MINI-SENTINEL SYSTEMATIC EVALUATION OF HEALTH OUTCOME OF INTEREST DEFINITIONS FOR STUDIES USING ADMINISTRATIVE DATA

CARDIAC ARRHYTHMIAS REPORT

Prepared by: Leonardo Tamariz, MD, MPH, Thomas Harkins, MA, MPH, and Vinit Nair, BPharm, MS, RPh

Author Affiliation: Humana, Miami, FL

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Mini-Sentinel is a pilot project sponsored by the U.S. Food and Drug Administration (FDA) to inform and facilitate development of a fully operational active surveillance system, the Sentinel System, for monitoring the safety of FDA-regulated medical products. Mini-Sentinel is one piece of the Sentinel Initiative, a multi-faceted effort by the FDA to develop a national electronic system that will complement existing methods of safety surveillance. Mini-Sentinel Collaborators include Data and Academic Partners that provide access to healthcare data and ongoing scientific, technical, methodological, and organizational expertise. The Mini-Sentinel Coordinating Center is funded by the FDA through the Department of Health and Human Services (HHS) Contract number HHSF223200910006I.

Mini-Sentinel Systematic Evaluation Of Health Outcome Of Interest Definitions For Studies Using Administrative Data

Cardiac Arrhythmias Report

I. EXECUTIVE SUMMARY

A. OVERVIEW OF PROJECT

The Food and Drug Administration (FDA) Mini-Sentinel contract is a pilot program that aims to conduct active surveillance to detect and refine safety signals that emerge for marketed medical products. To perform this active surveillance, it is necessary to develop and understand the validity of algorithms for identifying health outcomes of interest in administrative data. Thus, the goal of this project was to identify algorithms used to detect selected health outcomes of interest using administrative data sources and describe the performance characteristics of these algorithms as reported by the studies in which they were used. This report summarizes the process and findings of the cardiac arrhythmias algorithm review.

B. SUMMARY OF FINDINGS

The highest diagnostic accuracy statistics were seen when ICD-9 codes 427 and 798 were used. Use of specific subcodes of the 427 ICD-9 codes suggesting ventricular tachycardia or fibrillation yielded the highest results when the codes were used independently. At the same time, use of all specific codes and subcodes for ventricular arrhythmias and sudden death together as an algorithm yielded the best results. When ICD-9 code 426 was added to the algorithm, the reported positive predictive value (PPV) was reduced as compared to algorithms that did not use the code, and decreased the ability to identify patients with cardiac arrhythmias. Findings were similar when all subcodes or selected subcodes of 426 were used. More recent studies that used only specific ICD-9 subcodes of 427.x and 798 had higher PPVs and sensitivity.

The PPV differed by location of the arrhythmic event. The PPV was higher when the event occurred among inpatients than when it occurred among outpatient. The PPV was also higher when the codes were used in any position as compared to the principal position.

C. RECOMMENDATION FOR ALGORITHMS AND SUGGESTION FOR FUTURE RESEARCH

The most important and obvious flaw in many of the studies was not reporting the specific ICD-9 codes that were utilized to identify cardiac arrhythmias. Many manuscripts simply did not list the code or codes that were used. Another important gap was minimal use of other data that is available in administrative files, such as pharmacy, procedure, and DRG codes. Also, there is a lack of evaluations of algorithms in high risk patients, particularly those with heart failure. In addition, very few validation studies have been conducted utilizing ICD-10 codes or in patients of different race/ethnicities in whom the criteria published to date may have varying sensitivities and specificities.

II. PROJECT OBJECTIVES

The primary objective of this project was to identify studies that have validated algorithms used to identify various health outcomes of interest (HOIs) using administrative data from the United States or Canada, and to summarize the results of those validation studies. If fewer than five validation studies were identified, a secondary objective was to identify non-validated algorithms that have been used to identify the HOIs using administrative data.

III. BACKGROUND

The Food and Drug Administration (FDA) Mini-Sentinel contract is a pilot program that aims to conduct active surveillance to detect and refine safety signals that emerge for marketed medical products. In order to perform this work, the program needed to identify algorithms used to detect various health outcomes of interest using administrative data sources and to identify the performance characteristics of these algorithms as measured in the studies in which they were used. The data sources of interest were limited to those from the United States or Canada to increase their relevance to the Mini-Sentinel data sources, which are all from the United States. The Mini-Sentinel Protocol Core developed a preliminary list of approximately 140 potential health outcomes of interest, based on several criteria. These criteria included: 1) previous validation studies identified in a textbook chapter reviewing the validity of drug and diagnosis data used in pharmacoepidemiologic studies [1]; 2) a list of designated medical events from a proposed FDA rule on the safety reporting requirements for human drug and biological products [2]; and 3) Observational Medical Outcomes Partnership (OMOP) commissioned reports on algorithms used to identify health outcomes using administrative data [3].

From the original list of 140 HOIs, the Protocol Core worked with FDA to select 20 for which reviews of algorithms would be completed. HOIs for which OMOP had already commissioned reports were purposefully excluded in order to avoid duplication of effort.

Cardiac arrhythmia was one of the 20 HOIs selected for review. This report describes the review process and findings for the cardiac arrhythmias definition algorithms.

IV. METHODS

A. SEARCH STRATEGY

The general search strategy was developed based on prior work by OMOP and its contractors, and modified slightly for these reports. Originally, OMOP contracted with two organizations to perform reviews of 10 HOIs. Because the search strategies used by each organization resulted in very different sets of articles, OMOP investigators reviewed the PubMed indexing of the articles deemed useful in final reports and developed a strategy that would identify the majority of these citations while maintaining efficiency in the number of abstracts that would need to be reviewed. Mini-Sentinel investigators made minor changes to this strategy that would result in the identification of more citations, and confirmed empirically that the majority of relevant articles from one set of OMOP reports (angioedema) [4, 5] would be identified using this approach. The base search strategy was then combined with PubMed terms representing the HOIs. Medical subject heading (MeSH) terms were generally preferred as HOI search terms due to their likely specificity. Text word searches were sometimes used, particularly when the MeSH search resulted in a small number of citations for review. The workgroup also searched the database of the Iowa Drug Information Service (IDIS) using a similar search strategy to identify other relevant articles that were not found in the PubMed search. For a limited number of outcomes where very few citations were identified from PubMed and IDIS searches, Embase searches were conducted. Search results were restricted to articles published on or after January 1, 1990.

University of Iowa investigators compiled the search results from different databases and eliminated duplicate results using a citation manager program. The results were then output into two sets of files, one containing the abstracts for review and the other containing documenting abstract review results.

The search strategy and results for cardiac arrhythmias are detailed in the Results section. The PubMed search was conducted on May 10, 2010, and the IDIS searches on May 4, 2010.

B. ABSTRACT REVIEW

1. Abstract Review Methods

Each abstract was reviewed independently by two investigators to determine whether the full-text article should be reviewed. Exclusion criteria were documented sequentially (i.e., if exclusion criterion 1 was met then the other criteria were not documented). If the reviewers disagreed on whether the full-text should be reviewed, then it was selected for review. Inter-rater agreement on whether to include or exclude an abstract was calculated using a Cohen's kappa statistic. The goal was to review any administrative database study that used data from the United States or Canada and studied the HOI, as validation components of studies are not necessarily included in the abstract and other relevant citations might be identified from the references of such studies.

2. Abstract Exclusion Criteria

1. Did not study the HOI.
2. Not an administrative database study. Eligible sources included insurance claims databases as well as other secondary databases that identify health outcomes using billing codes.
3. Data source not from the United States or Canada.

C. FULL-TEXT REVIEW

1. Full-Text Review Methods

Full-text articles were reviewed independently by two investigators, with a goal of identifying validation studies described in the article itself or from the reference section of the article. Citations from the article's references were selected for full-text review if they were cited as a source for the HOI algorithm, or were otherwise deemed likely to be relevant. Full-text review exclusion criteria were applied sequentially, since if fewer than 5 validation studies were identified, up to 10 of the articles excluded based on the second criterion would need to be incorporated into the final report. If there was disagreement on whether a study should be included, the two reviewers attempted to reach consensus on inclusion by discussion. If the reviewers could not agree, a third investigator would be consulted to make the final the decision.

2. Full-Text Exclusion Criteria

1. Poorly described HOI identification algorithm that would be difficult to operationalize.
2. No validation of outcome definition or reporting of validity statistics.

D. MINI-SENTINEL INVESTIGATOR SURVEY

Mini-Sentinel investigators were surveyed to request information on any published or unpublished studies that validated an algorithm to identify an HOI in administrative data. Studies that would not be excluded by one of the aforementioned criteria were included in the final report.

E. EVIDENCE TABLE CREATION

A single investigator abstracted each study for the final evidence table. The data included in the table were confirmed by a second investigator for accuracy.

F. CLINICIAN OR TOPIC-EXPERT CONSULTATION

A clinician or topic-expert was consulted to review the results of the evidence table and discuss how they compare and contrast to diagnostic methods currently used in clinical practice. This included whether certain diagnostic codes used in clinical practice were missing from the algorithms and the appropriateness of the validation definitions compared to diagnostic criteria currently used in clinical practice. A summary of this consultation was included in the results.

V. RESULTS

A. SEARCH STRATEGY AND RESULTS

The following summarizes the search results obtained from PubMed and IDIS searches. The PubMed search identified 649 citations (Table 1), and the two IDIS searches identified 28 citations (Table 2). The total number of unique citations from the combined searches was 664. An additional PubMed search was conducted at a later date to amend the original search strategy with names of relevant databases that were not included in the original search. This search identified 8 citations (Table 3).

