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

VENOUS THROMBOEMBOLISM 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

Venous Thromboembolism Report

I. EXECUTIVE SUMMARY

A. OVERVIEW OF PROJECT

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

B. SUMMARY OF FINDINGS

The combined use of ICD-9 series 415.1x (pulmonary embolism and infarction), series 451.xx (phlebitis and thrombophlebitis), and 453.xx series (other venous embolism and thrombosis) as a VTE event consistently yielded the highest positive predictive value (PPV). This was particularly true when the Medicare population was used to evaluate the ICD-9 codes.

If a specific event like deep vein thrombosis (DVT) or pulmonary embolism (PE) was evaluated, the PPV was lower than when the combined events were sought. The 415.1x code series for pulmonary embolism yielded particularly high PPVs and codes for deep vein thrombosis performed better when 451.x codes were used than when 453.x codes were used.

The addition of CPT procedure codes for embolectomy and evaluation of prothrombin tests during follow-up improved the PPVs; however ICD-9 procedure codes indicating the placement of inferior vena cava filters did not.

The addition of outpatient pharmacy claims for anticoagulants to DVT ICD-9 codes improved the PPV when compared to the use of DVT ICD-9 codes alone in patients suspected of having a DVT after a hospitalization.

The performance of VTE ICD-9 codes was dependent on the population. ICD-9 codes evaluated in higher risk subjects like postsurgical patients or Medicare patients consistently reported the highest PPVs.

The use of ICD-9 codes that indicate VTE in pregnant women (ICD-9 codes in the 600 range) yielded lower PPV than codes normally used for all patients (ICD-9 codes in the 400 range).

The performance of VTE codes differed importantly by the position in which the code was located. Individual or combined codes in the principal position yielded much higher PPVs when compared to those codes in the secondary position.

C. RECOMMENDATION FOR ALGORITHMS AND SUGGESTION FOR FUTURE RESEARCH

The most important gap is the inconsistent reporting of the objective criteria used for the diagnosis of VTE. Other important gaps include the lack of use of other data commonly included in administrative files like pharmacy, procedure, and DRG codes. Also, there is a dearth of knowledge of the influence of

prevalence on the performance of the PPV in high risk patients (e.g., orthopedic patients). In addition, no validation studies have been conducted on ICD-10 codes or in patients of different race/ethnicities in whom the criteria published to date may have varying sensitivities and specificities.

II. PROJECT OBJECTIVES

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

III. BACKGROUND

The Food and Drug Administration (FDA) Mini-Sentinel contract is a pilot program that aims to conduct active surveillance to detect and refine safety signals that emerge for marketed medical products. In order to perform this work, the program needed to identify algorithms used to detect various health outcomes of interest using administrative data sources and 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 were identified in a textbook chapter reviewing the validity of drug and diagnosis data used in pharmacoepidemiologic studies,[1] 2) a list of designated medical events from a proposed FDA rule on the safety reporting requirements for human drug and biological products,[2] 3) the Observational Medical Outcomes Partnership (OMOP)[i] commissioned reports on algorithms used to identify the health outcome using administrative data.[3]

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

Venous thromboembolism was one of the 20 HOIs selected for review. This report describes the review process and findings for the venous thromboembolism 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

[i] For more information about OMOP see http://omop.fnih.org.

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

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

The search strategy and results for venous thromboembolism are detailed in the Results section. The PubMed search was conducted on May 7, 2010, and the IDIS searches on June 11, 2010.

B. ABSTRACT REVIEW

1. Abstract Review Methods

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

2. Abstract Exclusion Criteria

1. Did not study the HOI.

2. Not an administrative database study. Eligible sources included insurance claims databases as well as other secondary databases that identify health outcomes using billing codes.

