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

ATRIAL FIBRILLATION REPORT

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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 health care 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

Atrial Fibrillation 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 to 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 atrial fibrillation (AF) algorithm review.

B. SUMMARY OF FINDINGS

The ICD-9 code for AF, 427.31, is the criterion most frequently used in algorithms to identify AF within administrative databases. All 16 studies that validated AF diagnoses incorporated an ICD-9 diagnosis code for 427.31 (either alone or as captured by the broader code 427.3) in their algorithms. The proportion of prevalent AF cases identified by an inpatient or outpatient code of 427.31 that was valid ranged from 56 to 100% (median 85%). No study specifically examined what was added by including the ICD-9 diagnosis code for atrial flutter, 427.32, but AF and atrial flutter are related arrhythmias and some patients have both these arrhythmias at different points in time. Studies incorporating ICD-9 codes 427.32 and the more general 427.3 (AF and atrial flutter) in addition to 427.31 had positive predictive values (PPVs) in line with studies using 427.31 alone. A substantial proportion of the variation in PPV across studies may be due to the choice of different criteria for confirming AF, with lower PPV reported by studies which used a more stringent criteria, i.e. requiring that the medical record contain an electrocardiogram (ECG) showing AF.

Seven studies examined the sensitivity of algorithms to identify AF within administrative databases and reported sensitivities ranging from 57 to 95% (median 79%).[1-7] The sensitivity of these algorithms may depend heavily on the specifications of the underlying database and in particular, how many ICD-9 codes are recorded for each encounter. Very few studies provided this kind of information about their database.

A few studies used algorithms that incorporated data from electronic ECG databases in addition to administrative claims data for case identification or validation.[6,8-10] These approaches offer promise but require further investigation, since few validation data are available.

Combining inpatient and outpatient AF diagnosis codes with AF diagnoses from an electronic ECG database appears to be an especially promising tool. However, no study has validated this approach using medical record review as the gold standard.

Identifying incident, rather than prevalent, AF is likely to be of primary interest for the Sentinel Initiative. There was very little information on the PPV of a first AF ICD-9 code for incident AF in patients with no prior ICD-9 code for AF. Only two studies specifically addressed this question; they reported PPVs of 62% and 77%.[7,11]

C. RECOMMENDATION FOR ALGORITHMS AND SUGGESTION FOR FUTURE RESEARCH

The results of this literature review suggest that overall, the ICD-9 code 427.31 (or, more broadly, 427.3) performs relatively well, but conclusions about the validity of specific algorithms are hindered by the lack of recent data and the fact that many studies focused on only the inpatient setting. It is likely that the best algorithm to identify incident AF – the condition of greatest interest for active surveillance—would draw on ICD-9 codes from both inpatient and outpatient encounters as well as electronic ECG data (where available) and would require a multi-year lead-in period (for example, 2 to 5 years) before the drug exposure of interest. The algorithm would require no ICD-9 codes for AF and no ECGs showing AF during the lead-in period, and incident AF after drug exposure would be defined by either an ICD-9 code or an ECG showing AF. No prior studies have examined the validity of such an algorithm to identify incident AF. Whether both an ICD-9 code and an ECG should be required needs further study. Other questions that merit further study include the number of encounters with an AF diagnosis that should be required and the length of the time window during which the encounters should be required to occur. These questions could be explored in a validation study set within an integrated health care system with electronic ECG data.

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 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 that had been identified in a textbook chapter reviewing the validity of drug and diagnosis data used in pharmacoepidemiologic studies,[12] 2) a list of designated medical events from a proposed FDA rule on the safety reporting requirements for human drug and biological products,[13] 3) the Observational Medical Outcomes Partnership (OMOP)[i] commissioned reports on algorithms used to identify the health outcome using administrative data .[14]

[i] For more information, visit the OMOP website.

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.

Atrial fibrillation (AF) was one of the 20 HOIs selected for review. This report describes the review process and findings for the AF 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)[15,16] 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 for documenting abstract review results.

The search strategy and results for AF are detailed in the Results section. The PubMed search was conducted initially on May 14, 2010 and again on July 6, 2010 with additional keywords, and the IDIS searches were conducted on June 11, 2010.

B. ABSTRACT REVIEW

1. Abstract Review Methods

AF team members initially reviewed a “training set” of 30 abstracts selected at random from among those identified by the search, applying the criteria below and comparing results. The goal was to increase consistency across reviewers. Next, the remaining abstracts were 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. 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. Inter-rater agreement on whether to include or exclude an abstract was calculated using a Cohen's kappa statistic. Results for the 30 abstracts used as the "training set" were excluded from this calculation.

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. All team members initially reviewed a "training set" of 10 articles, applying the criteria below, and compared results. The goal was to increase consistency across reviewers.

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 was consulted to make the final decision. Inter-rater agreement on whether to include or exclude a full-text article was calculated using a Cohen's kappa statistic, based on reviewers' initial determinations (prior to discussion with other reviewers). Results from the 10 articles comprising the "training set" were excluded from this calculation.

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 checked 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 with 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 tables summarize the search results obtained from PubMed and IDIS searches. The PubMed search identified 521 citations (Table 1), and the two IDIS searches identified 49 unique citations (Table 2). The total number of unique citations from the combined searches was 538. 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 7 citations (Table 3). One of those 7 was a duplicate, bringing the total number of unique abstracts to 544.

Table 1. PubMed Search Strategy and Results (521): Performed on 05/14/10

Search	Query	Results
#1	("atrial fibrillation"[All Fields]) OR "atrial fibrillation"[MeSH Terms] Limits: Humans, English, Publication Date from 1990/01/01 to 2010/06/01	19875
#2	("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 2010/06/01	1844870
#3	("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	395141

	("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 2010/06/01	
#4	("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 2010/06/01	2701937
#5	Search #10 and #11 and #12 Limits: Humans, English, Publication Date from 1990/01/01 to 2010/06/01	971
#6	Search #14 not #13 Limits: Humans, English, Publication Date from 1990/01/01 to 2010/06/01	521

Table 2. IDIS Search Strategy and Results (49 unique citations): Performed on 06/11/10

Search 1: 40 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 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"

AND NOT **Author**:

"(editorial)" or "(Letter to Ed)"

AND **Abstract**:

"atrial" and fib*

Years: 1990-2010

Records = 40

Search 2: 42 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**: 427.3 (note FIBRILLATION, ATRIAL 427.3)

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"

AND NOT **Author**:

"(editorial)" or "(Letter to Ed)"

Years: 1990-2010

Records = 42

Table 3. Search to Update the Original PubMed Search with Additional Database Names: Performed on 07/06/10, Results = 7

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 1990/01/01 to 2011/01/01	399576

#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 (("atrial fibrillation"[All Fields]) OR "atrial fibrillation"[MeSH Terms]) Limits: Humans, English, Publication Date from 1990/01/01 to 2011/01/01	7

B. ABSTRACT REVIEWS

Of the 544 abstracts identified, 249 were selected for full-text review. 21 were excluded because they did not study AF, 153 because they were not administrative database studies, and 65 because the data source was not from the United States or Canada. For an additional 56 articles, reviewers agreed that the study should be excluded but disagreed on the reason for exclusion. Cohen's kappa for agreement between reviewers on inclusion vs. exclusion of abstracts was 0.62 (95% confidence interval, 0.55 to 0.69).

C. FULL-TEXT REVIEWS

A total of 281 full text articles were reviewed, including 249 from the original search strategy and an additional 32 identified mainly from review of the references from articles located in the original search. Ultimately, 18 articles reporting 16 unique validation studies were cited in the evidence tables,[1,3-11,17-24] including 2 cited only in the footnotes (see below). Reviewers achieved consensus on all included full-text articles. Cohen's kappa for agreement between reviewers on inclusion vs. exclusion of articles before consensus discussions was 0.83 (95% confidence interval, 0.68 to 0.98).[ii]

[ii] In calculating this statistic, we did not include 10 articles that the whole team reviewed as a training set, nor the 32 additional citations identified mainly from references. This statistic was calculated by considering two cases where one abstractor was unsure whether to include the article as representing a discordant decision between abstractors. If we exclude those two cases, the kappa is 0.89 (95% confidence interval, 0.76 to 1.00).

Of the 249 articles from the original search selected for full-text review, 14 were included in the final evidence tables. 20 were excluded because the HOI identification algorithm was poorly defined and 65 because they included no validation of the outcome definition or reporting of validity statistics. Additional exclusions were made for the following reasons: not an administrative database study (48 articles); data source not from the U.S. or Canada (3 articles); and other (8 articles). For 91 articles, reviewers agreed that the study should be excluded but disagreed on the reason for exclusion.

Reviewers identified 32 additional citations for review. 30 of these were identified from the references of the articles from the original search. One article was identified serendipitously during article retrieval because of substantial overlap of authors and title between the additional article[25] and an article from the original search that had been selected for inclusion in the evidence table.[24] One article was identified by a peer reviewer of this report.[7] Of these 32, 4 were included in the final report. 3 were excluded because the HOI algorithm was poorly defined, and 4 were excluded because they included no validation of the outcome definition or reporting of validity statistics. Additionally, 5 articles were excluded because they did not study the HOI and 5 because they were not administrative database studies. For 11 articles, reviewers agreed that the study should be excluded but disagreed on the reason for exclusion.

D. MINI-SENTINEL INVESTIGATOR SURVEY

No information was provided by Mini-Sentinel investigators about published reports of validation studies. One member of the AF HOI review team provided additional information about an unpublished validation study, the validation statistics from which have been cited in published reports[11,19] but the methodologic details of which have not been published.