Table 1. PubMed Search Strategy and Results: Performed on 05/10/10

Results = 649

Search	Query	Results
#1	("Pharmaceutical preparations/adverse effects"[Mesh] OR "Pharmaceutical preparations/contraindications"[Mesh] OR "Pharmaceutical preparations/poisoning"[Mesh] OR "Pharmaceutical preparations/therapeutic use"[Mesh] OR "Pharmaceutical preparations/toxicity"[Mesh] OR "Pharmaceutical preparations/therapy"[Mesh] OR "Pharmaceutical preparations/analysis"[Mesh] OR "Chemical actions and uses/adverse effects"[Mesh] OR "Chemical actions and uses/contraindications"[Mesh] OR "Chemical actions and uses/poisoning"[Mesh] OR "Chemical actions and uses/therapeutic use"[Mesh] OR "Chemical actions and uses/toxicity"[Mesh] OR "Chemical actions and uses/therapy"[Mesh] OR "Chemical actions and uses/analysis"[Mesh] OR "Chemical actions and uses/epidemiology"[Mesh] OR "Drug toxicity"[Mesh] OR "Diseases Category/chemically induced"[Mesh] OR "Diseases Category/drug therapy"[Mesh] OR "Diseases Category/epidemiology"[Mesh] OR "Validation Studies"[pt] OR "Validation Studies as Topic"[Mesh] OR "Sensitivity and Specificity"[Mesh] OR "Predictive Value of Tests"[Mesh] OR "Reproducibility of Results"[Mesh] OR "Predictive Value"[tw]) Limits: Humans, English, Publication Date from 1990/01/01 to 2011/01/01	1844889
#2	("Premier"[All] OR "Solucient"[All] OR "Cerner"[All] OR "Ingenix"[All] OR "LabRx"[All] OR "IHCIS"[All] OR "marketscan"[All] OR "market scan"[All] OR "Medstat"[All] OR "Thomson"[All] OR "pharmetrics"[All] OR "healthcore"[All] OR "united healthcare"[All] OR "UnitedHealthcare"[All] OR "UHC"[All] OR "GPRD"[All] OR "general practice research database"[All] OR "Research Database"[All] OR "Group Health"[All] OR "HCUP"[All] OR ("Healthcare Cost"[All] AND "Utilization Project"[All]) OR ("Health Care Cost"[All] AND "Utilization Project"[All]) OR "MEPS"[All] OR "Medical Expenditure Panel Survey"[All] OR "NAMCS"[All] OR "National Hospital Ambulatory Medical Care Survey"[All] OR "National Ambulatory Medical Care Survey"[All] OR "NHIS"[All] OR "National Health Interview Survey"[All] OR "Kaiser"[All] OR "HMO Research"[All] OR "Health Maintenance Organization"[All] OR "HMO"[All] OR "Cleveland Clinic"[All] OR "Lovelace"[All] OR "Department of Defense"[All] OR "Henry Ford"[All] OR ("Denmark"[All] AND "Epidemiology"[All]) OR "i3 Drug Safety"[All] OR "i3"[All] OR "Aetna"[All] OR "Humana"[All] OR "Wellpoint"[All] OR "IMS"[All] OR "Intercontinental Marketing Services"[All] OR "IMS Health"[All] OR "Geisinger"[All] OR "GE Healthcare"[All] OR "MQIC"[All] OR "PHARMO"[All] OR "Institute for Drug Outcome Research"[All] OR "Pilgrim"[All] OR "Puget Sound"[All] OR "Regenstrief"[All] OR "Saskatchewan"[All] OR "Tayside"[All] OR "MEMO"[All] OR "Medicines Monitoring Unit"[All] OR "Veterans Affairs"[All] OR "Partners Healthcare"[All] OR "Mayo Clinic"[All] OR "Rochester Epidemiology"[All] OR "Indiana Health Information Exchange"[All] OR "Indiana Health"[All] OR "Intermountain"[All] OR "THIN"[All] OR "The health improvement network"[All] OR "blue cross"[All] OR "health partners"[All] OR "health plan"[All] OR "health services"[All] OR "Nationwide Inpatient Sample"[All] OR "National Inpatient Sample"[All] OR "medicaid"[All] OR "medicare"[All] OR "MediPlus"[All] OR "Outcome Assessment"[All] OR "insurance database"[All] OR "insurance databases"[All] OR "Data Warehouse"[All] OR "ICD-9"[All] OR "international statistical classification"[All] OR "international classification of diseases"[All] OR "ICD-10"[All] OR "Database Management Systems"[Mesh] OR "Medical Records Systems, Computerized"[Mesh] OR "CPT"[All] OR "Current procedural terminology"[All] OR "drug surveillance"[All] OR ("claims"[tw] AND "administrative"[tw]) OR ("data"[tw] AND "administrative"[tw]) OR "Databases, Factual"[Mesh] OR "Databases as topic"[Mesh] OR "Medical Record Linkage"[Mesh] OR "ICD-9-CM"[All Fields] OR "ICD-10-CM"[All Fields] Limits: Humans, English, Publication Date from 1990/01/01 to 2011/01/01	395147
#3	("Clinical Trial"[pt] OR "Editorial"[pt] OR "Letter"[pt] OR "Meta-Analysis"[pt] OR "Randomized Controlled Trial"[pt] OR "Clinical Trial, Phase I"[pt] OR "Clinical Trial, Phase II"[pt] OR "Clinical Trial, Phase III"[pt] OR "Clinical Trial, Phase IV"[pt] OR "Comment"[pt] OR "Controlled Clinical Trial"[pt] OR "case reports"[pt] OR "Clinical Trials as Topic"[Mesh] OR "double-blind"[All] OR "placebo-	2701949

	controlled"[All] OR "pilot study"[All] OR "pilot projects"[Mesh] OR "Review"[pt] OR "Prospective Studies"[Mesh]) Limits: Humans, English, Publication Date from 1990/01/01 to 2011/01/01	
#4	Search #1 AND #2 Limits: Humans, English, Publication Date from 1990/01/01 to 2011/01/01	117951
#5	Search #4 NOT #3 Limits: Humans, English, Publication Date from 1990/01/01 to 2011/01/01	71403
#6	("Arrhythmias, Cardiac"[Mesh:NoExp] OR "Brugada Syndrome"[Mesh:NoExp]) OR "Cardiac Complexes, Premature"[Mesh]) OR "Commotio Cordis"[Mesh:NoExp]) OR "Heart Block"[Mesh]) OR "Long QT Syndrome"[Mesh]) OR "Parasystole"[Mesh]) OR "Pre-Excitation Syndromes"[Mesh]) OR "Tachycardia"[Mesh]) OR "Ventricular Fibrillation"[Mesh]) OR "Ventricular Flutter"[Mesh]) OR "Death, Sudden, Cardiac"[Mesh]) OR "Torsades de Pointes"[Mesh]) OR "Heart Arrest"[Mesh]) OR "Tachycardia, Supraventricular"[Mesh] Limits: Humans, English, Publication Date from 1990/01/01 to 2011/01/01	48995
#7	Search #5 AND #6 Limits: Humans, English, Publication Date from 1990/01/01 to 2011/01/01	649

Table 2. IDIS Search Strategy and Results: Performed on 05/04/10

Results = 28

Search 1: 24 Results

ADVANCED SEARCH

All Fields:

"Premier" OR "Solucient" OR "Cerner" OR "Ingenix" OR "LabRx" OR "IHCIS" OR "marketscan" OR "market scan" OR "Medstat" OR "Thomson" OR "pharmetrics" OR "healthcore" OR "united healthcare" OR "UnitedHealthcare" OR "UHC" OR "GPRD" OR "general practice research database" OR "Research Database" OR "Group Health" OR "HCUP" OR ("Healthcare Cost" AND "Utilization Project") OR ("Health Care Cost" AND "Utilization Project") OR "MEPS" OR "Medical Expenditure Panel Survey" OR "NAMCS" OR "National Hospital Ambulatory Medical Care Survey" OR "National Ambulatory Medical Care Survey" OR "NHIS" OR "National Health Interview Survey" OR "Kaiser" OR "HMO Research" OR "Health Maintenance Organization" OR "HMO" OR "Cleveland Clinic" OR "Lovelace" OR "Department of Defense" OR "Henry Ford" OR ("Denmark" AND "Epidemiology") OR "i3 Drug Safety" OR "i3" OR "Aetna" OR "Humana" OR "Wellpoint" OR "IMS" OR "Intercontinental Marketing Services" OR "IMS Health" OR "Geisinger" OR "GE Healthcare" OR "MQIC" OR "PHARMO" OR "Institute for Drug Outcome Research" OR "Pilgrim" OR "Puget Sound" OR "Regenstrief" OR "Saskatchewan" OR "Tayside" OR "MEMO" OR "Medicines Monitoring Unit" OR "Veterans Affairs" OR "Partners Healthcare" OR "Mayo Clinic" OR "Rochester Epidemiology" OR "Indiana Health Information Exchange" OR "Indiana Health" OR "Intermountain" OR "THIN" OR "The health improvement network" OR "blue cross" OR "health partners" OR "health plan" OR "health services" OR "Nationwide Inpatient Sample" OR "National Inpatient Sample" OR "medicaid" OR "medicare" OR "MediPlus" OR "Outcome Assessment" OR "insurance database" OR "insurance databases" OR "Data Warehouse" OR "ICD-9" OR "international statistical classification" OR "international classification of diseases" OR "ICD-10" OR "Database Management Systems" OR "Medical Records Systems, Computerized" OR "CPT" OR "Current procedural terminology" OR "drug surveillance" OR ("claims" AND "administrative") OR ("data" AND "administrative") OR "Databases, Factual" OR "Databases" OR "Medical Record Linkage" OR "ICD-9-CM" OR "ICD-10-CM"