3. Data source not from the United States or Canada.

C. FULL-TEXT REVIEW

1. Full-Text Review Methods

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

2. Full-Text Exclusion Criteria

1. Poorly described HOI identification algorithm that would be difficult to operationalize.

2. No validation of outcome definition or reporting of validity statistics.

D. MINI-SENTINEL INVESTIGATOR SURVEY

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

E. EVIDENCE TABLE CREATION

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

F. CLINICIAN OR TOPIC-EXPERT CONSULTATION

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

V. RESULTS

A. SEARCH STRATEGY AND RESULTS

The following summarizes the search results obtained from PubMed and IDIS searches. The PubMed search identified 301 citations (Table 1) and the two IDIS searches identified 63 unique citations (Table 2). The total number of unique citations from the combined searches was 345. 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 2 citations (Table 3).

Table 1. PubMed Search Strategy and Results (301): Performed on 05/07/10

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 1980/01/01 to 2011/01/01	2133008
#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 1980/01/01 to 2011/01/01	437272
#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	3207185

	"placebo-controlled"[All] OR "pilot study"[All] OR "pilot projects"[Mesh] OR "Review"[pt] OR "Prospective Studies"[Mesh]) Limits: Humans, English, Publication Date from 1980/01/01 to 2011/01/01	
#4	Search #1 AND #2 Limits: Humans, English, Publication Date from 1980/01/01 to 2011/01/01	123566
#5	Search #4 NOT #3 Limits: Humans, English, Publication Date from 1980/01/01 to 2011/01/01	75587
#6	"Venous Thromboembolism"[Mesh] Limits: Humans, English, Publication Date from 1990/01/01 to 2011/01/01	1226
#7	"Venous Thrombosis"[Mesh] Limits: Humans, English, Publication Date from 1990/01/01 to 2011/01/01	17853
#8	Search #6 OR #7 Limits: Humans, English, Publication Date from 1990/01/01 to 2011/01/01	18947
#9	Search #5 AND #8 Limits: Humans, English, Publication Date from 1990/01/01 to 2011/01/01	301

Table 2. IDIS Search Strategy and Results (63 unique citations): Performed on 06/11/10

Search 1: 33 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**:

453. EMBOLISM/THROMBOSIS, VN NEC

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 = 33

Search 2: 32 Results

ADVANCED SEARCH

All Fields:

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

AND **Descriptor**:

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

AND NOT **Author**:

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

AND **Abstract**:

"thrombosis" or "thromboembolism"

Years: 1990-2010

Records = 32

Table 3. Search to Update the Original PubMed Search with Additional Database Names: Performed on 07/06/10, Results = 2

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 ("Venous Thromboembolism"[Mesh] OR "Venous Thrombosis"[Mesh]) Limits: Humans, English, Publication Date from 1990/01/01 to 2011/01/01	2

B. ABSTRACT REVIEWS

Of the 345 abstracts reviewed, 65 were selected for full-text review; 37 were excluded because they did not study venous thromboembolism (VTE), 193 were excluded because they were not administrative database studies, and 50 were excluded because the data source was not from the United States or Canada. Cohen's kappa for agreement between reviewers on inclusion vs. exclusion of abstracts was 0.58.

C. FULL-TEXT REVIEWS

Of the 65 full-text articles reviewed, 10 were included in the final evidence tables; 18 were excluded because the HOI identification algorithm was poorly defined and 37 were excluded because they included no validation of the outcome definition or reporting of validity statistics. Reviewers identified 7 citations for review from full-text article references. Of these, all 7 were included in the final report. Cohen's kappa for agreement between reviewers on inclusion vs. exclusion of full-text articles reviewed was 1.0.

D. MINI-SENTINEL INVESTIGATOR SURVEY

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

E. EVIDENCE INCLUDED IN TABLE

Of the 20 studies included in the evidence table (Table 4), ten were identified from the initial search strategy, seven were identified from the review of references of studies obtained from the initial strategy, two[7, 12] were identified from previous research of one of the VTE HOI report authors, and one[25] was a recent publication identified during the writing and review of this project. The purpose of all but two studies[6, 7] was to evaluate the incidence of VTE in postsurgical or medical hospital admissions and to validate the codes utilized to identify cases in administrative claims against medical records.