E. EVIDENCE INCLUDED IN TABLES

There are 18 published articles cited in the tables,[1,3-11,17-24] including 2 cited only in table footnotes (please see below). Of these 18, 14 were identified from the initial search strategy,[1,6,8-11,17-23] 3 from the references of articles that underwent full-text review,[3-5] and 1 from peer review of this report.[7] A member of the systematic review team for AF provided additional information about one unpublished validation study that was cited in 2 studies identified from the initial search.[11,19] In three cases, two or more published studies included the same validation data.[8-11,19-21] For these sets of references, the primary reference cited in the evidence table is either the article providing more detailed information or, if the studies were equivalent, the article published first. The other article citing the same validation study is included only in the footnotes to the evidence table. Thus, the number of published articles cited in the table is 18 (including 2 found only in footnotes), but the number of unique validation studies is only 16. The material below (Sections F and G) will refer to the total number of unique validation studies, rather than the number of published articles.

F. SUMMARY AND DISCUSSION OF ALGORITHMS AND VALIDATION

The methods and data sources used to identify AF from administrative data varied across studies. Ten studies used only inpatient data.[1,3,4,7,17,18,20,22-24] Six studies used outpatient data,[2,5,6,9-11] four of which also used inpatient data.[2,6,10,11] Three of the 16 studies incorporated information from electronic ECG databases for either case identification or validation.[6,9,10] Across the validation studies, the PPV of

algorithms to identify AF ranged from 56 to 100% (median 85%). The sensitivity of algorithms to detect AF was calculated in 7 studies[1-7] and ranged from 57 to 95% (median 79%).

Summary of Algorithms Using Only Inpatient Data. Studies using only inpatient data to identify AF differed according to which particular ICD-9 codes were used and what positions were searched. Of the 10 studies identifying AF solely from inpatient data (Table 4), 7 used an inpatient/discharge diagnosis of ICD-9 code 427.31 (atrial fibrillation) in any position to identify AF.[1,7,17,18,20,23,24] Of the 3 remaining studies, one required a hospital discharge ICD-9 diagnosis code of 427.31 in any position or 427.32 (atrial flutter) within the first three positions;[22] another required inpatient ICD-9 code 427.3, 427.31, or 427.32 in any position;[3] and the last required inpatient ICD-9 code 427.3 appearing in any one of five diagnosis fields.[4] In these studies using inpatient data, no attempt was made to categorize AF as prevalent or incident on the basis of ICD-9 diagnosis codes.

Algorithms Using Outpatient Data. Similar to studies using only inpatient data, studies utilizing outpatient data differed according to which ICD-9 codes were required (Table 5). However, none had any requirement for the position of those codes. Two studies used inpatient, outpatient, or emergency department ICD-9 diagnosis codes 427.31 or 427.32 in any position to identify prevalent[19] or incident[11] AF or atrial flutter. One study used inpatient, outpatient, or extended care ICD-9 diagnosis codes 427.3 or 427.31.[6] One study used one or more outpatient visits with ICD-9 diagnosis code 427.31.[5]

Two articles described algorithms for prevalent AF incorporating electronic ECG data in addition to inpatient and outpatient diagnosis codes, although they did not actually validate these algorithms.[9,10] One algorithm had the following requirements: (1) an outpatient ICD-9 diagnosis code of 427.31 and an electronic ECG showing AF, or (2) at least two outpatient diagnosis codes of 427.31.[9] The other algorithm required one of the following: (1) one or more outpatient ICD-9 diagnosis codes of 427.31 or (2) one or more ECGs in an electronic ECG database showing AF or (3) at least one principal hospital discharge diagnosis code of 427.31.[10]

Use of Four vs. Five Digit ICD-9 Codes. All of the studies that we reviewed except for two[4,5] explicitly incorporated ICD-9 diagnosis code 427.31 in their algorithm. Borzecki[5] and Yuan[4] both used ICD-9 diagnosis code 427.3 as their identification criterion, and no further details were provided about how that code was implemented or operationalized. Possible interpretations include the exact four-character string “427.3” or alternatively, anything beginning with “427.3” (i.e., 427.30, 427.31, 427.32, etc.). It may be that in some databases, only 4-digit ICD-9 codes were available, but this was not explicitly stated in any of the articles.

Validation Methods and Criteria. The approach used to validate AF also differed across studies. Most (14 of 16) validated the diagnosis of AF by medical record review. Four of these studies[3,7,17,18] had a cardiologist or other physician review ECGs found in the medical record, and two studies incorporated information from electronic ECG databases.[9,10] In one study,[6] the authors did not explicitly calculate sensitivity of their algorithm, but from the data presented we were able to calculate the sensitivity of their algorithm compared to the “gold standard” of their institution’s electronic ECG database. The remaining study[4] used as a “gold standard” the presence of ICD-9 diagnosis code 427.3 in discharge records from a teaching hospital database which contained up to 27 diagnosis fields (in contrast to the primary database of interest which contained only 5 diagnosis fields for each hospitalization).

Differences between Studies: Patient Population. While validation techniques were similar across many of the studies, the PPV of a test is highly influenced by the prevalence of the disease in the source

population. Many studies focused on older individuals (age 65 or older)[3,4,18,20,23,24] and/or high-risk populations (e.g., people with hypertension[5] or known cardiovascular disease,[1] who are at increased risk for developing AF.) As a result, the PPVs calculated in many of the studies may be higher than would be seen in a study of the general population. This may explain some of the variation in PPV across the different studies. For example, studies by Brass[18] and Flaker[20] were limited to Medicare patients 65 years and older. Patients with stroke were over-represented in the study by Brass. The resulting PPV observed by Brass (97.0%) was higher than the PPV observed by Flaker (90.2%), and was likely at least partly due to of Brass' use of a higher risk population.

Some differences between studies may be related to population differences in gender or race/ethnicity. Only one study reported validation statistics stratified by race/ethnicity.[7] Alonso , et al.[7] found that an algorithm for AF had sensitivity of 80% in African Americans and 85% in whites. Specificity was 99% in African Americans and 97% in whites. Confidence intervals for these estimates were not provided, and they were based on a modest number of subjects (n=161). No studies discussed whether validity statistics differed by gender. It is plausible that algorithm validity might differ by these characteristics, for several reasons. First, minorities may have more limited access to healthcare than whites. Second, there is potential for bias in clinical diagnosis of AF based on provider assumptions about disease prevalence and risk factors. Third, differences in the underlying prevalence of AF by race and/or gender may lead to differences in PPV for these subgroups.

Impact of Algorithm Requirements: Number of Codes; Time Window. In general, the use of more stringent requirements in the algorithm used to identify AF resulted in a lower sensitivity and a higher specificity. Borzecki[5] examined the impact of varying the number of AF codes required and the number of years of claims data used. Requiring at least one claims diagnosis for AF within one year correctly classified 80% of those with prevalent AF as having AF (sensitivity) and 99% of those without prevalent AF as not having AF (specificity). Increasing the requirement to at least two claims diagnoses for AF decreased the sensitivity to 67%, while the specificity remained at 99%. Extending the time period during which claims occurred from one to two years resulted in a sensitivity of 86% and a specificity of 97% when one or more claims diagnosis was required. Requiring at least two claims for AF within the same two-year period decreased the sensitivity to 74% and increased the specificity to 99%

Impact of More vs. Less Stringent Validation Criteria. A substantial amount of the variation in PPV across studies may be due to differing validation criteria. Some studies used very stringent criteria, requiring that an ECG or rhythm strip showing AF be found within the medical record. This would be expected to result in a lower PPV for the algorithm being examined. In contrast, other studies accepted any mention of AF in the chart as confirmation of the presence of AF. This more lax approach would be expected to result in a higher apparent PPV for the algorithm being examined. Two studies explicitly examined the impact of different validation criteria on algorithm validity. Brass[18] used as the looser criterion any documented history of AF within the medical record and as the more stringent criteria a documented history of AF along with dates and specific treatments for AF. The first criterion resulted in a PPV of 97.0%, in contrast to the stricter criteria which resulted in a PPV of 89.8%. Similarly, Flaker, et al.[20] reported that a more lax criterion based on any physician acknowledgement of AF yielded a PPV of 90.2%, while the more stringent criteria requiring an ECG or rhythm strip confirming AF yielded a PPV of only 70%.

Database Considerations: Number of Diagnosis Fields Retained. An additional consideration is that in some databases, limitations on the number of diagnosis codes recorded or retained may limit the ability

to identify AF from claims data. This will predominantly affect the sensitivity of algorithms. Compared to a database retaining a larger number of codes, databases retaining fewer codes will have lower sensitivity for AF. Different databases include a different maximum number of ICD-9 codes for each encounter (inpatient or outpatient), and the maximum number of codes likely has varied across time for individual databases. This characteristic of the source database was not explicitly discussed in the majority of studies. While seven of the sixteen studies we reviewed discuss which positions they searched for an AF ICD-9 code (e.g., primary only; first 3; etc.)[2,4,11,18,20,22,23] only one states how many fields were available in their database in their time period.[4] This study by Yuan, et al. examined the sensitivity of using hospital discharge records that are limited to five diagnosis fields as compared to more expansive records including up to 27 diagnosis fields. The study found that 87.7% of Medicare beneficiaries aged 65 years and older with an inpatient ICD-9 code for 427.3 in any of 27 diagnosis fields also had that code included among their first five diagnosis fields. The inability of the more limited database to capture 12% of patients with AF (for whom AF was not included among the top 5 diagnosis codes) is one indication of the potential for diminished sensitivity in databases that limit the number of diagnosis codes recorded.

G. SUMMARY OF EXCLUDED POPULATIONS AND DIAGNOSES

In the one study examining incident (newly-diagnosed) AF, patients with a past history of AF were excluded.[11] In other studies, patients were often excluded on the basis of the specific study question: Flaker[20] excluded patients with rheumatic heart disease or a recent history of a cardiothoracic procedure; Hravnak[1] excluded people who had not undergone CABG; Whittle[24] excluded patients who had undergone open heart surgery; and Yuan[4] excluded patients who had suffered a stroke, venous thrombosis, or cancer in the prior year. The highly specialized population included in the study by Hravnak, et al.[1] (patients undergoing CABG) makes this study much less relevant for the purposes of active drug safety surveillance because of limited generalizability. In contrast, the exclusion of patients with rheumatic heart disease (e.g., Flaker[20]) may be beneficial for projects such as the Sentinel Initiative which aim to conduct active surveillance for medication-related AF, in that it excludes patients at particularly high risk of developing AF in whom AF is more likely to be due to pre-existing structural heart disease rather than medication exposure. A similar argument can be made for excluding patients with a recent cardiac surgery or procedure or acute coronary syndrome.