AND **Descriptor**:

82 not ("CASE REPORT ADULT 0" or "FDA APPROVAL PACKAGE 155" OR "FDA BLACK BOX WARNING 165" OR "PIVOTAL STUDY 162" OR "FDA ADVISORY COMMITTEE 164" or "CASE REPORT PEDIATRIC 1" or "CASE REPORT GERIATRIC 2" or "REVIEW ADULT 6" or "STUDY NON-CLINICAL 8" or "REVIEW PEDIATRIC 21" or "REVIEW GERIATRIC 23" or "STUDY RANDOMIZE ADULT 135" or "STUDY RANDOMIZE PEDIATRIC 136" or "STUDY RANDOMIZE GERIATRIC 137" or "CROSS-OVER 144" or "META-ANALYSIS 145" or "N-OF-ONE TRIAL 146" or "PRACTICE GUIDELINE 156" or "SYSTEMATIC REVIEW 161" or "ANNOTATED BIBLIOGRAPHY 167" or "PRIORITY CLIN PRACT GUIDE 168")

(NOTE: SIDE EF CARDIOVASCULAR 82)

AND **Abstract**:

"arrhythmia"

Years: 1990-2010

Records = 24

Search 2: 4 Results

ADVANCED SEARCH

All Fields:

"Premier" OR "Solucient" OR "Cerner" OR "Ingenix" OR "LabRx" OR "IHCIS" OR "marketscan" OR "market scan" OR "Medstat" OR "Thomson" OR "pharmetrics" OR "healthcore" OR "united healthcare" OR "UnitedHealthcare" OR "UHC" OR "GPRD" OR "general practice research database" OR "Research Database" OR "Group Health" OR "HCUP" OR ("Healthcare Cost" AND "Utilization Project") OR ("Health Care Cost" AND "Utilization Project") OR "MEPS" OR "Medical Expenditure Panel Survey" OR "NAMCS" OR "National Hospital Ambulatory Medical Care Survey" OR "National Ambulatory Medical Care Survey" OR "NHIS" OR "National Health Interview Survey" OR "Kaiser" OR "HMO Research" OR "Health Maintenance Organization" OR "HMO" OR "Cleveland Clinic" OR "Lovelace" OR "Department of Defense" OR "Henry Ford" OR ("Denmark" AND "Epidemiology") OR "i3 Drug Safety" OR "i3" OR "Aetna" OR "Humana" OR "Wellpoint" OR "IMS" OR "Intercontinental Marketing Services" OR "IMS Health" OR "Geisinger" OR "GE Healthcare" OR "MQIC" OR "PHARMO" OR "Institute for Drug Outcome Research" OR "Pilgrim" OR "Puget Sound" OR "Regenstrief" OR "Saskatchewan" OR "Tayside" OR "MEMO" OR "Medicines Monitoring Unit" OR "Veterans Affairs" OR "Partners Healthcare" OR "Mayo Clinic" OR "Rochester Epidemiology" OR "Indiana Health Information Exchange" OR "Indiana Health" OR "Intermountain" OR "THIN" OR “The health improvement network" OR "blue cross" OR "health partners" OR "health plan" OR "health services" OR "Nationwide Inpatient Sample" OR "National Inpatient Sample" OR "medicaid" OR "medicare" OR "MediPlus" OR "Outcome Assessment" OR "insurance database" OR "insurance databases" OR "Data Warehouse" OR "ICD-9" OR “international statistical classification" OR “international classification of diseases" OR "ICD-10" OR "Database Management Systems" OR "Medical Records Systems, Computerized" OR "CPT" OR "Current procedural terminology" OR "drug surveillance" OR (“claims” AND “administrative”) OR (“data” AND “administrative”) OR "Databases, Factual" OR "Databases" OR "Medical Record Linkage" OR "ICD-9-CM" OR "ICD-10-CM"

AND **Disease**:

427. or 427.4 or 785.0 (NOTE: DYSRHYTHMIA, CARDIAC NEC 427., FIBRILLATION, VENTRICULAR 427.4, TACHYCARDIA NEC 785.0)

AND NOT **Descriptor**:

"CASE REPORT ADULT 0" or “FDA APPROVAL PACKAGE 155” OR “FDA BLACK BOX WARNING 165” OR “PIVOTAL STUDY 162” OR "FDA ADVISORY COMMITTEE 164" or "CASE REPORT PEDIATRIC 1" or "CASE REPORT GERIATRIC 2" or "REVIEW ADULT 6" or "STUDY NON-CLINICAL 8" or "REVIEW PEDIATRIC 21" or "REVIEW GERIATRIC 23" or "STUDY RANDOMIZE ADULT 135" or "STUDY RANDOMIZE PEDIATRIC 136" or "STUDY RANDOMIZE GERIATRIC 137" or "CROSS-OVER 144" or "META-ANALYSIS 145" or "N-OF-ONE TRIAL 146" or "PRACTICE GUIDELINE 156" or "SYSTEMATIC REVIEW 161" or "ANNOTATED BIBLIOGRAPHY 167" or "PRIORITY CLIN PRACT GUIDE 168"

Years: 1990-2010

Records = 4

Table 3. Search to Update the Original PubMed Search with Additional Database Names: Performed on 07/06/10

Results = 8

Search	Query	Results
#1	("Pharmaceutical preparations/adverse effects"[Mesh] OR "Pharmaceutical preparations/contraindications"[Mesh] OR "Pharmaceutical preparations/poisoning"[Mesh] OR "Pharmaceutical preparations/therapeutic use"[Mesh] OR "Pharmaceutical preparations/toxicity"[Mesh] OR "Pharmaceutical preparations/therapy"[Mesh] OR "Pharmaceutical preparations/analysis"[Mesh] OR "Chemical actions and uses/adverse effects"[Mesh] OR "Chemical actions and uses/contraindications"[Mesh] OR "Chemical actions and uses/poisoning"[Mesh] OR "Chemical actions and uses/therapeutic use"[Mesh] OR "Chemical actions and uses/toxicity"[Mesh] OR "Chemical actions and uses/therapy"[Mesh] OR "Chemical actions and uses/analysis"[Mesh] OR "Chemical actions and uses/epidemiology"[Mesh] OR "Drug toxicity"[Mesh] OR "Diseases Category/chemically induced"[Mesh] OR "Diseases Category/drug therapy"[Mesh] OR "Diseases Category/epidemiology"[Mesh] OR "Validation Studies"[pt] OR "Validation Studies as Topic"[Mesh] OR "Sensitivity and Specificity"[Mesh] OR "Predictive Value of Tests"[Mesh] OR "Reproducibility of Results"[Mesh] OR "Predictive Value"[tw]) Limits: Humans, English, Publication Date from 1990/01/01 to 2011/01/01	1867752
#2	("Premier"[All] OR "Solucient"[All] OR "Cerner"[All] OR "Ingenix"[All] OR "LabRx"[All] OR "IHCIS"[All] OR "marketscan"[All] OR "market scan"[All] OR "Medstat"[All] OR "Thomson"[All] OR "pharmetrics"[All] OR "healthcore"[All] OR "united healthcare"[All] OR "UnitedHealthcare"[All] OR "UHC"[All] OR "GPRD"[All] OR "general practice research database"[All] OR "Research Database"[All] OR "Group Health"[All] OR "HCUP"[All] OR ("Healthcare Cost"[All] AND "Utilization Project"[All]) OR ("Health Care Cost"[All] AND "Utilization Project"[All]) OR "MEPS"[All] OR "Medical Expenditure Panel Survey"[All] OR "NAMCS"[All] OR "National Hospital Ambulatory Medical Care Survey"[All] OR "National Ambulatory Medical Care Survey"[All] OR "NHIS"[All] OR "National Health Interview Survey"[All] OR "Kaiser"[All] OR "HMO Research"[All] OR "Health Maintenance Organization"[All] OR "HMO"[All] OR "Cleveland Clinic"[All] OR "Lovelace"[All] OR "Department of Defense"[All] OR "Henry Ford"[All] OR ("Denmark"[All] AND "Epidemiology"[All]) OR "i3 Drug Safety"[All] OR "i3"[All] OR "Aetna"[All] OR "Humana"[All] OR "Wellpoint"[All] OR "IMS"[All] OR "Intercontinental Marketing Services"[All] OR "IMS Health"[All] OR "Geisinger"[All] OR "GE Healthcare"[All] OR "MQIC"[All] OR "PHARMO"[All] OR "Institute for Drug Outcome Research"[All] OR "Pilgrim"[All] OR "Puget Sound"[All] OR "Regenstrief"[All] OR "Saskatchewan"[All] OR "Tayside"[All] OR "MEMO"[All] OR "Medicines Monitoring Unit"[All] OR "Veterans Affairs"[All] OR "Partners Healthcare"[All] OR "Mayo Clinic"[All] OR "Rochester Epidemiology"[All] OR "Indiana Health Information Exchange"[All] OR "Indiana Health"[All] OR "Intermountain"[All] OR "THIN"[All] OR "The health improvement network"[All] OR "blue cross"[All] OR "health partners"[All] OR "health plan"[All] OR "health services"[All] OR "Nationwide Inpatient Sample"[All] OR "National Inpatient Sample"[All] OR "medicaid"[All] OR "medicare"[All] OR "MediPlus"[All] OR "Outcome Assessment"[All] OR "insurance database"[All] OR "insurance databases"[All] OR "Data Warehouse"[All] OR "ICD-9"[All] OR "international statistical classification"[All] OR "international classification of diseases"[All] OR "ICD-10"[All] OR "Database Management Systems"[Mesh] OR "Medical Records Systems, Computerized"[Mesh] OR "CPT"[All] OR "Current procedural terminology"[All] OR "drug surveillance"[All] OR ("claims"[tw] AND "administrative"[tw]) OR ("data"[tw] AND "administrative"[tw]) OR "Databases, Factual"[Mesh] OR "Databases as topic"[Mesh] OR "Medical Record Linkage"[Mesh] OR "ICD-9-CM"[All Fields] OR "ICD-10-CM"[All Fields] Limits: Humans, English, Publication Date from	399576

