DIAGNOSTIC ALGORITHMS FOR IDENTIFICATION OF CARDIOVASCULAR DEATH IN ADMINISTRATIVE CLAIMS DATABASES: A SYSTEMATIC REVIEW

Sonal Singh, MD, MPH,[1]* Hassan Fouyazi, MS,[1] Kathryn Anzuoni, MPH,[1] Leah Goldman, BA,[1] Jea Young Min, PharmD, MPH,[2] Marie Griffin, MD, MPH,[2] Carlos G. Grijalva, MD, MPH,[2] James A. Morrow, AS,[2] Christine Whitmore, PhD,[2] Charles E. Leonard, PharmD, MSCE,[3] Mano Selvan, PhD,[4] Vinit Nair, BPharm, MS,[4] Yunping Zhou, MS,[4] Sengwee Toh, ScD,[5] Andrew Petrone, MPH,[5] James Williams, MBA,[5] Elnara Fazio-Eynullayeva, MA,[5] Richard S. Swain, PhD, MPH,[6] D. Tyler Coyle, MD, MS,[6] Susan Andrade, ScD[1]

1. Meyers Primary Care Institute, University of Massachusetts Medical School, Worcester, MA; 2. Vanderbilt University Medical Center, Nashville, TN; 3. Department of Biostatistics, Epidemiology, and Informatics, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA; 4. Humana, Louisville, KY; 5. Department of Population Medicine, Harvard Medical School and Harvard Pilgrim Healthcare Institute, Boston, MA; 6. Office of Surveillance and Epidemiology, Center for Drug Evaluation and Research, United States Food and Drug Administration, Silver Spring, MD

BACKGROUND

Valid algorithms for identification of cardiovascular (CV) deaths allow researchers to assess the cardiovascular safety of medications which is of importance to regulatory science, patient safety, and public health.

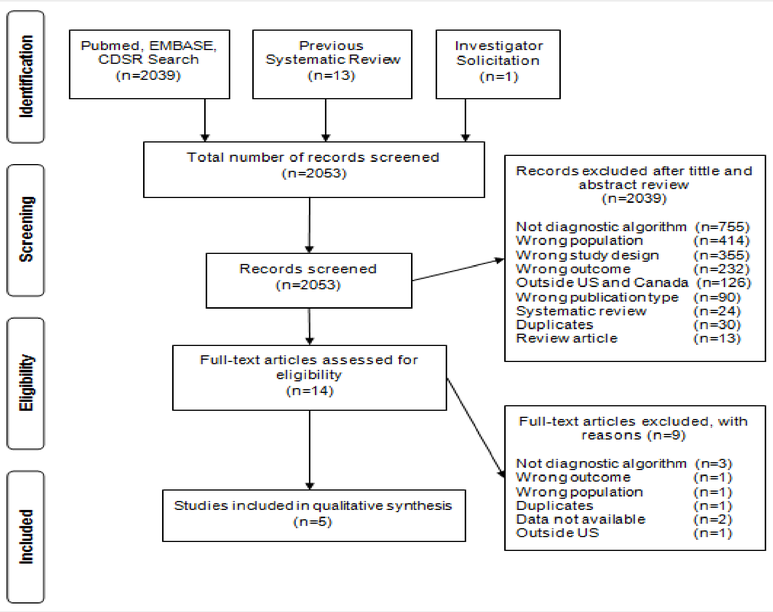
OBJECTIVE

To conduct a systematic review of validated algorithms to identify CV death in administrative health plan claims databases.

METHODS

- Systematic searches of MEDLINE, EMBASE, and Cochrane Library for English-language studies published between January 1, 2012 and October 17, 2017.
- Selected any observational study using electronic health care data to evaluate the sensitivity, specificity, positive predictive value (PPV), or negative predictive value (NPV) of algorithms for identifying CV death (sudden cardiac death [SCD], myocardial infarction [MI]-related death, or stroke-related death) among adults aged ≥18 years in the United States.
- Data extraction by two independent reviewers with disagreements resolved through further discussion and consensus.
- The Quality Assessment of Diagnostic Accuracy Studies-2 instrument (QUADAS-2) was used to assess the risk of bias.
- Protocol Registration : PROSPERO 2017 CRD42017078745

Figure 1. Flow Sheet of Included Studies



RESULTS

Five studies (n=1 on MI- and stroke-related death, n=4 on SCD) were included after a review of 2,053 citations. The PRISMA Flow Sheet is shown in **Figure 1.** The characteristics of included studies is shown in **Table 1**.

Sudden Cardiac Death

- **Chung et al.** validated a computer case definition of SCD (underlying cause) among Medicaid enrollees 30-74 years of age, utilizing linked database with Medicaid files, and state death certificate files (covering ICD-9 and ICD-10 periods).
- The study validated the definitions using medical record review as reference.
- Overall PPV (86.8%) was high and similar between SCD coded by ICD-9 (85.1%) or ICD-10 (87.5%).

- **Fox et al.** examined the degree of overestimation of SCD in death certificates compared to physician adjudicated cases in the Framingham Heart Study.
- SCD defined as out-of-hospital coronary heart disease (CHD) death occurring within one hour of symptom onset without other probable cause based on medical record review and next-of-kin interviews.
- Reference standard included reviews of each CV event by a three-member physician panel.
- Sensitivity, specificity, PPV, and NPV were 46%, 71%, 32%, and 82%, respectively.