H. EVIDENCE TABLES

Table 4. Articles That Identified Atrial Fibrillation from Only Inpatient Data

Abbreviations: AF, atrial fibrillation; CABG, coronary artery bypass grafting; ECG, electrocardiogram; ICD, International Classification of Diseases; PPV, positive predictive value; SN, sensitivity; SP, specificity.

Citation	Study Population and Time Period	Description of Outcome(s) Studied	Algorithm*	Validation/Adjudication Procedure and Operational Definition	Validation Statistics
Alonso (2009)[7]	1987-2004 Atherosclerosis Risk in Communities cohort study, set in 4 U.S. communities (in Minnesota, Maryland,	Prevalent and incident AF	Hospital discharge ICD-9 code of 427.31	1. Physician review of hospital discharge summaries and inpatient ECGs 2. Medical record review for presence of AF during or 4 weeks before the	1. PPV 89% (111/125) for any AF PPV 62% (78/125) for incident AF 2. SN 84%

	Mississippi and North Carolina). Age 45-65 in 1987-9; excluded if baseline ECG showed AF. Substudy 1: participants with a first inpatient ICD-9 code for AF. Substudy 2: Suspected stroke cases. Overall population was 55% women and 27% African American.			hospitalization	(135/161); 80% in African Americans and 85% in whites SP 98% (1351/1385) for prevalent AF; 99% in African Americans and 97% in whites
Antani (1996)[17]	4/1992 – 5/1992 Inpatients discharged from 2 teaching hospitals in Cleveland, OH. Inpatient AF cases included in the study (after further selection criteria) were 56% male, and 86% white, with 14% aged <65 years, 33% 65-74 years, and 54% >=75 years.	Prevalent AF	Hospital discharge ICD-9 code of 427.31	Medical record review including review of ECGs	178/196 (90.8%) had confirmed prevalent AF (PPV)
Brass (1997)[18]	1/1/1994 – 6/30/1994 Medicare patients aged ≥ 65 years who were discharged from nongovernmental, acute care hospitals in Connecticut. Limited to patients without a principal diagnosis of acute myocardial infarction or non-stroke embolic event. Patients with a primary diagnosis of ischemic stroke were matched 1:1 to patients without such a diagnosis (matched on age, sex, and selected secondary diagnoses.) AF cases included in the study (after further selection criteria) were 37% male and 94%	Prevalent AF	Hospital discharge ICD-9 code of 427.31 in primary or secondary position.	Trained abstractors reviewed medical records seeking ECGs with official interpretation of AF. If none was found, a cardiologist reviewed the record including ECGs and ECG rhythm strips. “Detailed” history of AF was defined as present when notes included dates of AF or specific treatments for AF. History defined as “vague” if no clinical details were provided other than “history of AF.”	686/707 (97.0%) had a documented history of AF or ECG showing AF (PPV) 635/707 (89.8%) had a “detailed” history of AF or ECG showing AF (more strict PPV)

	white, with 18% aged 65-74 years, 46% 75-84 years, and 35% ≥ 85 years.				
Flaker (1999)†[20]	10/1/1993 – 12/31/1994 Missouri Medicare patients aged ≥ 65 years who were hospitalized and did not have rheumatic heart disease or a recent cardiothoracic procedure and who didn't leave against medical advice or die during the admission and who were not transferred to another acute-care facility. Slight oversampling of smaller hospitals. AF cases included in the study (after further selection criteria) were 45% male and 97% white, with a mean age of 80 years.	Prevalent AF	Inpatient principal or secondary diagnosis of ICD-9 427.31	Medical record review. Looser criterion: physician acknowledgement of AF in the progress notes or discharge summary. Stricter criterion: AF confirmed by ECG or rhythm strip.	1035/1147 (90.2%) had physician acknowledgment of AF (PPV) 800/1147 (70%) had physician-confirmed AF on ECG or rhythm strip (stricter PPV)
Hravnak (2001)[1]	5/1/1996 – 5/31/1998 Inpatients > 18 years old undergoing CABG at one university-affiliated medical center in Pennsylvania. Excluded if prior history of AF, underwent other cardiac surgery, history of prior cardiac surgery, perioperative or postoperative myocardial infarction, or died in the operating room or within 12 hours of surgery. AF cases included in the study (after further selection criteria) were 68% male and 96% white, with a mean age of 65 years.	Incident post-operative (post-CABG) AF	Inpatient ICD-9 code 427.31	Additional patients with incident AF were identified from 2 sources: 1. A word search for atrial fibrillation (including word variations) run on the clinical database 2. Pharmacy data indicating procainamide administration For all 3 groups, discharge summaries (and if needed, complete medical records) were reviewed to verify AF and determine whether it was a new condition (that is, incident).	148/260 (56.9%) of those with confirmed incident AF had an inpatient ICD-9 code for AF (Sensitivity)
Psaty (1997)[3]	6/1989 – 4/1996 Cardiovascular Health	Prevalent AF or atrial flutter	Inpatient ICD-9 code	Validation study: A physician reviewed all ECGs found in	29/41 (70.7%) patients with ECG-

	Study: a random sample of Medicare-eligible adults in 4 geographic areas. All eligible adults in household could participate. Eligibility: age ≥ 65 years old), not institutionalized, and did not require a proxy respondent. Excluded if had a pacemaker or AF at baseline. The CHS population at risk for AF in this study (after further selection criteria) had a mean age of 73 years and was 42% male and 5% black. Validation study: 76 patients with potential cerebrovascular event in 9/1992 and 238 with potential cardiovascular event in 4/1996.‡		of 427.3, 427.31, 427.32	the hospital records and identified 41 patients with ECG-documented AF or atrial flutter.	documented AF or atrial flutter had a hospital discharge code for AF or atrial flutter (Sensitivity)
Shen (2008)[22]	1/1/1995 – 12/31/2000 Adult members of Kaiser Permanente Southern California who were hospitalized; 100 randomly selected inpatients with an ICD-9 code for AF were studied. The population with AF was 56.9% male, with mean age of 72, and 77.5% had hypertension. 78.5% were white, 8.1% African-American, 9.5% Hispanic, and 3.9% Asian.	Prevalent AF or atrial flutter	Hospital discharge diagnosis codes; ICD-9 code 427.31 in any position or 427.32 among the first three codes	Review of medical records (including ECGs)	PPV 96%
Shireman (2004)[23]	4/1/1998 - 3/31/1999 Inpatient, fee-for-service Medicare beneficiaries discharged from acute-care hospitals; 750 with primary or secondary diagnosis of AF were randomly sampled	Prevalent AF	Inpatient ICD-9 427.31 as principal or secondary diagnosis code.	Confirmed AF through review of inpatient records for the index AF hospitalization.	27,674/38,924 (71.1%) confirmed on chart review (PPV)

	from each US state or territory. AF cases included in the study (after further selection criteria) had a mean age of 77 years and were 50% male.				
Whittle (1997)[24]	7/1/1993 – 6/30/1994 Hospitalized Medicare beneficiaries aged ≥ 65 years who had not undergone open heart surgery and were discharged from 5 small Pennsylvania hospitals. This population was 60% female with a mean age of 80 years.	AF present during hospitalization	Discharge diagnosis code of ICD-9 427.31	Initial medical record review by a nurse to confirm diagnosis of AF. 10% were then randomly selected for review by a 3-person team, including a registered nurse, a licensed practical nurse, and a data management specialist. The 3-person team then conferred on areas of disagreement with the study physician.	PPV 85% 274/322 (85%) experienced AF during hospitalization (PPV)
Yuan (1998)[4]	1985 Medicare beneficiaries aged ≥ 65 years hospitalized at a teaching hospital in Cleveland, OH. Exclusions: stroke or venous thrombosis in the prior year; cancer; race unknown or "other." AF cases included in the study (after further selection criteria) had a mean age of 78 years and were 43% male and 5% black.	Prevalent AF	Inpatient ICD-9 427.3 appearing in any one of five diagnosis fields	Hospital discharge records containing up to 27 diagnosis fields from a teaching hospital were considered the gold standard.	SN 87.7%, SP 100.0%, PPV 100%, NPV 98.6% 279/318 (87.7%) identified from hospital discharge file were also identified from Medicare claims data (sensitivity) 2773/2773 (100%) without AF from hospital discharge file also did not indicate AF from Medicare claims data (specificity)

*Unless otherwise specified, the position of ICD-9 codes was not described in the article.
†A second study, Gage (2000),[21] used the same data and presented the same validation statistics as Flaker(1999).[20]
‡Psaty, et al. also conducted a study of people who appeared to have had incident AF during follow-up based on hospital discharge diagnoses. Based on review of medical records, 98.6% (209/212) truly had AF. This is not actually the PPV for incident (vs. prevalent) AF because people who on review were found to have had AF pre-dating study entry were excluded (removed from both numerator and denominator). Information was not presented about the PPV for incident AF, specifically.

Table 5. Articles That Identified AF from Outpatient Data (Including Some Which Also Used Inpatient Data)

Abbreviations: AF, atrial fibrillation; ECG, electrocardiogram; HMO, health maintenance organization; ICD, International Classification of Diseases; PPV, positive predictive value; SN, sensitivity; SP, specificity; VA, Veterans Administration.