	1990/01/01 to 2011/01/01	
#3	("Clinical Trial"[pt] OR "Editorial"[pt] OR "Letter"[pt] OR "Meta-Analysis"[pt] OR "Randomized Controlled Trial"[pt] OR "Clinical Trial, Phase I"[pt] OR "Clinical Trial, Phase II"[pt] OR "Clinical Trial, Phase III"[pt] OR "Clinical Trial, Phase IV"[pt] OR "Comment"[pt] OR "Controlled Clinical Trial"[pt] OR "case reports"[pt] OR "Clinical Trials as Topic"[Mesh] OR "double-blind"[All] OR "placebo-controlled"[All] OR "pilot study"[All] OR "pilot projects"[Mesh] OR "Review"[pt] OR "Prospective Studies"[Mesh]) Limits: Humans, English, Publication Date from 1990/01/01 to 2011/01/01	2729582
#4	#1 NOT #2 Limits: Humans, English, Publication Date from 1990/01/01 to 2011/01/01	1748136
#5	#4 NOT #3 Limits: Humans, English, Publication Date from 1990/01/01 to 2011/01/01	819148
#6	(TennCare [tiab]) OR (RAMQ [tiab]) OR (Cigna [tiab]) OR ((british columbia[tiab]) AND ((health[tiab]) OR (data[tiab]) OR (database[tiab]) OR (population[tiab]))) OR (CIHI [All Fields]) OR ((manitoba[tiab]) AND ((center for health policy[all fields]) OR (population[tiab]) OR (health insurance[tiab]))) OR ((ontario[tiab]) AND ((population[tiab]) OR (OHIP[tiab]) OR (registered persons database[tiab]) OR (health insurance [tiab]) OR (ICES[All Fields]) OR (Institute for Clinical Evaluative Sciences[All Fields]))) OR ((Alberta[tiab]) AND ((health[tiab]) OR (data[tiab]) OR (database[tiab]) OR (population[tiab]) OR (Alberta Health and Wellness[All Fields]))) Limits: Humans, English, Publication Date from 1990/01/01 to 2011/01/01	5128
#7	#5 AND #6 Limits: Humans, English, Publication Date from 1990/01/01 to 2011/01/01	1579
#8	Search #7 AND (("Arrhythmias, Cardiac"[Mesh:NoExp] OR "Brugada Syndrome"[Mesh:NoExp]) OR "Cardiac Complexes, Premature"[Mesh]) OR "Commotio Cordis"[Mesh:NoExp]) OR "Heart Block"[Mesh]) OR "Long QT Syndrome"[Mesh]) OR "Parasystole"[Mesh]) OR "Pre-Excitation Syndromes"[Mesh]) OR "Tachycardia"[Mesh]) OR "Ventricular Fibrillation"[Mesh]) OR "Ventricular Flutter"[Mesh]) OR "Death, Sudden, Cardiac"[Mesh]) OR "Torsades de Pointes"[Mesh]) OR "Heart Arrest"[Mesh]) OR "Tachycardia, Supraventricular"[Mesh]) Limits: Humans, English, Publication Date from 1990/01/01 to 2011/01/01	8

B. ABSTRACT REVIEWS

Of the 664 abstracts reviewed, 29 were selected for full-text review; 378 were excluded because they did not study cardiac arrhythmias, 219 were excluded because they were not administrative database studies, and 37 were excluded because the data source was not from the United States or Canada. One abstract was a duplicate entry (#250 and #253). Cohen's kappa for agreement between reviewers on inclusion vs exclusion of abstracts was 0.54.

C. FULL-TEXT REVIEWS

Of the 29 full-text articles reviewed, 7 were included in the final evidence tables; 7 were excluded because the HOI identification algorithm was poorly defined, and 15 were excluded because they included no validation of the outcome definition or reporting of validity statistics. Cohen's kappa for agreement between reviewers on inclusion vs exclusion of full-text articles reviewed was 1.0.

D. MINI-SENTINEL INVESTIGATOR SURVEY

Mini-Sentinel investigators provided no published and no unpublished reports of validation studies that had been completed by their teams.

E. EVIDENCE INCLUDED IN TABLE

Of the 9 studies included in the evidence table (Table 1), 7 were identified from the initial search strategy [6-12] and 2 were provided by the Mini-Sentinel HOI Project Coordinator [14, 15]. The purpose of all but three studies included in the evidence table was to evaluate a different hypothesis than the validation of the codes against medical records. The hypothesis most commonly evaluated was the development of cardiac arrhythmias after exposure to medications.

Administrative Databases Evaluated. Of the 9 studies, only one evaluated administrative claims from a national health insurance company [6]. Two evaluated private state/local health plans [7, 12], while the remaining evaluated Medicare and Medicaid databases.

F. SUMMARY AND DISCUSSION OF ALGORITHMS AND VALIDATION

Codes Used in Algorithms. Six of the 9 studies listed in the evidence table reported the algorithms of International Classification of Diseases (ICD-9) codes used to identify patients with cardiac arrhythmias; the remaining studies did not report the codes necessary for replication [10-12]. All of the reported codes were ICD-9 diagnosis codes. No ICD-9 procedure codes or diagnosis related group (DRG) codes were utilized in the algorithms.

In all studies that reported ICD-9 codes included in the evidence table, at least two ICD-9 codes were used for identification of ventricular arrhythmias. The most commonly used codes for ventricular arrhythmias were 426.xx and 427.xx.

No study compared ICD-10 diagnostic codes, ICD-9 procedure codes, or DRG codes with medical records for the validation of cardiac arrhythmias.

Validation Criteria and Method. All but one study [9] included in the table validated administrative coding data through abstraction of medical charts. Documentation of cardiac arrhythmias in the medical records was generally based on clinical encounters; only two studies based their definition solely on electrocardiographic diagnosis [6, 15]. Two studies relied on electrocardiographic validation of ventricular fibrillation/torsade de pointes codes and reported PPVs of 10% and 84% [6, 15].

Four studies validated administrative codes using clinical encounters (outpatient, inpatient, and emergency room documentation) and reported PPVs of 5%, 47%, 73% and 74%[7, 10, 11, 15]. One study linked a Medicare ventricular arrhythmia dataset with a detailed clinical registry and reported a sensitivity of 77% [9].

Validation Algorithms. One study [6] used all of the sub-codes within the ICD-9 code classification for 426 (conduction disorders) and 427 (cardiac dysrhythmias) and confirmed the diagnosis in only 14 out of the 146 cases identified (PPV 10%). Another study that used the individual ICD-9 codes within the 427.x code reported high PPV (89%-100%) [14].

One study used a limited and specific set of codes for ventricular arrhythmias (427.1, 427.4, 427.5) compared to a registry and found a sensitivity of 77% and specificity of 94% [9]. When an inclusive set of codes within the 427.xx and 798.x (sudden death, cause unknown) codes was used the PPV was 92% [8].

When an even more inclusive algorithm was used within the 426.xx, 427.xx, 780.x (general symptoms) and 785.xx (symptoms involving cardiovascular symptoms) codes, there was only confirmation of cardiac arrhythmia in five percent of the population (PPV 5%) [7].

Selected Patient Populations. Four studies included subjects who used medications (cisapride, metoclopramide and proton pump inhibitors) to determine if those subjects had a higher risk of developing cardiac arrhythmias [6-8, 12]. In those studies the purpose of the inclusion and exclusion criteria was to assure that subjects used the medication in question and did not use antiarrhytmics. Within this study population, a smaller sample of charts were reviewed when a cardiac arrhythmia occurred, permitting the reporting of only positive predictive value.

Three studies did not restrict the study sample to patients with specific diseases[9-11]. These studies included the entire health plan membership or all Medicare beneficiaries without other restrictions. The study samples were segmented into those with a claim for cardiac arrhythmias and those without, permitting the reporting of all diagnostic accuracy measures.

Age of Study Population. Most studies included only adult populations, with many studies including older patients (≥65 years). Studies that included younger patients were generally those that included the entire member populations of the health plans who were over a certain age (most commonly 15 years of age and older). Only one study [10] reported the effect that age had on the validity of arrhythmia claims when compared to medical records and found a lower PPV (8%) in subjects 75 years and older when compared to younger populations (23%).