Of the 20 studies, only one[8] evaluated administrative claims from a national private health insurance company. Eleven studies evaluated private state/local health plans and seven evaluated Medicare and Medicaid databases. One study[9] used a cohort of subjects in the Cardiovascular Health Study and Atherosclerosis Risk in Communities Study.

F. SUMMARY AND DISCUSSION OF ALGORITHMS AND VALIDATION

Codes Used in Algorithms. Sixteen of the 20 studies listed in the evidence table reported the algorithms of International Classification of Diseases , 9th Revision (ICD-9) codes to identify patients with venous thromboembolism. The remaining four studies[7, 10-12] did not report the codes necessary for replication.

Two studies[6, 8] added pharmacy codes to ICD-9 codes and one study[13] added CPT codes to ICD-9 codes when validating against medical records. No study compared ICD-10 or DRG codes with medical records for the validation of venous thromboembolism.

Validation Criteria and Method. All studies included in the report validated administrative coding data through abstraction of medical charts. Documentation of venous thromboembolism in the medical records was generally based on clinical encounters. Sixteen studies evaluated codes for the occurrence of VTE in an inpatient setting or as a complication of medical or surgical inpatient stay. Four studies included study populations from inpatient, outpatient, or emergency room settings.[7, 13-15]

The validation of the ICD-9 codes was done by medical record abstraction evaluating for confirmation of objective diagnostic testing or documentation of the diagnosis in physician notes. When objective diagnostic testing was used, the diagnosis of deep vein thrombosis (DVT) was confirmed with a venogram or ultrasound, while the diagnosis of pulmonary embolism (PE) was confirmed with CT scan and angiogram.

Nine studies[6, 8, 11, 12, 15-19] used confirmation of the diagnosis by imaging and only one study[18] reported on both methods of validation. When objective diagnostic evidence of VTE was used as the reference standard, the PPV was substantially higher than when compared to the use of documentation in physician notes.

Three studies used validation criteria classifying patients by categories of suspicion of VTE as definite, probable, or negative.[6, 14, 15] For the purpose of this review we used the definite category for the diagnosis of VTE. All other studies classified subjects as having or not having VTE.

Validation Algorithms. For pulmonary embolism, several codes were evaluated. When ICD-9 series 415.1x (pulmonary embolism and infarction) was used the reported PPV was 72%.[8, 9] One study used

the 415.1x codes for PE and CPT codes 33910 and 33915 (pulmonary embolectomy) and reported a PPV of 92%.[13] When the codes 415.1x, 451.11 [Phlebitis and thrombophlebitis of femoral vein (deep) (superficial)] and 451.19 (Phlebitis and thrombophlebitis of other) were used individually or in combination, the reported PPV was 24%.[20]

For deep vein thrombosis several codes were evaluated. When an individual ICD-9 code was used - 453.8 (Embolism and thrombosis of other specified veins) - the reported PPV was 36%.[16] One study[9] compared the PPV for individual ICD-9 codes for the diagnosis of DVT: 80% for 453.8, 74% for 451.11, and 50% for 453.2 (Embolism and thrombosis of vena cava). When ICD-9 codes 451.11, 451.19, 451.81 (Phlebitis and thrombophlebitis of iliac vein) and 453.2, as well as the subcodes that indicate the vein where the thrombosis occurred, were included the reported PPV was 84%. For non-specific codes 451.2 (Phlebitis and thrombophlebitis of lower extremities unspecified), 453.8 (Venous embolism and thrombosis of other specified veins), and 453.9 (Embolism and thrombosis of unspecified site) the reported PPV was 79%.[13] When pharmacy codes for anticoagulants following inpatient claims consistent for DVT were used, the reported PPV was 65%.[6]