Citation	Study Population and Time Period	Description of Outcome Studied	Algorithm*	Validation/Adjudication Procedure and Operational Definition	Validation Statistics
Borzecki (2004)[5]	1998 – 1999 Outpatients from 10 VA sites across the country. "Regular" VA users (≥ 2 clinic visits at least 6 months apart in 1999). 100 users with a claims diagnosis of hypertension and 20 without were randomly selected from each site. No data were provided about age, sex or race of the population.	Prevalent AF	Outpatient ICD-9 diagnosis code of 427.3: ≥1 code in 1 year Examined impact of varying # of codes required and # of years of claims data used.	Medical record review of outpatient chart for all clinic visits in 1999. AF defined as present if mentioned at least once in notes during that year. Rule-out diagnoses were ignored.	≥1 claims diagnosis in 1 yr: SN 80%, SP 99%, PPV 84% ≥2 claims diagnoses in 1 yr: SN 67%, SP 99% ≥1 diagnosis in 2 yrs: SN 86%, SP 97% ≥2 diagnoses in 2 yrs: SN 74%, SP 99%
Brophy (2004)[6]	1/1/1997 – 5/1/2001 All users of the VA Boston Healthcare System (VABHCS) with ECG-documented AF in their electronic ECG database between 1/1/1998 and 5/1/2001, and ≥ 1 documented healthcare encounter at VABHCS between 1/1/1997 and 5/1/2001. In the final study population, 53% were < 75 years old.	Prevalent AF	ICD-9 427.3, 427.31	An ECG in the Marquette Universal Storage for Electrocardiograms (MUSE) database showing AF was taken as the gold standard for calculating sensitivity.	2619/3366 (77.8%) had ICD-9 code for AF (sensitivity)
Dublin 2006[19]	1989 – 1998 HMO members (Group Health, in Washington State); controls in a study, frequency-matched to myocardial infarction cases on age, sex and presence of hypertension. The mean age in the population from which controls were drawn was 69 years.	Prevalent AF or atrial flutter	ICD-9 codes 427.31 or 427.32 in any position from an inpatient, outpatient, or ED encounter	Medical record review	236/248 (95%) of confirmed AF patients had ICD-9 code for AF (sensitivity) 244/247 (99%) of subjects confirmed not to have AF did not have ICD-9 code for AF (specificity)

Glazer (2007)[11]	10/1/2001 – 9/30/2002 HMO members (Group Health, in Washington State) without a previous ICD-9 diagnosis of AF at GH before 10/1/2001. AF cases included in the study (after further selection criteria) were 46% female and 91% white and had a mean age of 69 years.	Incident AF or atrial flutter	ICD-9 427.31 or 427.32 in any position from an inpatient, outpatient or ED encounter and no prior ICD-9 code for AF during their GHC enrollment	Medical record review	333/1438 had prior history of AF according to medical record. Thus, PPV for incident AF = 1105/1438 = 76.8%
Go (2000)[9]†	7/1/1996 – 12/31/1997 HMO members (Kaiser Permanente) in Northern California. AF cases included in the study (after further selection criteria) had a mean age of 72 years and were 57% male.	Prevalent AF	Validation study: > 1 outpatient code of 427.31 but no electronic ECG showing AF Main study: ≥1 outpatient 427.31 and an electronic ECG showing AF; or > 1 outpatient 427.31	ECG showing AF in medical record Algorithm for main study not validated	PPV 78% (39/50)
Go (2001)[10]	7/1/1996 – 12/31/1997 HMO members (Kaiser Permanente) in Northern California aged ≥ 20 years. AF cases included in the study (after further selection criteria) were 57% male and 85% white and had a mean age of 71 years.	Prevalent AF	Validation study: 1 outpatient 427.31 but no electronic ECG showing AF Main study: ≥ 1 outpatient 427.31, inpatient primary 427.31 or ≥ 1 electronic ECG showing AF	ECG showing AF in medical record Algorithm for main study not validated	PPV 56% (28/50)

*Unless otherwise specified, the position of ICD-9 codes was not described in the article.
†A second study, Go (1999),[8] was performed on the same data and presented the same validation statistics as Go(2000).[9]

I. CLINICIAN OR TOPIC-EXPERT CONSULTATION

Algorithms: Choice of ICD-9 Codes. The ICD-9 codes used in the validation studies described above are appropriate. No relevant codes have been omitted. The decision about whether to include atrial flutter (ICD-9 code 427.32) is discussed below.

Validation: Choice of a "Gold Standard". In clinical practice, the "gold standard" for diagnosing AF is the 12-lead ECG. This is a well-established and non-invasive technology that has been available for many years. It has not been supplanted by newer technologies or diagnostic approaches, although certainly there are some newer technologies that could provide relevant information about the presence of AF (e.g., event monitors, catheter-based electrophysiologic studies, or pacemakers which record information about heart rhythm.) However, few of the validation studies described above required the

presence of an ECG showing AF as part of their "gold standard." Instead, most studies considered AF to be confirmed if there was any mention of AF in the medical record. For the identification of prevalent AF, the use of this looser "gold standard" has both pros and cons. It will (appropriately) identify a substantial number of people with paroxysmal AF or a remote history of AF who would be (incorrectly) considered as free of AF if ECGs alone were used to define the gold standard. On the other hand, relying on any mention of AF in the chart could lead to misclassification, as some patients reported to have AF, particularly a history of AF, may not truly have such a history. In contrast, if the clinical entity of interest is incident AF, then it may be more reasonable to compare algorithms against the more stringent gold standard (which requires a positive ECG), because in actual clinical practice, people with newly detected (incident) AF are more likely to undergo ECG than people with longstanding chronic AF or with AF that is believed to have resolved. It seems plausible that the use of a more lax "gold standard" will result in a higher PPV than a more stringent "gold standard," and indeed this is confirmed by the studies discussed above. On the other hand, the more lax "gold standard" probably will result in claims algorithms appearing to have lower sensitivity than they would if compared to a more stringent "gold standard."

Clinically, it is not uncommon for AF to be detected on a rhythm strip during a hospitalization and not to be captured by ECG. If the goal of active surveillance is to identify any occurrence of AF (even if it is transient or does not result in clinically important symptoms), then using a "gold standard" that excludes AF identified only from a rhythm strip may not be appropriate. It is difficult to tell how this aspect of the gold standard would affect results obtained for the validity of different algorithms. If AF that is captured only on the rhythm strip (but not an ECG) ultimately leads to a patient being assigned an AF ICD-9 code at discharge, then the use of the more stringent "gold standard" of a confirmatory ECG could result in worse apparent specificity and PPV of the algorithm. On the other hand, if AF that is captured only on a rhythm strip is not considered clinically significant enough to be documented among discharge diagnoses, then the apparent sensitivity of claims-data algorithms will be lower when compared to a looser gold standard that includes AF identified solely on a rhythm strip (which is less accurate than a 12-lead ECG for confirming the diagnosis of AF.)

Inpatient vs. Outpatient Diagnoses. No validation studies compared the validity of algorithms using only outpatient or only inpatient diagnosis codes to algorithms using both. Some patients with AF may be diagnosed in the outpatient setting and this condition may not be captured in any inpatient data (e.g., if AF is detected during an outpatient visit, and the patient is not hospitalized for another reason during the time window of the study). For other patients, documentation of AF may occur only in the inpatient setting (for instance, if AF was present only during hospitalization and this information was not communicated to the physicians who care for the patient in the outpatient setting). Thus, the sensitivity of using only outpatient codes or only inpatient codes may be lower than approaches which make use of both types of data. This type of misclassification may not significantly reduce the power of active surveillance studies to identify a true safety signal if one is present, but it may limit the ability to generalize beyond the outpatient or inpatient setting.

Incident vs. Prevalent AF. There were few studies that evaluated algorithms for identifying incident, rather than prevalent, AF. Similarly, in the clinical setting it can be difficult to determine whether AF is new or pre-existing. This may be particularly difficult for patients whose AF is recognized at the time of a hospitalization. If a patient has not been hospitalized at the same hospital previously and does not recall whether s/he has had AF in the past, the treating physician will likely be unable to distinguish new from prevalent AF. This means that, in general, it would be desirable to conduct validation studies in settings where there is access to outpatient records, particularly primary care records, and ideally where there is

long-term follow-up of patients. Review of inpatient records alone will provide limited ability to accurately distinguish incident from prevalent AF when defining the gold standard, as will review of records for patients who have only recently begun to receive care within a given health care system or health plan. Thus, settings with considerable patient turnover will be less useful for evaluating the validity of algorithms if a primary goal is to identify incident, rather than prevalent, AF.

Inclusion of Atrial Flutter. Only four of the studies included in the evidence table explicitly included atrial flutter (ICD-9 code 427.32).[2,3,11,22] Three additional studies[4-6] most likely included some cases of atrial flutter because they used a four-digit ICD-9 code, 427.3. It is somewhat surprising that the remaining 8 studies chose not to include people with atrial flutter in their population of interest because AF and atrial flutter share many features.[26] The risk factors are similar and both arrhythmias occur in similar patient populations, often occurring within the same individual. Atrial flutter is often preceded or followed by AF. The potential complications and clinical management of atrial flutter and AF are also very similar. Key themes in management include rate control and prevention of systemic emboli. Although it is usually not difficult to distinguish the two arrhythmias at a single point in time, because AF results in an irregular ventricular response while atrial flutter usually results in a regular one, physician documentation and encounter coding may not distinguish atrial flutter from AF when both arrhythmias have been present. Thus, it may not be possible to distinguish atrial flutter from AF consistently using administrative data, except in cases where isolated atrial flutter is present.

VI. SUMMARY AND CONCLUSIONS

A. RECOMMENDATIONS FOR ALGORITHMS

Across a broad range of administrative data sets, an inpatient or outpatient ICD-9 diagnosis code of 427.31 was valid (that is, identified prevalent AF) in 56% to 100% (median 85%) of patients. No study specifically examined what was added by including 427.32 (atrial flutter), but AF and atrial flutter are related arrhythmias and some patients have both these arrhythmias at different points in time. Because of the substantial overlap between these conditions, their similar clinical implications, and the difficulty in distinguishing the two arrhythmias using administrative data, we recommend that the final algorithm include both AF and atrial flutter.