Patient Sex. One study [10] reported the validity of ICD-9 claims by patient's sex and found higher PPVs in males (63%) when compared to females (37%).

Patient Race. Only one study reported on differences in the validity of claims for cardiac arrhythmias by race. The study [10] reported on the validity of ventricular arrhythmias and found that blacks had similar PPV (16%) when compared to whites (18%).

Time Period of Data Collection. This report includes populations studied between 1984 and 2004. Half of the studies report on study populations identified between 1985 and 1995. The reported validation statistics did not vary substantially in earlier study periods (i.e., prior to 1995) compared to later study periods (i.e., 1995 and later). However, two of the three studies [6, 7] prior to 1990 had the lowest reported PPV values.

Incident vs Prevalent Outcome Validation. Seven of the studies reported on the incidence of cardiac arrhythmias and three studies reported on the prevalence of cardiac arrhythmias. The studies reporting on incidence were cohort studies in which the purpose of the study was to evaluate whether medications increased the risk of cardiac arrhythmias. For studies reporting on the prevalence of cardiac arrhythmias, administrative claims databases were compared to medical records [9-11]. The validity statistics between incident and prevalent studies were similar.

Principal vs Secondary Diagnosis. Four studies [8, 9, 12, 15] reported on the performance of the ICD-9 codes in the principal position as a discharge diagnosis of cardiac arrhythmias or in any position. One study used Medicaid databases (CA, FL, NY, OH, PA) and reported a PPV for ICD-9 codes 427 and 798 of 92% when used in any position [8]. A study using the Medicare database reported that the sensitivity of ICD9 code 427 as a principal diagnosis was 77% [9]. Another Medicaid (CA, FL, NY, OH, PA) study validated ICD-9 codes as principal diagnoses using electrocardiographic criteria and reported PPVs of 92% for sudden death codes, 74% for ventricular arrhythmia codes, and 85% when either code was used [15]. A study using claims data for principal discharge diagnosis from Saskatchewan Health confirmed 27 cases among 199 chart reviews (PPV 14%) [12].

Hospitalization Diagnosis vs Outpatient Encounter. The studies included in this report examined hospitalizations, outpatient encounters, and emergency room visits to identify cardiac arrhythmias. Studies evaluating the validity of inpatients claims compared to medical records reported a PPV of 100% [14] and a sensitivity of 77% [9]. Several studies employed algorithms that included both inpatient and outpatient diagnoses; however, they did not directly compare one of these algorithms versus the other. Studies that used a combination of both inpatient and outpatient claims reported PPVs that ranged between 5-73% [7, 10].

G. SUMMARY OF EXCLUDED POPULATIONS AND DIAGNOSES

Four studies excluded populations who were not users of specific medications that could be related to cardiac arrhythmias [6-8, 12]. The most important exclusion of subjects was geographical since several studies that evaluated the Medicaid database only included specific states [10, 11, 14, 15]. Only three studies mentioned age restrictions for patients, however, the age of included patients ranged from 18 to 84 years old [6, 11, 14].

H. EVIDENCE TABLE

Table 1. Diagnostic Accuracy by Algorithm

Citation	Study Population and Time Period	Description of Outcome Studied	Algorithm	Validation/Adjudication Procedure and Operational Definition Validation Statistics
Enger et al. (2002) [6]	United Healthcare administrative claims database from 1993 to 1998. Study included those 28,078 subjects (60% female and 40% male) aged 65 and younger who used cisapride and not using antiarrhythmic drugs. Data was gathered from healthcare plans in Rhode Island, Massachusetts, North Carolina, Ohio, Michigan, Missouri, Georgia and Utah.	Composite primary outcome to identify incident serious arrhythmic event defined ventricular fibrillation, ventricular tachycardia, syncope, collapse or cardiac arrest.	426.xx 427.xx	Trained abstractors conducted medical record review and defined arrhythmias as electrocardiographic documentation of ventricular fibrillation or torsade de pointes. Arrhythmias occurring during the course of a myocardial infarction or surgical procedures were not counted as events. 146 cases of claims identified arrhythmias only 14 were confirmed as serious ventricular arrhythmias (PPV=10%).
Hanrahan et al. (1995) [7]	Harvard Community Health Plan in New England from 1988 to 1990. Study included those who had filled prescriptions for antihistamines in pharmacy files (N=26,320). Women represented 62% of population. 25% of cohort older than 40. 7% were 55 years or older.	The most severe outcome on a single day was used for analysis: Sudden death, torsades de pointes, complex ectopy, and hospitalization for ventricular arrhythmia, syncope, and simple ectopy.	426, 426.0, 426.1, 426.10, 426.11, 426.12, 426.13, 426.3, 426.4, 426.5, 426.50, 426.51, 426.52, 426.53, 426.54, 426.6, 426.7, 426.8, 426.81, 426.89, 426.9, 427, 427.1, 427.4, 427.41, 427.42, 427.5, 427.6, 427.60, 427.61, 427.69, 427.9, 429, 429.2, 429.9, 780, 780.2, 780.3, 780.4, 785, 785.0, 785.1,	All ambulatory, inpatient and emergency room encounters (clinical records and ECG's) were reviewed and evaluated by two physician investigators. A panel of four physicians blinded to the antihistamine exposure classified events. 61 cases of confirmed arrhythmias in the 1290 patients who were identified with events in the screening process (PPV=5%).

			785.5, 785.50, 785.51	
Hennessy et al. (2008) [8]	Medicaid programs of California, Florida, New York, Ohio and Pennsylvania from 1999-2000. Study included users of cisapride, metoclopramide and proton pump inhibitor users. 145 cases and 7,250 controls were identified. 58% of cases were female. Mean age: 63 years.	Cases: any hospitalization with a discharge diagnosis for ventricular arrhythmia or sudden cardiac death.	427.1 paroxysmal ventricular tachycardia 427.4 ventricular fibrillation and flutter 427.41 ventricular fibrillation 427.42 ventricular flutter 427.5 cardiac arrest 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	78% of the requested records were obtained. Operational definition was witnessed sudden collapse with the person found unconscious or dead, with evidence that the person had been alive in the preceding 24 hours, or evidenced cardiac arrest or ventricular arrhythmia. The validation definition was met in 118 of the 126 records: PPV 92% (95% CI 86-96).when the codes were used in any position. For hospitalizations with a diagnosis of interest 7/7 met the validation definition thus the PPV for the diagnosis of interest was 100% (95% CI 59-100) For outpatients with a diagnosis of interest the PPV was 19%
McDonald et al.(2002) [9]	Healthcare financing administration's Medicare Provider Analysis and Review (MEDPAR) inpatient hospitalization file from 1984 to 1995 of 4,073 patients aged 65 years and older with a principal discharge diagnosis of arrhythmia.	Hospital discharge with a principal discharge diagnosis of ventricular tachycardia or ventricular fibrillation/cardiac arrest.	427.1 paroxysmal ventricular tachycardia 427.4 ventricular fibrillation and flutter 427.5 cardiac arrest	The Medicare ventricular arrhythmia cohort was compared to the Seattle-area Myocardial Infarction and Triage Intervention (MITI) registry. Sensitivity 77% Specificity 94%
Ray et al.	Tennessee Medicaid	Probable sudden	Not Reported	Study nurses reviewed the records of all

(2001) [11]	enrollees between 1998-1993. Study included patients who were aged 15-84 years, were not in a long term facility and did not have life threatening illnesses. 54% were aged 15-44 years, 21% were 45-64 years, 25% were aged 65 years or older. Females made up 70% of the cohort. 59% of cohort was white.	cardiac death was defined as witnessed sudden collapse with no pulse or respiration, an unwitnessed collapse in a person known to be alive within the previous hour, ventricular fibrillation or tachycardia before the start of cardiopulmonary resuscitation, or autopsy findings consistent with a ventricular tachyarrhythmia.		medical care encounters including hospital/emergency room and medical examiner reports. A study physician masked with regard to medication use classified each reviewed death; questionable cases were reviewed by an electrophysiologist. 1487 deaths of which 701 were classified as probable sudden cardiac death (PPV 47%).
Staffa et al. (1998) [10]	Ohio Medicaid population from 1986 to 1992. Individual paid medical claims submitted for reimbursement under Medicaid. Examined any claim for either astemizole or sedating antihistamines (SA). There were 15.585 patients in astemizole group and 30,105 patients in SA group.	Ventricular arrhythmias (paroxysmal ventricular tachycardia, fibrillation and flutter) ad sudden cardiac death.	Not reported	18 cases were pulled for validation of cardiac arrhythmias among antihistamine users. For 11 of the cases medical records were obtained. Of these 11 cases 72% were females and 55% older than 50 years. Medical records were reviewed on all inpatient and outpatient claims that occurred between 90 days before and 60 days after the outcome reviewed by physician. Definite cases were confirmed by medical records or death certificates 8 out of 11 cases had a validated diagnosis of ventricular arrhythmia (PPV=73%).
Walker et al. (1998) [12]	Saskatchewan Health administrative claims from 1990 to 1995. Included subjects were beneficiaries who received cisapride	Arrhythmic events were defined as subjects with serious ventricular arrhythmia (ventricular fibrillation, sustained ventricular tachycardia and torsade de pointes). Records were screened with primary hospital discharge codes.	Not reported	Experienced abstractors were trained and sent to each hospital and physician practice in which events occurred to determine the characteristics and timing of events 27 cases of arrhythmic events were identified among 199 chart reviews (PPV=14%).

