BACKGROUND
Valid algorithms for identification of cardiovascular (CV) death 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 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

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 ≥37 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. Although 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.
• Hennessey et al. identified outpatient-occurring SCD arrest/ventricular arrhythmia events resulting in hospitalization 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 PPV s for SCD defined using the PPV was 92.3% (83.0%-97.5%).
• Ibrahim et al. used death certificate data 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) included both the sensitivity (87%) and PPV (27%), but resulted in decreased specificity (66%).

Mi- and stroke-related death
• Suets 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%, specificity=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%).

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.

Table 1. Study Characteristics

<table>
<thead>
<tr>
<th>Author Year</th>
<th>Objectives</th>
<th>Population</th>
<th>Inclusion/Exclusion Criteria</th>
<th>Outcome Studied</th>
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</thead>
<tbody>
<tr>
<td>Chung et al. 2010</td>
<td>Develop/validate a computer case definition of SCD among Medicaid enrollees 1990-2005, 30-74 years of age, 75+ years prior enrollment with full pharmacy benefits/evidence of regular use of medical care, including one prescription filled</td>
<td>Medicaid enrollees</td>
<td>Exclude: Patients in nursing homes (185), life-threatening illness, hospitalized in last 30 days with serious non-CV illness (cancer, HIV, etc.) or with diagnosed recreational drug dependency</td>
<td>Probable SCD: Witnessed/unknown sudden collapse with no pulse/respiration or witnessed collapse known to be alive in previous hour. Possible SCD: Unwitnessed arrest but known to be alive last 24 hours. Overestimation (number of SCD cases by death certificate divided by physician-adjudicated cases)</td>
</tr>
<tr>
<td>Fox et al. 2005</td>
<td>Examine degree of overestimation of SCD in death certificates versus physician-adjudicated cases</td>
<td>Framingham Heart Study population 1950-1999</td>
<td>Include: All SCDs by physician adjudication or heart disease deaths identified by the death certificate</td>
<td>Sudden death/CV/ventricular arrhythmia</td>
</tr>
<tr>
<td>Hennessey et al. 2010</td>
<td>Determine PPV of algorithm to identify outpatient-occurring SCD and non-sustained ventricular arrhythmia leading to hospital presentation</td>
<td>Medicaid beneficiaries of California, Florida, New York, Ohio, and Pennsylvania (with and without dual coverage by Medicare) during 1999-2002</td>
<td>Include: Medicaid enrollees with non-principal cause and/or non-principal, first listed or later listed during study and no event in first 6 months of study</td>
<td>Incident SCD/CV/ventricular arrhythmia</td>
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<tr>
<td>Ibrahim et al. 1998</td>
<td>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)</td>
<td>30-74 year old residents in S 5 communities that were part of the Minnesota Heart Health Program (MHH), 1989-1998 (n=108,676)</td>
<td>Include: Location of death outside of hospital; SCD-I codes Excluded: Death certificate listing neoplastic, COPD, injury, poisoning, accident, suicide, or homicide as underlying cause of death</td>
<td>Sensitivity, specificity, and PPV estimated for each of the 24 ICD-9 code definitions</td>
</tr>
<tr>
<td>Suets et al. 2011</td>
<td>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</td>
<td>Newly initiated Medicare Advantage Part D Plan enrollees in 2012 on an antimuscarinic medication indicated for treatment of overactive bladder (OAB) (darifenacin, tolfenamic, darifenacin, solifenacin, trospium, or fesoterodine)</td>
<td>Include: At least 6 months of continuous enrollment in the health plan prior to the index date. No OAB drug use in 6 months prior to index date</td>
<td>Mortality outcomes including cause of death, CV mortality, CHD mortality and stroke mortality</td>
</tr>
</tbody>
</table>

RISK OF BIAS
• Apart from the abstract by Suets et al., which did not have sufficient information on the details of the QUADAS instrument and was likely not relevant for 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 (Hennessey et al. and Suets et al.), intermediate results (Hennessey et al. Ibrahim et al. and Suets et al.) or whether the index algorithm was interpreted without knowledge of the reference standard (Fox et al. and Ibrahim 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 pharmacoeconomic studies.
• Developing valid algorithms identifying MI- and stroke-related death should be a research priority.

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