usually difficult to retrospectively reconstruct the clinical scenario in enough detail to examine the accuracy of the physician's diagnosis¹⁴. Of the putative outcomes identified electronically (N = 84), less than half occurred in patients of practices participating in the AIS follow-up scheme (N = 38), thereby limiting the scope of our study. Although the PPV for any occurrence of SD/VA was 93% (95% CI, 78% to 99%), it was only 23% (95% CI, 10% to 42%) for identifying events occurring in the outpatient setting, which were our outcomes of interest, since we were studying outpatient drug exposures. Additionally, including events with an unknown location as outpatient events only improved the PPV modestly (50%, 95% CI, 31% to 69%).

Given these results, the PPV for this outcome in the GPRD seems too low to be used in pharmacoepidemiologic studies of drug-induced SD/VA in outpatients. While it is possible that a subset of diagnosis codes may perform better than the list as a whole, our limited sample size did not allow us to make such inferences. Thus, researchers wishing to conduct such studies using the GPRD should verify each putative outcome. This will limit the scope of such studies to data from AIS-participating practices.

This study has a number of limitations. First, 55% of the putative outcomes identified occurred in patients of GPs not participating in the AIS follow-up scheme. While we have no reason to expect that these practices, patients, or events differ from the rest, the possibility exists. Second, while GPs principally relied on the electronic medical record to verify events, a small proportion relied on their memory. Events for which the GP relied on memory occurred during the mid-1990s, in many cases more than 10 years prior to receipt of our questionnaire, which raises the question of recall accuracy. Third, we identified SD/VA events nested within users of specific drugs of interest. Therefore, the validation results may not be generalizable to other populations, such as those using other drugs, or those using no drugs. Finally, we did not evaluate the accuracy of the GP's initial SD/VA diagnosis; we simply compared the GP-assigned diagnosis to the electronic record.

Studies of outpatient drug-induced arrhythmia depend on the ability to validly identify outcomes of interest using computerized data. While the occurrence of SD/VA in the GPRD validated well versus physician report, the computerized codes performed poorly in

identifying events that originated in outpatients, who constitute the population of interest in pharmacoepidemiologic studies using the GPRD.

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Figure 1.
Classification of Putative Cases

Table 1

Read and Oxford Medical Information System (OXMIS) codes for sudden cardiac death and ventricular arrhythmia

OXMIS/Read code	Description
4279EA	arrhythmia ventricular (benign)
4272D	cardiac arrest
G575.00	cardiac arrest
SP11000	cardiac arrest as a complication of care
G575000	cardiac arrest with successful resuscitation
G575z00	cardiac arrest, unspecified
G574011	cardiac arrest – ventricular fibrillation
7L1H.13	defibrillation
K3093	defibrillation by catheter (IV)
328..00	ECG: ventricular arrhythmia
328Z.00	ECG: ventricular arrhythmia NOS
3283.00	ECG: ventricular fibrillation
3282.00	ECG: ventricular tachycardia
2241.00	O/E: collapse – cardiac arrest
G571.00	paroxysmal ventricular tachycardia
G57yA00	re-entry ventricular arrhythmia
4279AC	rhythm ventricular arrhythmia
G575100	sudden cardiac death, so described
4279E	ventricular fibrillation
G574000	ventricular fibrillation
G574.00	ventricular fibrillation and flutter
G574z00	ventricular fibrillation and flutter, NOS
4279GL	ventricular flutter
G574100	ventricular flutter
G571.11	ventricular tachycardia
4279HV	ventricular tachycardia paroxysmal

IV = intravenous; ECG = electrocardiogram; NOS = not otherwise specified; O/E = on examination

Table 2

Positive predictive values (PPVs) of Read and OXMIS codes

	occurrence of SD/VA, regardless of location		outpatient-occurring SD/VA	
OXMIS/Read code	N (validated/total)	PPV [95%CI]	N (validated/total)	PPV [95%CI]
4279EA	0/1	0% [0 – 98] *	0/1	0% [0 – 98] *
4272D	7/7	100% [59 – 100] *	0/7	0% [0 – 41] *
G571.00	2/3	67% [9 – 99]	1/3	33% [1 – 91]
G575.00	16/16	100% [79 – 100] *	5/16	31% [11 – 59]
G575100	1/1	100% [3 – 100] *	1/1	100% [3 – 100] *
G574000	2/2	100% [16 – 100] *	0/2	0% [0 – 84] *
Overall	28/30	93% [78 – 99]	7/30	23% [10 – 42]

* one-sided, 97.5% confidence interval