Combining inpatient and outpatient AF diagnosis codes with AF diagnoses from an electronic ECG database appears to be an especially promising tool for identifying prevalent AF. However, no study has validated this approach using medical record review as the gold standard.

Identifying incident AF, rather than prevalent AF, may be of primary interest for active drug safety surveillance. There was very little information on the positive predictive value of a first AF ICD-9 code for incident AF in patients with no prior AF ICD-9 code.

B. SUGGESTIONS FOR FUTURE RESEARCH BASED ON EVIDENCE GAPS

As previously discussed, there are many limitations that must be considered when comparing the validation statistics from different studies. Each of the studies presented in this report examined AF in a different source population, each with its own distribution of age, cardiovascular risk factors, and other factors that influence the prevalence of AF and thus the PPV of an algorithm identifying AF. Unfortunately, most studies provided limited information about the characteristics of the source

population from which AF cases were ascertained. This makes it difficult to assess to what degree differences in validation results were due to differences in the underlying source populations. Additionally, the use of different gold standards for AF between studies inhibits our ability to directly compare the sensitivity, specificity, and PPV of algorithms identifying AF from administrative claims data.

While many studies focused on identifying prevalent AF, very few examined the validity of algorithms to identify incident AF using administrative data. The purpose of active drug safety surveillance, as in the Sentinel Initiative, will presumably be to identify incident cases of AF occurring after medication exposure. More research is needed to determine the optimal algorithms for identifying incident AF from administrative data, with or without electronic ECG data, and to measure their validity in the population of interest.

Most of the studies addressing the validity of algorithms identifying AF using administrative data were done using data from 10 to 15 years ago. Only 3 studies used data from less than 10 years ago.[6,7,11] This is particularly relevant because the prevalence of AF has increased considerably over the past two decades. Thus, studies using data from 10 to 15 years ago may not accurately predict the validity of these algorithms if applied to more recent data. We would anticipate that overall, the PPV of these algorithms may be higher in the current era, as the prevalence of AF in the underlying population is higher now than it was in the past, and PPV increases as the prevalence of the condition in the source population goes up. In addition, the number of codes per encounter retained in electronic databases has generally increased over time. Thus, the sensitivity of algorithms may be higher in contemporary data than our results suggest.

Many health plans will shift from using ICD-9 codes to ICD-10 codes in the near future. None of the studies included in our evidence tables examined the validity of algorithms using ICD-10 codes to identify AF from administrative data. There was one study which was not included which examined both ICD-9 and ICD-10 codes.[27] It did not provide adequate detail about the algorithms used and so it cannot provide specific algorithms for consideration. Further, their results regarding algorithm validity are difficult to interpret. It may be useful to conduct additional validation studies once ICD-10 codes are in widespread use to determine the validity of algorithm(s) being used for surveillance of adverse drug effects and to optimize their validity in the new coding environment. However, we expect that algorithm validity may be similar in that setting because the general approach to categorizing these arrhythmias has not changed from ICD-9 to ICD-10.

Further study is needed of methods for identifying incident AF. Given the ultimate goals of the Sentinel Initiative, this is the most critical area currently in need of study. The results of this literature review suggest that the best algorithm to identify incident AF may involve the use of both inpatient and outpatient diagnosis codes and, where available, electronic ECG data, with the availability of a multi-year lead-in period (for example, 2-5 years) before the drug exposure of interest. The algorithm would require that subjects have no ICD-9 codes for AF and no ECGs showing AF during the lead-in period. Incident AF after drug exposure would be defined by either an ICD-9 code or an ECG showing AF. Whether both an ICD-9 code and an ECG should be required needs further study. We recommend that additional validation work be conducted within health care systems where electronic ECG data can be accessed and in which a substantial proportion of older patients receive care over moderately long periods of time (e.g., >= 2 years), with the goal of determining the best algorithms for identifying incident AF from electronic healthcare data. It will also be important to understand the impact of

applying the final algorithm in a broader range of databases, many of which may not include the ability to access patient records for validation and so validity of algorithms in their populations cannot be directly measured. To address this question, a combination of data collection and simulation studies could be used to estimate the likely validity of certain algorithms in different data environments, including settings with only inpatient data, settings without access to electronic ECGs, and settings with limited longitudinal follow-up of patients. This work would also shed light on which settings are most appropriate for future surveillance studies of drug-related incident AF.

VII. REFERENCES

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VIII. APPENDICES

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

Alonso A, Agarwal SK, Soliman EZ, Ambrose M, Chamberlain AM, Prineas RJ, Folsom AR. Incidence of atrial fibrillation in whites and African-Americans: the Atherosclerosis Risk in Communities (ARIC) study. *Am Heart J*. 2009; 158(1): 111-7.

OBJECTIVES: To define the incidence and cumulative risk of atrial fibrillation (AF) in a population-based cohort of whites and African Americans. BACKGROUND: African-Americans reportedly have a lower risk of AF than whites despite their higher exposure to AF risk factors. However, precise estimates of AF incidence in African Americans have not been previously published. METHODS: We studied the incidence of AF in the Atherosclerosis Risk in Communities (ARIC) study, which has followed up 15,792 men and women 45 to 65 years of age at baseline from 4 communities in the United States since 1987. Atrial fibrillation cases were identified from electrocardiograms conducted at baseline and 3 follow-up visits, and from hospitalizations and death certificates through the end of 2004. During follow-up, 1,085 new cases of AF were identified (196 in African Americans, 889 in whites). RESULTS: Crude incidence rates of AF were 6.7, 4.0, 3.9, and 3.0 per 1,000 persons per year in white men, white women, African-American men, and African-American women, respectively. Increasing age was exponentially associated with an elevated risk of AF. Compared to whites, African-Americans had a 41% (95% CI: 8%-62%) lower age- and sex-adjusted risk of being diagnosed with AF. The cumulative risk of AF at 80 years of age was 21% in white men, 17% in white women, and 11% in African-American men and women. CONCLUSION: In this population-based cohort, African Americans presented a lower risk of AF than whites. Still, the burden of AF among the former is substantial, with 1 in 9 receiving a diagnosis of AF before 80 years of age.

Antani MR, Beyth RJ, Covinsky KE, Anderson PA, Miller DG, Cebul RD, Quinn LM, Landefeld CS. Failure to prescribe warfarin to patients with nonrheumatic atrial fibrillation. *J Gen Intern Med*. 1996 Dec; 11(12): 713-20.

OBJECTIVE: To determine how often warfarin was prescribed to patients with nonrheumatic atrial fibrillation in our community in 1992 when randomized trials had demonstrated that warfarin could prevent stroke with little increase in the rate of hemorrhage, and to determine whether warfarin was prescribed less frequently to older patients-the patients at highest risk of stroke but of most concern to physicians in terms of the safety of warfarin. DESIGN: Cross-sectional study. Appropriateness of warfarin was classified for each patient based on the independent judgments of three physicians applying relevant evidence and guidelines. SETTING: Two teaching hospitals and five community-based practices. PATIENTS: Consecutive patients with nonrheumatic atrial fibrillation (n = 189). MEASUREMENTS AND MAIN RESULTS: Warfarin was prescribed to 44 (23%) of the 189 patients. Warfarin was judged appropriate in 98 patients (52%), of whom 36 (37%) were prescribed warfarin. Warfarin was prescribed to 11 (14%) of 76 patients aged 75 years or older with hypertension, diabetes mellitus, or past stroke, the group at highest risk of stroke. In a multivariable logistic regression model controlling for appropriateness of warfarin and other patient characteristics, patients aged 75 years or older were less likely than younger patients to be treated with warfarin (odds ratio 0.25; 95% confidence interval 0.10, 0.65). CONCLUSIONS: Warfarin was prescribed infrequently to these patients with nonrheumatic atrial fibrillation, especially the older patients and even the patients for whom warfarin was judged appropriate. These findings indicate a substantial opportunity to prevent stroke.

Borzecki AM, Wong AT, Hickey EC, Ash AS, Berlowitz DR. Identifying hypertension-related comorbidities from administrative data: what's the optimal approach? *Am J Med Qual*. 2004 Sep-Oct; 19(5): 201-6.

The objective was to determine the best strategy for identifying outpatients with hypertension-related diagnoses using Veterans Affairs (VA) administrative databases. We reviewed 1176 outpatient charts from 10 VA sites in 1999, taking the presence of 11 diagnoses relevant to hypertension management as the "gold standard" for identifying the comorbidity. We calculated agreement, sensitivity, and specificity for the chart versus several administrative data-based algorithms. Using 1999 data and requiring 1 administrative diagnosis, observed agreement ranged from 0.98 (atrial fibrillation) to 0.85 (hyperlipidemia), and kappas were generally high. Sensitivity varied from 38% (tobacco use) to 97% (diabetes); specificity exceeded 91% for 10 of 11 diagnoses. Requiring 2 years of data and 2 diagnoses improved most measures, with minimal sensitivity decrease. Agreement between the database and charts was good. Administrative data varied in its ability to identify all patients with a given diagnosis but identified accurately those without. The best strategy for case-finding required 2 diagnoses in a 2-year period.

Brass LM, Krumholz HM, Scinto JM, Radford M. Warfarin use among patients with atrial fibrillation. *Stroke*. 1997 Dec; 28(12): 2382-9.