Chung et al. (2010) [14]	Tennessee Medicaid enrollees between 1988 and 1993 aged 18 to 84 years who had at least 365 days of enrollment and had no evidence of life threatening disease	Incident sudden death associated to ventricular arrhytmias	427.1 – paroxysmal ventricular tachycardia 427.4 – ventricular fibrillation and flutter 427.5 – cardiac arrest 427.9 – cardiac dysrhythmias, unspecified	Study nurses abstracted records of medical encounters around the time of death as well as autopsy reports. 926 cases were evaluated for confirmation of the codes. The reported PPV were 427.1 = 100% 427.4= 100% 427.5=78% 427.9= 89%
Hennessy et al. (2010) [15]	Medicaid programs in California, Florida, New York, Ohio, and Pennsylvania from 1999 to 2002.	Incident sudden cardiac death as principal/first listed diagnosis	Codes for ventricular arrhythmias: 427.1 – paroxysmal ventricular tachycardia 427.4 - ventricular fibrillation and flutter 427.41 - ventricular fibrillation and flutter 427.42 - ventricular flutter 427.5 cardiac arrest Codes for sudden death: 798 – sudden death, cause unknown 798.1 – Instantaneous death	Clinician diagnosed sudden death, cardiac or cardiorespiratory arrest or ventricular arrhythmias as evidenced in the medical record of inpatient and emergency department claims combined. When all criteria were used: verbatim statement of sudden death or ventricular arrhythmias, ECG confirmation, a person found unconscious. The reported PPV for principal diagnosis when compared to different medical record review strategies were: 85% when sudden death or ventricular arrhythmia was used 74% when ventricular arrhythmia was used 92% when sudden death was used When a verbatim statement was found of sudden death: 66% when sudden death or ventricular arrhythmia was used 16% when ventricular arrhythmia was used 97% when sudden death was used When a verbatim statement was found of ventricular arrhythmias:

			798.2 – Death occurring in less than 24 hours from onset of symptoms	59% when sudden death or ventricular arrhythmia was used 91% when ventricular arrhythmia was used 32% when sudden death was used <u>When a ECG diagnosis was used:</u> 48% when sudden death or ventricular arrhythmia was used 84% when ventricular arrhythmia was used 19% when sudden death was used

I. CLINICIAN OR TOPIC-EXPERT CONSULTATION

Use of ICD-9 codes 427.x (cardiac arrhythmias) and 798.x (sudden death) for identifying cardiac arrhythmia appear most appropriate based on this review.

The purpose of the majority of the studies was to test the hypothesis that specific medications increased the risk of cardiac arrhythmias. In those studies only a sample of ICD-9 codes were validated against a medical record and therefore only positive predictive values were reported.

In several studies, diagnostic accuracy statistics and ICD-9 algorithms were not provided and had to be calculated by the cardiac arrhythmia HOI investigators.

The distinction between criteria for validation is a fundamental issue that will need to be addressed. Specifically, it will be important to specify at the outset of a study which type of diagnosis is made. Electrocardiographic diagnosis is the gold standard of cardiac arrhythmias, but it is sometimes difficult to ascertain. Consequently, several studies relied on clinical records. Mixing of diagnosis modalities will have an impact on validation statistics.

Further study is warranted to determine how the use of procedure, pharmacy, and DRG codes as part of the algorithm will affect PPV. For example, how does the presence of a code indicating the use of an antiarrhythmic medication, completion of electrophysiological testing, or use of automatic implantable cardiac defibrillators impact the PPV if included in the algorithm? This may be particularly helpful for identifying at risk patients since no studies were done in heart failure patients who are at higher risk for developing arrhythmias.

VI. SUMMARY AND CONCLUSIONS

A. RECOMMENDATIONS FOR ALGORITHMS

The highest diagnostic accuracy statistics were seen when ICD-9 codes 427 and 798 were used. The use of specific subcodes of the 427 ICD-9 codes suggesting ventricular tachycardia or fibrillation yielded the

highest results when the codes were used independently. At the same time, the use of all specific codes and subcodes for ventricular arrhythmias and sudden death together as an algorithm yielded best results. When ICD-9 code 426 was added to the algorithm the reported PPV lowered when compared to algorithms that did not use the code, and therefore decreased the ability to identify patients with cardiac arrhythmias. The PPV differed by the location of the arrhythmic event. When the event occurred among inpatients the PPV was higher than when the event occurred among outpatients. The PPV was higher when the codes were used in any position as compared to the principal position.

B. SUGGESTIONS FOR FUTURE RESEARCH BASED ON EVIDENCE GAPS

The most important and obvious flaw in many of the studies was not reporting the specific ICD-9 codes that were utilized to identify cardiac arrhythmias. Many studies simply did not list the code or codes that were used. Another important gap was the minimal use of other data that is available in administrative files, such as pharmacy, procedure, and DRG codes. Also, there is a lack of evaluation of algorithms in high risk patients, particularly those with heart failure. In addition, very few validation studies have been conducted utilizing ICD-10 codes or in patients of different race/ethnicities in whom the criteria published to date may have varying sensitivities and specificities. Another important limitation is the lack of inclusion of subjects who have cardiac arrest in the field and do not survive the arrest and therefore do not have administrative claims.

VII. REFERENCES

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VIII. APPENDICES

A. APPENDIX A: ABSTRACTS OF STUDIES INCLUDED IN EVIDENCE TABLE

Enger C, Cali C, Walker AM. Serious ventricular arrhythmias among users of cisapride and other QT-prolonging agents in the United States. *Pharmacoepidemiol Drug Saf*. 2002; 11: 477-486.

PURPOSE: To evaluate the risk of serious ventricular arrhythmia (SVA) with cisapride use in the United States. METHODS: The study population included 28,078 patients under the age of 65 years who received cisapride between 1993 and 1998 with no history of antiarrhythmia treatment. Each follow-up day was classified according to use of cisapride and other factors. Outcomes of SVAs were identified using medical claims records and National Death Index search, and confirmed by medical record review. Rates of events were calculated for time on and off cisapride. Poisson regression analysis was used to calculate adjusted rate ratios. RESULTS: There were 23 cases of SVAs; 10 during periods of cisapride use and 13 during periods of non-use. The adjusted rate ratio comparing SVA events in cisapride use time to non-use time was 1.60 (95% CI: 0.67-3.82), and that identified for the other QT-prolonging drugs was 1.60 (95% CI: 0.65-3.98). CONCLUSIONS: The evidence for an increased risk of SVAs associated with cisapride was equivocal after taking observation time on and off cisapride into account, and adjusting for risk factors, though we cannot exclude the possibility of a 3.8-fold increased risk. Overall, the plausible risks of cisapride were similar to those of other QT-prolonging drugs.

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. *Ann Epidemiol*. 1995; 5: 201-209.

This study compared the occurrence of syncope, ventricular arrhythmias, and corrected QT interval (QTc) prolongation over a 2 1/2-year period in persons prescribed terfenadine versus other prescription antihistamines among 265,000 members of the Harvard Community Health Plan (HCHP), the largest staff-model health maintenance organization in New England. HCHP maintains an automated medical record system with coded diagnoses for each ambulatory and hospital visit, and a similar automated pharmacy system with information for each member on all prescriptions filled at its pharmacies. Among 0.86 million exposure days of terfenadine and 1.04 million exposure days of other antihistamines, we found no excess risk of either clinical/arrhythmia events (odds ratio (OR), 0.86; 95% confidence interval (CI), 0.52 to 1.44) or QTc prolongation (OR, 1.00; 95% CI, 0.64 to 1.57) during courses of terfenadine versus those of other antihistamines. Joint courses of antihistamines and oral erythromycin were associated with an increased risk of QTc prolongation (OR, 2.33; 95% CI, 1.31 to 4.15), and there was a trend for this to be observed more frequently with terfenadine (OR, 2.37; 95% CI, 0.73 to 7.51; P = 0.14).

Hennessy S, Leonard CE, Newcomb C, Kimmel SE, Bilker WB. Cisapride and ventricular arrhythmia. *Br J Clin Pharmacol*. 2008; 66: 375-385.

WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT Case reports have linked cisapride to ventricular arrhythmia and sudden cardiac death. However, two prior epidemiological studies have failed to show an association between cisapride and serious arrhythmia. WHAT THIS STUDY ADDS Overall, cisapride was associated with a doubling to tripling of the risk of hospitalization for sudden cardiac death and ventricular arrhythmia, and a near eightfold risk in the initial prescription period. Although potentially arrhythmogenic CYP3A4 inhibitors were associated with an increased risk in cisapride users, this appears to be due to a direct effect of the drugs themselves rather than an

interaction with cisapride. AIMS We aimed to examine the association between cisapride and ventricular arrhythmia, and examine the relationship to dose and CYP3A4 inhibitors. METHODS A nested case-control study was conducted in Medicaid beneficiaries exposed to cisapride, metoclopramide or a proton pump inhibitor (PPI) from 1999 to 2000. Cases were hospitalized with a principal International Classification of Diseases-9 code indicating sudden cardiac death or ventricular arrhythmia. Controls had at least as much event-free person time following the study prescription as its matched case. RESULTS A total of 145 cases and 7250 controls were identified. The unadjusted rate ratio for cisapride vs PPIs was 1.49 (95% confidence interval 0.96, 2.25). The adjusted odds ratio (OR) for cisapride vs PPIs was 2.10 (1.34, 3.28). Excluding persons in managed care, the adjusted OR for cisapride was 2.92 (1.55, 5.49). In the initial prescription period, the adjusted OR for cisapride vs PPIs was 7.85 (1.95, 31.60). Non-arrhythmogenic CYP3A4 inhibitors were not associated with an increased risk in users of cisapride or PPI inhibitors. The OR for potentially arrhythmogenic CYP3A4 inhibitors was 3.79 (1.76, 8.15) in cisapride users and 3.47 (2.06, 5.83) in PPI users. CONCLUSIONS Cisapride was associated with a doubling to tripling of the risk of hospitalization for ventricular arrhythmia, and a nearly eightfold risk in the initial prescription period. Although use of potentially arrhythmogenic CYP3A4 inhibitors was associated with an increased risk, this appears to be due to a direct effect of the drugs themselves rather than an interaction with cisapride.