- **Hennessy et al.** identified outpatient-occurring SCD arrest/ventricular arrhythmia events resulting in hospital presentation using first-listed ICD-9 codes on emergency department (ED) or inpatient medical claims (PPV=92.3%).
- The study validated the definitions using medical record review as reference.
- Using a first-listed ICD-9 discharge diagnosis of sudden death for hospitalization and ED visits respectively, the PPVs for SCD algorithm was 92.3% (83.0%-97.5%).

- **Iribarren et al.** used death certificate information to define SCD using ICD-9 code for cardiac arrest as first contributory or underlying cause of death plus location of death listed as out of hospital.
- Reference standard was physician-based review.
- PPV was 19%, sensitivity was 24% and specificity was 85%. An expanded definition of SCD which added ICD-9 codes for acute MI (ICD-9 410) and chronic CAD (411-414) increased both the sensitivity (87%) and PPV (27%), but resulted in decreased specificity (66%).

MI- and stroke-related death

- **Suehs et al.** identified members with diagnoses of CHD with any of the three-digit ICD-9 codes and for stroke in terminal medical encounters.
- Mortality determined using date of death in enrollment files. Cause of death determined based on ICD-9 codes preceding the recorded date of death. The results were compared to the National Death Index-based cause of death.
- PPV and sensitivity were low for CV mortality (PPV=36.4%, sensitivity=36.8%), CHD mortality (PPV=28.3%, sensitivity=36.8%), and stroke mortality (PPV=34.5%, sensitivity=44.9%), although the specificity and NPV for these outcomes were high (CV mortality NPV=98.7%, specificity=98.7%; CHD mortality NPV=98.9%, specificity=98.8%; and stroke-related death NPV=99.7%, specificity=99.6%).

Table 1. Study Characteristics

Author Year	Objectives	Population	Inclusion/Exclusion Criteria	Outcome Studied
Chung et al. 2010	Develop/validate a computer case definition of SCD	Medicaid enrollees 1990-2005; 30-74 years of age, 730+ days prior enrollment with full pharmacy benefits/evidence of regular use of medical care, including one prescription filled	Exclude: Patients in nursing homes (365 days), with evidence of life-threatening illness, hospitalized in last 30 days with a serious non-CV illness (cancer, HIV, etc.) or with diagnosed recreational drug dependency	Probable SCD: Witnessed/ unwitnessed sudden collapse with no pulse/respiration or unwitnessed collapse known to be alive in previous hour. Possible SCD: Unwitnessed arrest but known to be alive last 24 hours
Fox et al. 2005	Examine degree of overestimation of SCD in death certificates vs physician-adjudicated cases	Framingham Heart Study population 1950-1999	Include: All SCDs by physician adjudication or heart disease deaths identified by the death certificate	Overestimation (number of SCD cases ID by death certificate divided by physician-adjudicated cases)
Hennessy et al. 2010	Determine PPV of algorithm to identify outpatient-occurring SCD and ventricular arrhythmia leading to hospital presentation	Medicaid beneficiaries of California, Florida, New York, Ohio, and Pennsylvania (with and without dual coverage by Medicare) during 1999-2002	Include: Medicaid enrollees with no prior encounter of any type on any position (principal or non-principal, first listed or later listed) during study and no event in first 6 months of study	Incident SCD/ventricular arrhythmia
Iribarren et al. 1998	Evaluate performance of ascertaining out of hospital SCD using death certificate data (location of death and ICD-9 code for first contributory/underlying cause of death)	30-74 year old residents in 5 Minnesota metropolitan communities that were part of the Minnesota Heart Health Program (MHHP), 1985-1990 (n=108,676)	Include: Location of death outside of hospital; SCD ICD-9 codes Exclude: Death certificate listing neoplasm, COPD, injury, poisoning, accident, suicide, or homicide as underlying cause of death	Sensitivity, specificity, and PPV estimated for each of the 2 ICD-9 code definitions
Suehs et al. 2017	Assess ascertainment of all-cause and CV mortality among enrollees using the enrollment files and medical claims of a large, national health plan (Humana Inc.) compared to the NDI	Newly initiated Medicare Advantage Part D plan enrollees 2007-2012 on an antimuscarinic medication indicated for treatment of overactive bladder (OAB): oxybutynin, tolterodine, darifenacin, solifenacin, trospium, or fesoterodine	Include: At least 6+ months of continuous enrollment in the health plan prior to the index date. No OAB drug use in 6 month prior to index date	Mortality outcomes including cause of death, CV mortality, CHD mortality and stroke mortality

RISK OF BIAS

- Apart from the abstract by Suehs et al., which did not have sufficient information on the domains of the QAUADAS instrument and was rated as unclear risk of bias, the remaining 4 studies performed reasonably well on the domains of the QUADAS-2 instrument.
- A few studies did not report on the timing between the assessment of index and reference algorithm (Hennessy et al. and Suehs et al.), intermediate results (Hennessy et al. Irribaren et al. and Suehs et al.) or whether the index algorithm was interpreted without knowledge of the reference standard (Fox et al. and Irribaren et al.)

LIMITATIONS

We may have missed articles published in non-English languages. However, such studies are likely not relevant for future validation studies in the United States.

CONCLUSIONS

- Two existing algorithms based upon medical claims diagnoses +/- death certificates can accurately identify SCD to support pharmacoepidemiologic studies.
- Developing valid algorithms identifying MI- and stroke-related death should be a research priority.

ACKNOWLEDGEMENTS/DISCLOSURES

- This work was supported by the FDA through the Department of Health and Human Services (HHS) Contract number HHSF223201400030I.
- The authors have no conflicts of interest to disclose.