BACKGROUND AND PURPOSE: Warfarin reduces the rate of stroke among patients with atrial fibrillation. We sought to determine warfarin use within a population sample of elderly patients with atrial fibrillation. METHODS: The Connecticut Peer Review Organization conducted a chart review of Medicare patients aged > or = 65 years with a history of atrial fibrillation before a hospitalization during the first 6 months of 1994. RESULTS: Among 488 patients (308 women; 457 white; 173 aged > or = 85 years), 38% (184/488) had a relative contraindication to anticoagulation (history of bleeding, dementia, alcohol use, falls, cancer, or the need for nonsteroidal anti-inflammatory drugs). Among the remaining patients (with known atrial fibrillation, but without a contraindication), only 38% (117/304) had been prescribed warfarin. Of those not prescribed warfarin, 63% (117/187) were also not taking aspirin. There were 272 patients with at least one additional vascular risk factor and no contraindication to anticoagulation. Among these patients at moderate to high risk for stroke, anticoagulation had been prescribed in 40% (109/272). Overall, among those not prescribed warfarin, 58% (95/163) were not taking aspirin. Patients admitted with a stroke were more likely to be significantly underanticoagulated (with international normalized ratio < 1.5) (43.5% versus 20.9% for those without stroke; P < .005). Anticoagulation was most effective for those with an international normalized ratio > or = 2.0. CONCLUSIONS: Warfarin anticoagulation with atrial fibrillation, even among "ideal" candidates, appears dramatically underutilized. In addition, among those prescribed warfarin, patients are often undertreated. Increased warfarin use among patients with atrial fibrillation represents an excellent opportunity for stroke prevention in the elderly.

Brophy MT, Snyder KE, Gaehde S, Ives C, Gagnon D, Fiore LD. Anticoagulant use for atrial fibrillation in the elderly. *J Am Geriatr Soc*. 2004 Jul; 52(7): 1151-6.

OBJECTIVES: To determine the influence of advanced age on anticoagulant use in subjects with atrial fibrillation and to explore the extent to which risk factors for stroke and contraindications to anticoagulant therapy predict subsequent use. DESIGN: Retrospective cohort study. SETTING: The Veterans Affairs Boston Healthcare System. PARTICIPANTS: A total of 2,217 subjects with nonvalvular atrial fibrillation. MEASUREMENTS: Administrative databases were use to identify subject's age, anticoagulant use, and the presence of a diagnosis of atrial fibrillation, cerebrovascular accident, hypertension, diabetes mellitus, congestive heart failure, or gastrointestinal or cerebral hemorrhage. RESULTS: Unadjusted analysis showed no difference in

warfarin use between those aged 75 and older and younger subjects regardless of the presence (33.9% vs 35.7%, P=.37) or absence (33.4% vs 34.7%, P=.58) of contraindications to anticoagulant therapy. Multivariate modeling demonstrated a 14% reduction (95% confidence interval (CI)=4-22%) in anticoagulant use with each advancing decade of life. Intracranial hemorrhage was a significant deterrent (odds ratio (OR)=0.27 95% CI=0.06-0.85). History of hypertension (OR=2.90, 95% CI=2.15-3.89), congestive heart failure (OR=1.70, 95% CI=1.41-2.04), and cerebrovascular accident (OR=1.54, 95% CI=1.25-1.89) were significant independent predictors for anticoagulant use. CONCLUSION: Despite consensus guidelines to treat all atrial fibrillation patients aged 75 and older with anticoagulants, advancing age was found to be a deterrent to warfarin use. Better estimates of the risk:benefit ratio for oral anticoagulant therapy in older patients with atrial fibrillation are needed to optimize decision-making.

Dublin S, French B, Glazer NL, Wiggins KL, Lumley T, Psaty BM, Smith NL, Heckbert SR. Risk of new-onset atrial fibrillation in relation to body mass index. *Arch Intern Med*. 2006; 166(21): 2322-8.

BACKGROUND: Obesity is associated with increased risk of atrial fibrillation (AF), but it is unknown whether the association differs by duration or persistence of AF. It is also unknown to what extent cardiovascular risk factors may mediate this association. METHODS: This population-based case-control study included 425 subjects with new-onset AF and 707 controls. The AF cases were identified through International Classification of Diseases, Ninth Revision codes for inpatient and outpatient visits and verified by medical record review. Medical records provided data on height, weight, and cardiovascular risk factors. RESULTS: On average, AF risk was 3% higher (95% confidence interval [CI], 1%-5%) per unit increment in body mass index (BMI) (calculated as weight in kilograms divided by height in meters squared). For sustained AF (duration > or =6 months), risk was higher by 7% (95% CI, 3%-11%) per unit BMI increment; for intermittent AF (duration > or =8 days or recurrent), 4% (95% CI, 1%-6%); and for transitory AF (duration <8 days), 1% (95% CI, -1% to +4%). Compared with those with normal BMI, the odds ratios for overweight and obese subjects were as follows: overweight, 0.97 (95% CI, 0.68-1.38); obese class 1, 1.18 (95% CI, 0.80-1.73); obese class 2, 1.34 (95% CI, 0.82-2.18); and obese class 3, 2.31 (95% CI, 1.36-3.91) (P = .002 for trend). When diabetes mellitus, a possible mediator, was added to the model, the odds ratio per unit increment of BMI decreased from 1.034 to 1.028. Adjustment for other cardiovascular risk factors including hyperlipidemia and blood pressure did not attenuate the BMI-AF association. CONCLUSIONS: The association with BMI was stronger for sustained AF than for transitory or intermittent AF. The obesity-AF association appears to be partially mediated by diabetes mellitus but minimally through other cardiovascular risk factors.

Flaker GC, McGowan DJ, Boechler M, Fortune G, Gage B. Underutilization of antithrombotic therapy in elderly rural patients with atrial fibrillation. *Am Heart J*. 1999 Feb; 137(2): 307-12.

BACKGROUND: Antithrombotic agents are underutilized in elderly patients with atrial fibrillation. In a peer-review audit of antithrombotic use in Missouri, rural patients were given antithrombotic therapy less often than rural patients for unclear reasons. METHODS AND RESULTS: The charts of 597 hospitalized Medicare patients discharged between October 1, 1993, and December 31, 1994, from urban and rural hospitals in Missouri were reviewed. In addition to antithrombotic therapy prescribed at the time of discharge, patient and physician information, relative contraindications to antithrombotic therapy, and risk factors for stroke were identified. Rural and urban patients were similar in terms of age, sex, and risk factors for stroke. At least one stroke risk factor was noted in 87% of rural patients and in 84% of urban patients. Urban patients were more likely to have a relative contraindication to antithrombotic therapy compared with rural patients (66% vs 54%, P

=.04) but received antithrombotic therapy more often (58% vs 47%, P =.02). Cardiologists prescribed antithrombotic therapy significantly more often than noncardiologists (69% vs 52%, P =.003). CONCLUSIONS: Elderly rural patients with atrial fibrillation receive antithrombotic therapy less frequently than urban patients despite having a similar high-risk profile and fewer relative contraindications. Primary care physicians prescribe antithrombotic therapy less often than cardiologists, which is one of the reasons for this underutilization.

Gage BF, Boechler M, Doggette AL, Fortune G, Flaker GC, Rich MW, Radford MJ. Adverse outcomes and predictors of underuse of antithrombotic therapy in Medicare beneficiaries with chronic atrial fibrillation. *Stroke*. 2000; 31(4): 822-7.

BACKGROUND AND PURPOSE: Antithrombotic therapy can prevent strokes and transient ischemic attacks (TIAs) in carefully selected patients who have chronic nonvalvular atrial fibrillation (NVAF). Our objectives were 3-fold: to document the use of warfarin and aspirin therapy in Missouri Medicare beneficiaries with chronic NVAF; to identify factors associated with warfarin and aspirin underuse; and to determine the association between prescription of warfarin and aspirin at hospital discharge and adverse outcomes in this elderly, frail population. METHODS: We linked chart reviews from all Missouri hospitals to Medicare claims data from 1993 to 1996. From chart reviews, we documented Medicare beneficiaries' demographic factors, comorbid conditions, and antithrombotic therapy prescribed at the time of hospital discharge. From Medicare claims, we determined the date of outcomes-death from any cause or hospitalization for an ischemic event (a stroke, a TIA, or a myocardial infarction). RESULTS: Only 328 (55%) of the 597 Medicare beneficiaries were prescribed antithrombotic therapy at hospital discharge: 34% received warfarin and 21% received aspirin. Advanced age, female gender, and rural residency predicted underuse of antithrombotic therapy. After controlling for these factors, as well as stroke risk factors and contraindications to anticoagulation, the prescription of warfarin was associated with a 24% relative risk reduction (RRR) in adverse outcomes (P=0.003). Prescription of aspirin was associated with a nonsignificant 5% RRR in these events (P=0.56). CONCLUSIONS: The underuse of antithrombotic therapy in Medicare beneficiaries who have NVAF is associated with measurable adverse outcomes. The benefit of warfarin therapy may extend to frail, elderly patients, a group that was excluded from randomized controlled trials. The role of antiplatelet therapy in this population deserves further study because many of these patients have relative contraindications to warfarin.

Glazer NL, Dublin S, Smith NL, French B, Jackson LA, Hrachovec JB, Siscovick DS, Psaty BM, Heckbert SR. Newly detected atrial fibrillation and compliance with antithrombotic guidelines. *Arch Intern Med*. 2007 Feb 12; 167(3): 246-52.

BACKGROUND: Guidelines recommend the use of antithrombotic therapy for stroke prevention in patients with atrial fibrillation (AF), but compliance with such guidelines has not been widely studied among patients with newly detected AF. Our objective was to assess compliance with antithrombotic guidelines and to identify patient characteristics associated with warfarin use. METHODS: A population-based study of newly detected AF (patient age, 30-84 years) was conducted within a large health plan. Cardiovascular disease risk factors, comorbid conditions, medication use, and international normalized ratios were abstracted from the medical record. Patients were stratified by embolic risk according to American College of Chest Physicians (ACCP) criteria. We analyzed the proportion of patients with AF receiving warfarin or aspirin (> or =325 mg/d) during the 6 months following AF. Relative risk regression estimated the association of risk factors and patient characteristics with warfarin use. RESULTS: Overall, 73% of patients (418/572) with newly detected AF had evidence of antithrombotic use after AF onset. Among the 76%

(437/572) of patients with AF at high risk for stroke, 59% (257/437) used warfarin, 28% (123/437) used aspirin, and 24% (104/437) used neither. The major predictor of warfarin use was AF classification; intermittent or sustained AF had relative risks for warfarin use of 2.8 (95% confidence interval, 2.2-3.6) and 2.9 (95% confidence interval, 2.2-3.7), respectively, compared with transitory AF. CONCLUSIONS: Three quarters of the patients with newly detected AF received antithrombotic therapy, yet many at high risk of stroke did not receive warfarin. Atrial fibrillation classification, rather than stroke risk factors, was strongly associated with warfarin use.