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. *Am Heart J*. 2002; 144: 413-421.

BACKGROUND: Treatment options for patients with ventricular arrhythmias have undergone major changes in the last 2 decades. Trends in use of invasive procedures, clinical outcomes, and expenditures have not been well documented. METHODS: We used administrative databases of Medicare beneficiaries from 1985 to 1995 to identify patients hospitalized with ventricular arrhythmias. We created a longitudinal patient profile by linking the index admission with all earlier and subsequent admissions and with death records. RESULTS: Approximately 85,000 patients aged > or =65 years went to hospitals in the United States with ventricular arrhythmias each year, and about 20,000 lived to admission. From 1987 to 1995, the use of electrophysiology studies and implantable cardioverter defibrillators in patients who were hospitalized grew substantially, from 3% to 22% and from 1% to 13%, respectively. Hospital expenditures rose 8% per year, primarily because of the increased use of invasive procedures. Survival improved, particularly in the medium term, with 1-year survival rates increasing between 1987 and 1994 from 52.9% to 58.3%, or half a percentage point each year. CONCLUSION: Survival of patients who sustain a ventricular arrhythmia is poor, but improving. For patients who are admitted, more intensive treatment has been accompanied by increased hospital expenditures.

Ray WA, Meredith S, Thapa PB, Meador KG, Hall K, Murray KT. Antipsychotics and the risk of sudden cardiac death. *Arch Gen Psychiatry*. 2001; 58: 1161-1167.

BACKGROUND: Case reports link antipsychotic drugs with sudden cardiac deaths, which is consistent with dose-related electrophysiologic effects. Because this association has not been confirmed in controlled studies, we conducted a retrospective cohort study in Tennessee Medicaid enrollees, which included many antipsychotic users; there were also computer files describing medication use and comorbidity. The study was conducted before the introduction of risperidone and, thus, did not include the newer atypical agents. METHODS: The cohort included 481,744 persons with 1,282,996 person-years of follow-up. This included 26,749 person-years for current moderate-dose antipsychotic use (>100-mg thioridazine equivalents), 31,864 person-years for current low-dose

antipsychotic use, 37,881 person-years for use in the past year only, and 1 186,501 person-years for no use. The cohort had 1487 confirmed sudden cardiac deaths; from these, we calculated multivariate rate ratios adjusted for potential confounding factors. RESULTS: When current moderate-dose antipsychotic use was compared with nonuse, the multivariate rate ratio was 2.39 (95% confidence interval, 1.77-3.22; P<.001). This was greater than that for current low-dose (rate ratio, 1.30; 95% confidence interval, 0.98-1.72; P=.003) and former (rate ratio, 1.20; 95% confidence interval, 0.91-1.58; P<.001) use. Among cohort members with severe cardiovascular disease, current moderate-dose users had a 3.53-fold (95% confidence interval, 1.66-7.51) increased rate relative to comparable nonusers (P<.001), resulting in 367 additional deaths per 10,000 person-years of follow-up. CONCLUSIONS: Patients prescribed moderate doses of antipsychotics had large relative and absolute increases in the risk of sudden cardiac death. Although the study data cannot demonstrate causality, they suggest that the potential adverse cardiac effects of antipsychotics should be considered in clinical practice, particularly for patients with cardiovascular disease.

Staffa JA, Jones JK, Gable CB, Verspeelt JP, Amery WK. Risk of selected serious cardiac events among new users of antihistamines. *Clin Ther*. 1995; 17: 1062-1077.

This retrospective cohort study examined the risk of selected serious cardiac events in new users of either astemizole or sedating antihistamines identified from the COMPASS Ohio Medicaid population of approximately 1 million active lives per year (1986-1992). (COMPASS is an automated claims database.) There were 15,585 patients in the astemizole group and 30,105 in the sedating antihistamines group. Reports of ventricular arrhythmia or sudden death occurring within 30 days of the first antihistamine claim were identified from Medicaid claims. Medical records were obtained and reviewed by a clinician for validity of diagnoses. Records for patients without a full 30 days of follow-up were sought in the National Death Index. Death certificates were obtained for all patients who died within 30 days of the first antihistamine claim. Of 53 cases identified, 6 were in the astemizole group and 47 in the sedating antihistamines group. The relative risk for all selected cardiac events among astemizole users compared with sedating antihistamine users was 0.25 (95% confidence interval: 0.11 to 0.58), and this estimate did not change substantially when adjusted for age; sex; race; recent history of cardiovascular disease, arrhythmias, asthma/pulmonary disease, or malignant neoplasms; or concomitant prescription of other drugs. This study provided no evidence that astemizole users are at increased risk for cardiac events in the first month of use when compared with users of sedating antihistamines.

Walker AM, Szneke P, Weatherby LB, et al. The risk of serious cardiac arrhythmias among cisapride users in the United Kingdom and Canada. *Am J Med*. 1999; 107: 356-362.

PURPOSE: Serious, although rare, ventricular arrhythmias and deaths have been reported in patients taking cisapride monohydrate. Without quantification of the risk involved, it is impossible to develop rational therapeutic guidelines. SUBJECTS AND METHODS: Arrhythmic events (sudden deaths and other events compatible with serious ventricular arrhythmias) were sought among 36,743 patients prescribed cisapride in the United Kingdom and Saskatchewan, Canada. Prescriptions and cases were identified from computerized medical claims data and physicians' office records. We compared rates of events between periods of recent cisapride use and nonrecent use, using cohort analysis. Potential confounding factors, including concomitant treatment with agents that inhibit CYP3A4 metabolism or that prolong the QT interval, were assessed in a nested case-control study. RESULTS: In the cohort analysis, the incidence of the arrhythmic events was 1.6 times greater (95% confidence interval [CI]: 0.9 to 2.9) in periods of recent use. With adjustment for clinical history, use of CYP3A4 inhibitors, and use of drugs that prolong the QT interval, the odds ratio for cisapride and cardiac

outcomes was 1.0 (95% CI: 0.3 to 3.7). There was no identifiable increase in risk when cisapride was dispensed at about the same time as QT-prolonging drugs or CYP3A4 inhibitors. QT-prolonging agents were associated with a 2.5-fold increase in the risk of arrhythmic events (95% CI: 1.1 to 5.8). CONCLUSIONS: Serious rhythm disorders were not associated with cisapride use, although the upper confidence bounds do not rule out an increase in risk.

Chung CP, Murray KT, Stein CM, Hall K, Ray WA. A computer case definition for sudden cardiac death. *Pharmacoepidemiol Drug Saf*. 2010 Jun; 19(6): 563-72.

PURPOSE: To facilitate studies of medications and sudden cardiac death, we developed and validated a computer case definition for these deaths. The study of community dwelling Tennessee Medicaid enrollees 30-74 years of age utilized a linked database with Medicaid inpatient/outpatient files, state death certificate files, and a state 'all-payers' hospital discharge file. METHODS: The computerized case definition was developed from a retrospective cohort study of sudden cardiac deaths occurring between 1990 and 1993. Medical records for 926 potential cases had been adjudicated for this study to determine if they met the clinical definition for sudden cardiac death occurring in the community and were likely to be due to ventricular tachyarrhythmias. The computerized case definition included deaths with (1) no evidence of a terminal hospital admission/nursing home stay in any of the data sources; (2) an underlying cause of death code consistent with sudden cardiac death; and (3) no terminal procedures inconsistent with unresuscitated cardiac arrest. This definition was validated in an independent sample of 174 adjudicated deaths occurring between 1994 and 2005. RESULTS: The positive predictive value of the computer case definition was 86.0% in the development sample and 86.8% in the validation sample. The positive predictive value did not vary materially for deaths coded according to the ICO-9 (1994-1998, positive predictive value = 85.1%) or ICD-10 (1999-2005, 87.4%) systems. CONCLUSION: A computerized Medicaid database, linked with death certificate files and a state hospital discharge database can be used for a computer case definition of sudden cardiac death.

Hennessy S, Leonard CE, Freeman CP, Deo R, Newcomb C, Kimmel SE, Strom BL, Bilker WB. Validation of diagnostic codes for outpatient-originating sudden cardiac death and ventricular arrhythmia in Medicaid and Medicare claims data. *Pharmacoepidemiol Drug Saf*. 2010 Jun; 19(6): 555-62.