Go AS, Hylek EM, Borowsky LH, Phillips KA, Selby JV, Singer DE. Warfarin use among ambulatory patients with nonvalvular atrial fibrillation: the anticoagulation and risk factors in atrial fibrillation (ATRIA) study. *Annals of Internal Medicine*. 1999; 131(12): 927-34.

BACKGROUND: Warfarin dramatically reduces the risk for ischemic stroke in nonvalvular atrial fibrillation, but its use among ambulatory patients with atrial fibrillation has not been widely studied. OBJECTIVE: To assess the rates and predictors of warfarin use in ambulatory patients with nonvalvular atrial fibrillation. DESIGN: Cross-sectional study. SETTING: Large health maintenance organization. PATIENTS: 13428 patients with a confirmed ambulatory diagnosis of nonvalvular atrial fibrillation and known warfarin status between 1 July 1996 and 31 December 1997. MEASUREMENTS: Data from automated pharmacy, laboratory, and clinical-administrative databases were used to determine the prevalence and determinants of warfarin use in the 3 months before or after the identified diagnosis of atrial fibrillation. RESULTS: Of 11082 patients with nonvalvular atrial fibrillation and no known contraindications, 55% received warfarin. Warfarin use was substantially lower in patients who were younger than 55 years of age (44.3%) and those who were 85 years of age or older (35.4%). Only 59.3% of patients with one or more risk factors for stroke and no contraindications were receiving warfarin. Among a subset of "ideal" candidates to receive warfarin (persons 65 to 74 years of age who had no contraindications and had previous stroke, hypertension, or both), 62.1% had evidence of warfarin use. Among our entire cohort, the strongest predictors of receiving warfarin were previous stroke (adjusted odds ratio, 2.55 [95% CI, 2.23 to 2.92]), heart failure (odds ratio, 1.63 [CI, 1.51 to 1.77]), previous intracranial hemorrhage (odds ratio, 0.33 [CI, 0.21 to 0.52]), age 85 years or older (odds ratio, 0.35 [CI, 0.31 to 0.40]), and previous gastrointestinal hemorrhage (odds ratio, 0.47 [CI, 0.40 to 0.57]). CONCLUSIONS: In a large, contemporary cohort of ambulatory patients with atrial fibrillation who received care within a health maintenance organization, warfarin use was considerably higher than in other reported studies. Although the reasons why physicians did not prescribe warfarin could not be elucidated, many apparently eligible patients with atrial fibrillation and at least one additional risk factor for stroke, especially hypertension, did not receive anticoagulation. Interventions are needed to increase the use of warfarin for stroke prevention among appropriate candidates.

Go AS, Hylek EM, Phillips KA, Borowsky LH, Henault LE, Chang Y, Selby JV, Singer DE. Implications of stroke risk criteria on the anticoagulation decision in nonvalvular atrial fibrillation: the Anticoagulation and Risk Factors in Atrial Fibrillation (ATRIA) study. *Circulation*. 2000 Jul 4; 102(1): 11-3.

BACKGROUND: Warfarin dramatically reduces the risk of stroke in patients with nonvalvular atrial fibrillation (NVAF) but increases the likelihood of bleeding. Accurately identifying patients who need anticoagulation is critical. We assessed the potential impact of prominent stroke risk classification schemes on this decision in a large sample of patients with NVAF. METHODS AND RESULTS: We used clinical and electrocardiographic databases to identify 13 559 ambulatory patients with NVAF from July 1996 through December 1997. We compared the proportion of patients classified as having a low enough stroke risk to receive aspirin using published criteria from the Atrial Fibrillation

Investigators (AFI), American College of Chest Physicians (ACCP), and the Stroke Prevention in Atrial Fibrillation Investigators (SPAF). In this cohort, AFI criteria classified 11% as having a low stroke risk, compared with 23% for ACCP and 29% for SPAF (kappa range, 0.44 to 0.85). This 2- to-3-fold increase in low stroke risk patients by ACCP and SPAF criteria primarily resulted from the inclusion of many older subjects (65 to 75 years+/-men >75 years) with no additional clinical stroke risk factors. CONCLUSIONS: The age threshold for assigning an increased stroke risk has a dramatic impact on whether to recommend warfarin in populations of patients with NVAF. Large, prospective studies with many stroke events are needed to precisely determine the relationship of age to stroke risk in AF and to identify which AF subgroups are at a sufficiently low stroke risk to forego anticoagulation.

Go AS, Hylek EM, Phillips KA, Chang Y, Henault LE, Selby JV, Singer DE. Prevalence of diagnosed atrial fibrillation in adults: national implications for rhythm management and stroke prevention: the AnTicoagulation and Risk Factors in Atrial Fibrillation (ATRIA) Study. *JAMA*. 2001 May 9; 285(18): 2370-5.

CONTEXT: Atrial fibrillation is the most common arrhythmia in elderly persons and a potent risk factor for stroke. However, recent prevalence and projected future numbers of persons with atrial fibrillation are not well described. OBJECTIVE: To estimate prevalence of atrial fibrillation and US national projections of the numbers of persons with atrial fibrillation through the year 2050. DESIGN, SETTING, AND PATIENTS: Cross-sectional study of adults aged 20 years or older who were enrolled in a large health maintenance organization in California and who had atrial fibrillation diagnosed between July 1, 1996, and December 31, 1997. MAIN OUTCOME MEASURES: Prevalence of atrial fibrillation in the study population of 1.89 million; projected number of persons in the United States with atrial fibrillation between 1995-2050. RESULTS: A total of 17 974 adults with diagnosed atrial fibrillation were identified during the study period; 45% were aged 75 years or older. The prevalence of atrial fibrillation was 0.95% (95% confidence interval, 0.94%-0.96%). Atrial fibrillation was more common in men than in women (1.1% vs 0.8%; P<.001). Prevalence increased from 0.1% among adults younger than 55 years to 9.0% in persons aged 80 years or older. Among persons aged 50 years or older, prevalence of atrial fibrillation was higher in whites than in blacks (2.2% vs 1.5%; P<.001). We estimate approximately 2.3 million US adults currently have atrial fibrillation. We project that this will increase to more than 5.6 million (lower bound, 5.0; upper bound, 6.3) by the year 2050, with more than 50% of affected individuals aged 80 years or older. CONCLUSIONS: Our study confirms that atrial fibrillation is common among older adults and provides a contemporary basis for estimates of prevalence in the United States. The number of patients with atrial fibrillation is likely to increase 2.5-fold during the next 50 years, reflecting the growing proportion of elderly individuals. Coordinated efforts are needed to face the increasing challenge of optimal stroke prevention and rhythm management in patients with atrial fibrillation.

Hravnak M, Hoffman LA, Saul MI, Zullo TG, Cuneo JF, Whitman GR, Clochesy JM, Griffith BP. Atrial fibrillation: prevalence after minimally invasive direct and standard coronary artery bypass. *Ann Thorac Surg*. 2001 May; 71(5): 1491-5.

BACKGROUND: This study identified and compared the prevalence of new-onset atrial fibrillation (AFIB) following standard coronary artery bypass grafting (SCABG) with cardiopulmonary bypass (CPB) and minimally invasive direct vision coronary artery bypass grafting (MIDCAB) without CPB. A further comparison was made between AFIB prevalence in SCABG and MIDCAB subjects with two or fewer bypasses. METHODS: This is a retrospective, comparative survey. Patients with new-onset AFIB who underwent SCABG or MIDCAB alone were identified electronically using a triangulated method (International Classification of Diseases, 9th revision, Clinical Modification [ICD-9 CM] code; clinical database word search; and pharmacy database drug search). RESULTS: The total sample (n =

814; 94 MIDCAB, 720 SCABG) exhibited a trend toward lower AFIB prevalence in MIDCAB (23.4%) versus SCABG (33.1%) subjects (p = 0.059). AFIB prevalence in the SCABG subset with two or less vessel bypasses (n = 98; n = 18 single vessel, n = 80 double vessels) and MIDCAB subjects (n = 94; n = 90 single vessels, n = 4 double vessels) was almost identical (SCABG subset 24.5% versus MIDCAB 23.4%, p = 0.860). Slightly more than half (56.9%) of new-onset AFIB subjects were identified by ICD-9 CM codes, with the remainder by word search (37.7%) or procainamide query (5.4%). CONCLUSIONS: In this sample, the number of vessels bypassed seemed to have a greater influence on AFIB prevalence than the application of CPB or the surgical approach. Retrospective identification of AFIB cases by ICD-9 CM code grossly underestimated AFIB prevalence.

Psaty BM, Manolio TA, Kuller LH, Kronmal RA, Cushman M, Fried LP, White R, Furberg CD, Rautaharju PM. Incidence of and risk factors for atrial fibrillation in older adults. *Circulation*. 1997 Oct 7; 96(7): 2455-61.

BACKGROUND: This study aimed to describe the incidence of atrial fibrillation (AF) among older adults during 3 years of follow-up. METHODS AND RESULTS: In this cohort study, 5201 adults > or = 65 years old were examined annually on four occasions between June 1989 and May 1993. At baseline, participants answered questionnaires and underwent a detailed examination that included carotid ultrasound, pulmonary function tests, ECG, and echocardiography. Subjects with a pacemaker or AF at baseline (n=357) were excluded. New cases of AF were identified from three sources: (1) annual self-reports, (2) annual ECGs, and (3) hospital discharge diagnoses. Cox proportional-hazards models were used to assess baseline risk factors as predictors of incident AF. Among 4844 participants, 304 developed a first episode of AF during an average follow-up of 3.28 years, for an incidence of 19.2 per 1000 person-years. The onset was strongly associated with age, male sex, and the presence of clinical cardiovascular disease. For men 65 to 74 and 75 to 84 years old, the incidences were 17.6 and 42.7, respectively, and for women, 10.1 and 21.6 events per 1000 person-years. In stepwise models, the use of diuretics, a history of valvular heart disease, coronary disease, advancing age, higher levels of systolic blood pressure, height, glucose, and left atrial size were all associated with an increased risk of AF. The use of beta-blockers and high levels of alcohol use, cholesterol, and forced expiratory volume in 1 second were associated with a reduced risk of AF. CONCLUSIONS: The incidence of AF in older adults may be higher than estimated by previous population studies. Left atrial size appears to be an important risk factor, and the control of blood pressure and glucose may be important in preventing the development of AF.

Shen AY, Yao JF, Brar SS, Jorgensen MB, Wang X, Chen W. Racial/Ethnic differences in ischemic stroke rates and the efficacy of warfarin among patients with atrial fibrillation. *Stroke*. 2008 Oct; 39(10): 2736-43. [Epub 2008 Jul 17]

BACKGROUND AND PURPOSE: Warfarin reduces stroke risk in studies of predominantly white patients with atrial fibrillation (AF). Whether nonwhites also have lower rates of stroke while treated with warfarin is unclear. METHODS: A multiethnic stroke-free cohort hospitalized with nonrheumatic AF was identified in a large health maintenance organization. Stroke risk factors (advanced age, diabetes, hypertension, and heart failure), warfarin use, and anticoagulation intensity were assessed. Crude ischemic stroke rates were calculated by Poisson regression for each group while using and not using warfarin. Cox proportional hazard models were constructed to assess the independent effect of race/ethnicity on ischemic stroke. RESULTS: Between 1995 and 2000, we identified 18867 AF hospitalizations (78.5% white, 8% black, 9.5% Hispanic, and 3.9% Asian). Over the course of 63204 person-years follow-up (median, 3.3 years), 1226 ischemic strokes were identified. The percent-time on warfarin did not differ by race/ethnicity. The median percent-

time on warfarin that international normalized ratio was 2 to 3 was 54.5% overall, but it was lower in blacks at 47.8%, whereas the other groups had a rate of approximately 54%. The rate ratios (95% CI) of ischemic stroke with warfarin compared to without warfarin for whites, blacks, Hispanics, and Asians were 0.79 (0.68 to 0.90), 0.92 (0.65 to 1.30), 0.71 (0.48 to 1.05), and 0.65 (0.34 to 1.23), respectively. CONCLUSIONS: In this cohort, we did not observe a statistically significant lower rate of stroke with warfarin therapy among nonwhites (in particular blacks) with previous AF hospitalizations. The relatively small numbers of nonwhites renders our estimates less than precise and should be interpreted with caution.

Shireman TI, Howard PA, Kresowik TF, Ellerbeck EF. Combined anticoagulant-antiplatelet use and major bleeding events in elderly atrial fibrillation patients. *Stroke*. 2004 Oct; 35(10): 2362-7. [Epub 2004 Aug 26]

BACKGROUND AND PURPOSE: Bleeding risks from combined antiplatelet-warfarin therapy have not been well-described in clinical practice. We examined antiplatelet therapy among warfarin users and the impact on major bleeding rates. METHODS: Retrospective cohort analysis of persons discharged on warfarin after an atrial fibrillation admission using data from Medicare's National Stroke Project. Data included Medicare claims, enrollment information, and medical record abstracted data. Logistic regression and Cox proportional hazards models were used to predict concurrent antiplatelet use and hospitalization with a major acute bleed within 90 days after discharge from the index AF admission. RESULTS: 10,093 warfarin patients met inclusion criteria with a mean age of 77 years; 19.4% received antiplatelet therapy. Antiplatelet use was less common among women, older persons, and persons with cancer, terminal diagnoses, dementia, and bleeding history. Persons with coronary disease were more likely to receive an antiplatelet agent. Antiplatelets increased major bleeding rates from 1.3% to 1.9% (P=0.052). In the multivariate analysis, factors associated with bleeding events included age (OR, 1.03; 95% CI, 1.002 to 1.05), anemia (OR, 2.52; 95% CI, 1.64 to 3.88), a history of bleeding (OR, 2.40; 95% CI, 1.71 to 3.38), and concurrent antiplatelet therapy (OR, 1.53; 95% CI, 1.05 to 2.22). CONCLUSIONS: Although concerns about increased bleeding risk with combined warfarin-antiplatelet therapy are not unfounded, the risk of bleeding is moderately increased. The decision to use concurrent antiplatelet therapy appears to be tempered by cardiac and bleeding risk factors.

Whittle J, Wickenheiser L, Venditti LN. Is warfarin underused in the treatment of elderly persons with atrial fibrillation? *Arch Intern Med*. 1997 Feb 24; 157(4): 441-5.

BACKGROUND: Several randomized clinical trials have shown that among patients with atrial fibrillation, warfarin sodium use protects against stroke. Recently, experts have voiced concern about possible underuse of warfarin by practicing physicians. Few studies, however, have quantitated the amount of warfarin underuse. METHODS: We randomly sampled 65 Medicare beneficiaries discharged alive from each of 5 small Pennsylvania hospitals between July 1, 1993, and June 30, 1994, with a discharge diagnosis code for atrial fibrillation. Trained abstractors verified that atrial fibrillation was present at some time during the hospitalization, determined the presence of contraindications to anticoagulation, and identified warfarin or aspirin use at discharge for each patient. An internist used implicit criteria to identify the reason for warfarin nonuse in patients who had none of the explicit contraindications to warfarin and did not receive it. RESULTS: Of 322 charts reviewed, 48 patients were not in atrial fibrillation during the hospitalization, 79 had contraindications to warfarin use, 21 either died or were transferred to another hospital, and 2 were admitted with a complication of warfarin. Of the 172 remaining patients, 76 (44%) underwent anticoagulation. On implicit review of the 96 patients who did not undergo anticoagulation, the

internist judged that warfarin would not have been appropriate in 54. After excluding those patients, 76 (64%) of the remaining 118 patients underwent anticoagulation. Patients not receiving warfarin were slightly older (81.6 vs 78.3 years old), but this was not statistically significant after stratifying by hospital. Rates of warfarin use at the 5 hospitals varied widely (32%, 57%, 79%, 82%, 94%; P < .001, chi2 with 4 df). Patients with newly diagnosed atrial fibrillation were not more likely to undergo anticoagulation, nor were patients treated by internal medicine or cardiology specialists. CONCLUSIONS: There may be significant warfarin underuse in some hospitals. Overall, approximately one third of patients with atrial fibrillation for whom it appeared appropriate were not anticoagulated with warfarin. Although the fact that data were not available to or were missed by our review surely justifies some of the underuse, one should recall that even a small amount of underuse may affect a large number of people with this common condition.

Yuan Z, Bowlin S, Einstadter D, Cebul RD, Conners AR Jr, Rimm AA. Atrial fibrillation as a risk factor for stroke: a retrospective cohort study of hospitalized Medicare beneficiaries. *Am J Public Health*. 1998 Mar; 88(3): 395-400.

OBJECTIVES: This study examined the relationship between atrial fibrillation and (1) stroke and (2) all-cause mortality. METHODS: All eligible Medicare patients older than 65 years of age hospitalized in 1985 were followed up for 4 years. Kaplan-Meier and Cox proportional hazards models were used for assessment of risk of stroke and mortality. RESULTS: A total of 4,282,607 eligible Medicare patients were hospitalized in 1985. The mean age was 76.1 (+/- 7.7) years; 58.7% were female; 7.2% were Black; and 8.4% had a diagnosis of atrial fibrillation. During the follow-up period, 66,063 patients (32.6/1000 person-years) developed nonembolic stroke and 7285 (3.6/1000 person-years) developed embolic stroke. After adjustment for age, race, sex, and comorbid conditions, atrial fibrillation remained a significant risk factor for both nonembolic stroke (relative risk [RR] = 1.56) and embolic stroke (RR = 5.80) and for mortality (RR = 1.31). Approximately 4.5% of nonembolic and 28.7% of embolic strokes among hospitalized Medicare patients aged 65 years and older were attributable to atrial fibrillation. CONCLUSIONS: This study demonstrates that atrial fibrillation is associated with an appreciable increase in the risk of stroke (both embolic and nonembolic) and in the risk of mortality from all causes.

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

1. Studies Excluded Due to Poorly Defined Algorithms

Aboufakher R, Riba A, Jani SM, Goswami R, Schwartz S, Lins S, Gardin J, Smith DE, Kline-Rogers E, Share D, Moscucci M, Blue Cross Blue Shield of Michigan Cardiovascular C. Incidence, risk factors, and prognosis of inhospital heart failure after percutaneous coronary intervention: insight from the Blue Cross Blue Shield of Michigan Cardiovascular Consortium (BMC2). *American Heart Journal*. 2005; 150(3): 455-8.

Blacker DJ, Wijdicks EF, McClelland RL. Stroke risk in anticoagulated patients with atrial fibrillation undergoing endoscopy. *Neurology*. 2003; 61(7): 964-8.

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Miyasaka Y, Barnes ME, Gersh BJ, Cha SS, Bailey KR, Abhayaratna WP, Seward JB, Tsang TS. Secular trends in incidence of atrial fibrillation in Olmsted County, Minnesota, 1980 to 2000, and implications on the projections for future prevalence. *Circulation*. 2006; 114(2): 119-25.

Miyasaka Y, Barnes ME, Gersh BJ, Cha SS, Bailey KR, Seward JB, Iwasaka T, Tsang TS. Coronary ischemic events after first atrial fibrillation: risk and survival. *The American Journal of Medicine*. 2007; 120(4): 357-63.

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

Type of Code	Code	Description
ICD-9	427.3	Atrial fibrillation and flutter
ICD-9	427.31	Atrial fibrillation
ICD-9	427.32	Atrial flutter