PURPOSE: Sudden cardiac death (SD) and ventricular arrhythmias (VAs) caused by medications have arisen as an important public health concern in recent years. The validity of diagnostic codes in identifying SD/VA events originating in the ambulatory setting is not well known. This study examined the positive predictive value (PPV) of hospitalization and emergency department encounter diagnoses in identifying SD/VA events originating in the outpatient setting. METHODS: We selected random samples of hospitalizations and emergency department claims with principal or first-listed discharge diagnosis codes indicative of SD/VA in individuals contributing at least 6 months of baseline time within 1999-2002 Medicaid and Medicare data from five large states. We then obtained and reviewed medical records corresponding to these events to serve as the reference standard. RESULTS: We identified 5239 inpatient and 29 135 emergency department events, randomly selected 100 of each, and obtained 119 medical records, 116 of which were for the requested courses of care. The PPVs for an outpatient-originating SD/VA precipitating hospitalization or emergency department treatment were 85.3% (95% confidence interval [CI] = 77.6-91.2) overall, 79.7% (95%CI = 68.3-88.4) for hospitalization claims, and 93.6% (95%CI = 82.5-98.7) for emergency department claims. CONCLUSIONS: First-listed SD/VA diagnostic codes identified in inpatient or emergency department encounters had very good agreement with clinical diagnoses and functioned well to identify outpatient-originating events. Researchers using such

codes can be confident of the PPV when conducting studies of SD/VA originating in the outpatient setting.

B. APPENDIX B: LIST OF CITATIONS SELECTED FOR FULL-TEXT REVIEW BUT NOT INCLUDED, BY REASONS FOR EXCLUSION

1. Studies Excluded Due to Poorly Defined Algorithms

1. Kupersmith J, Hogan A, Guerrero P, et al. Evaluating and improving the cost-effectiveness of the implantable cardioverter-defibrillator. *Am Heart J*. 1995; 130: 507-515.

2. Mann JK, Tager IB, Lurmann F, et al. Air pollution and hospital admissions for ischemic heart disease in persons with congestive heart failure or arrhythmia. *Environ Health Perspect*. 2002; 110: 1247-1252.

3. Movahed MR, Hashemzadeh M, Jamal M. Increased prevalence of ventricular fibrillation in patients with type 2 diabetes mellitus. *Heart Vessels*. 2007; 22: 251-253.

4. Rawson NS, Cox JL, Stang M, Rawson MJ. New use of antiarrhythmia drugs in Saskatchewan. *Can J Cardiol*. 2002; 18: 43-50.

5. Ray WA, Murray KT, Meredith S, Narasimhulu SS, Hall K, Stein CM. Oral erythromycin and the risk of sudden death from cardiac causes. *N Engl J Med*. 2004; 351: 1089-1096.

6. Suissa S, Hemmelgarn B, Blais L, Ernst P. Bronchodilators and acute cardiac death. *Am J Respir Crit Care Med*. 1996; 154: 1598-1602.

7. Wang PS, Levin R, Zhao SZ, Avorn J. Urinary antispasmodic use and the risks of ventricular arrhythmia and sudden death in older patients. *J Am Geriatr Soc*. 2002; 50: 117-124.

2. Studies Excluded Due to Lack of Validation or Reporting of Validation Statistics

1. Baine WB, Yu W, Weis KA. Trends and outcomes in the hospitalization of older Americans for cardiac conduction disorders or arrhythmias, 1991-1998. *J Am Geriatr Soc*. 2001; 49: 763-770.

2. Chavers BM, Li S, Collins AJ, Herzog CA. Cardiovascular disease in pediatric chronic dialysis patients. *Kidney Int*. 2002; 62: 648-653.

3. Go AS, Barron HV, Rundle AC, Ornato JP, Avins AL. Bundle-branch block and in-hospital mortality in acute myocardial infarction. National Registry of Myocardial Infarction 2 Investigators. *Ann Intern Med*. 1998; 129: 690-69.

4. Groeneveld PW, Heidenreich PA, Garber AM. Trends in implantable cardioverter-defibrillator racial disparity: The importance of geography. *J Am Coll Cardiol*. 2005; 45: 72-78.

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6. Ismailov RM, Ness RB, Redmond CK, Talbott EO, Weiss HB. Trauma associated with cardiac dysrhythmias: Results from a large matched case-control study. *J Trauma*. 2007; 62: 1186-1191.

7. Kuppermann M, Luce BR, McGovern B, Podrid PJ, Bigger JT, Jr, Ruskin JN. An analysis of the cost effectiveness of the implantable defibrillator. *Circulation*. 1990; 81: 91-100.

8. Li JM, Nguyen C, Joglar JA, Hamdan MH, Page RL. Frequency and outcome of arrhythmias complicating admission during pregnancy: Experience from a high-volume and ethnically-diverse obstetric service. *Clin Cardiol*. 2008; 31: 538-541.

9. Liperoti R, Gambassi G, Lapane KL, et al. Conventional and atypical antipsychotics and the risk of hospitalization for ventricular arrhythmias or cardiac arrest. *Arch Intern Med*. 2005; 165: 696-701.

10. Marill KA, Greenberg GM, Kay D, Nelson BK. Analysis of the treatment of spontaneous sustained stable ventricular tachycardia. *Acad Emerg Med*. 1997; 4: 1122-1128.

11. Murman DH, McDonald AJ, Pelletier AJ, Camargo CA, Jr. U.S. emergency department visits for supraventricular tachycardia, 1993-2003. *Acad Emerg Med*. 2007; 14: 578-581.

12. Musher DM, Rueda AM, Kaka AS, Mapara SM. The association between pneumococcal pneumonia and acute cardiac events. *Clin Infect Dis*. 2007; 45: 158-165.

13. Pratt CM, Hertz RP, Ellis BE, Crowell SP, et al. Risk of developing life-threatening ventricular arrhythmia associated with terfenadine in comparison with over-the-counter antihistamines, ibuprofen and clemastine. *Am J Cardiol*. 1994; 73: 346-352.

14. Ruskin JN, Camm AJ, Zipes DP, Hallstrom AP, McGrory-Usset ME. Implantable cardioverter defibrillator utilization based on discharge diagnoses from Medicare and managed care patients. *J Cardiovasc Electrophysiol*. 2002; 13: 38-43.

15. Weiss JP, Saynina O, McDonald KM, McClellan MB, Hlatky MA. Effectiveness and cost-effectiveness of implantable cardioverter defibrillators in the treatment of ventricular arrhythmias among Medicare beneficiaries. *Am J Med*. 2002; 112: 519-527.

C. APPENDIX C: LIST AND DEFINITIONS OF ICD OR PROCEDURAL CODES INCLUDED IN ALGORITHMS

Type of Code	Code	Description
ICD-9	426	Conduction Disorders
ICD-9	426.0	Atrioventricular block, complete
ICD-9	426.1	Atrioventricular block, other and unspecified
ICD-9	426.10	Atrioventricular block, unspecified
ICD-9	426.11	First degree atrioventricular block
ICD-9	426.12	Mobitz Type II atrioventricular block
ICD-9	426.13	Other second degree atrioventricular block
ICD-9	426.2	Left bundle branch hemiblock
ICD-9	426.3	Other left bundle branch block
ICD-9	426.4	Right bundle branch block
ICD-9	426.5	Bundle branch block, other and unspecified
ICD-9	426.50	Bundle branch block, unspecified
ICD-9	426.51	Right bundle branch block and left posterior fascicular block
ICD-9	426.52	Right bundle branch block and left anterior fascicular block
ICD-9	426.53	Other bilateral bundle branch block
ICD-9	426.54	Trifascicular block
ICD-9	426.6	Other heart block
ICD-9	426.7	Anomalous atrioventricular excitation

ICD-9	426.8	Other specified conduction disorders
ICD-9	426.81	Lown-Ganong-Levine Syndrome
ICD-9	426.89	Other
ICD-9	426.9	Conduction disorder unspecified
ICD-9	427	Cardiac dysrhythmias
ICD-9	427.0	Paroxysmal supraventricular tachycardia
ICD-9	427.1	Paroxysmal ventricular tachycardia
ICD-9	427.2	Paroxysmal tachycardia (unspecified)
ICD-9	427.3	Atrial fibrillation and flutter
ICD-9	427.31	Atrial fibrillation
ICD-9	427.32	Atrial flutter
ICD-9	427.4	Ventricular fibrillation and flutter
ICD-9	427.41	Ventricular fibrillation
ICD-9	427.42	Ventricular flutter
ICD-9	427.5	Cardiac arrest
ICD-9	427.6	Premature beats
ICD-9	427.60	Premature beats, unspecified
ICD-9	427.61	Supraventricular premature beats
ICD-9	427.69	Other
ICD-9	427.8	Other specified cardiac dysrhythmias

ICD-9	427.81	Sinoatrial node dysfunction
ICD-9	427.89	Other
ICD-9	427.9	Cardiac dysrhythmias, unspecified
ICD-9	429	Ill defined description of heart disease
ICD-9	429.2	Cardiovascular disease, unspecified
ICD-9	429.9	Heart disease unspecified
ICD-9	780	General symptoms
ICD-9	780.2	Syncope and collapse
ICD-9	780.3	Convulsions
ICD-9	780.4	Dizziness and giddiness
ICD-9	785	Symptoms involving cardiovascular systems
ICD-9	785.0	Tachycardia, unspecified
ICD-9	785.1	Palpitations
ICD-9	785.5	Shock without trauma
ICD-9	785.50	Shock, unspecified
ICD-9	785.51	Cardiogenic shock
ICD-9	798	Sudden death, cause unknown
ICD-9	798.1	Instantaneous death
ICD-9	798.2	Death occurring in less than 24 hours from onset of symptoms, not otherwise explained