For venous thromboembolism defined as either pulmonary embolism or deep vein thrombosis, several codes were evaluated. When ICD-9 codes 451.11, 451.18 (a code not used in ICD-9), 451.2, 451.81, 451.9 (Phlebitis and thrombophlebitis of unspecified site), 453.1 (thrombophlebitis migrans), 453.8, 453.9 (Embolism and thrombosis of unspecified site) and 415.1x were used, the reported PPV was 96%.[17] When ICD-9 series 451.1x (Phlebitis and thrombophlebitis of deep veins of lower extremities) and 415.1x were used, the reported PPV was 93%.[8] When ICD-9 codes 671.xx (Venous complications in pregnancy and puerperium), 996.7 [Other complications of internal (biologic)(synthetic) prosthetic device implant and graft] and 997.2 (Peripheral vascular complications not elsewhere classified), 999.2 (Other vascular complications of medical care not classified elsewhere) were added to codes 415.1x, 451.x, and 453.x, the reported PPVs were 84% for DVT and 54% for PE.[24]

One study evaluated the validity of obstetrical codes (ICD-9 600 series); when used alone, the reported PPV was 30%.[21] When ICD-9 codes 671.33 (Deep phlebothrombosis antepartum) and 673.2x (Obstetrical blood clot embolism) were added to codes 415.1x, 451.x, and 453.x, the reported PPV was 77%.[21]

Selected Patient Populations. Two studies evaluated the diagnostic accuracy of ICD-9 codes for VTE in women. The first study[6] included oral contraceptive (OCP) users and the second one[21] included women before and after delivery. The first study determined incident VTE within 2 months of the initial OCP prescription and found that only 42% of the women with an ICD-9 code for DVT had probable disease. The second study determined the incidence of DVT associated with pregnancy and reported a PPV of 30% for the codes specific to pregnancy (ICD-9 600 series).

Two studies included only subjects who underwent hip and knee replacement.[17, 19] The first study evaluated the incidence of VTE after total hip arthroplasty using ICD-9 codes 451.11, 451.18, 451.2, 451.81, 451.9, 453.1, 453.2, 453.8, and 415.1x and reported that 96% of postoperative subjects with these codes were likely to have had VTE. The second study included subjects with primary total hip and knee arthroplasty and reported a sensitivity of 100% for ICD-9 codes for DVT (451.11, 451.18, 451.2, 451.81, 451.9, 453.2, 453.8, 453.9, and 997.2) and pulmonary embolism (415.1x). The PPV for DVT was 92%.

One study evaluated the diagnostic accuracy of ICD-9 codes in Medicare postsurgical patients and reported a PPV of 31% for DVT (451.11, 451.19, 451.2, 451.81, 451.9, 453.40, 453.41, 453.42, 453.8, and 453.9) and 24% for PE (415.1x).[20]

Three studies evaluated the validity of ICD-9 codes for incident cases of VTE as a complication of a medical and surgical hospitalization.[18, 22, 23] The three studies evaluated codes 415.1, 451.11, 451.19, 451.2, 451.2, 451.81, and 453.8. Two of the three studies reported PPV by medical or surgical complications. For postsurgical cases of VTE the reported PPVs were 67%[18] and 90%[23]. For medical cases of VTE the reported PPVs were 55%[18] and 76%[23].

One study[9] included patients from the Cardiovascular Health Study and the Atherosclerosis Risk in Communities Study and evaluated the diagnostic accuracy of individual and combined codes. It found that ICD-9 codes 451.1x and 415.1x had the highest PPVs, 74% and 72%, respectively.

Age of Study Population. Six studies included only Medicare patients (≥65 years).[13, 17, 18, 20, 22, 23] One study included only women between 15 to 44 years of age using oral contraceptives and reported a PPV of 42% for DVT.[6] For studies that included older patients, most utilized the Medicare database with a median reported PPV of 70% and a range between 29% and 96%.

Patient Sex. As previously mentioned, two studies evaluated the positive predictive value of ICD-9 codes for VTE in women. The first study[7] included women aged 15-44 years who were oral contraceptive users and reported a PPV of 42%. The second study[21] included women before and after childbirth and used ICD-9 specific codes for postpartum VTE. When ICD-9 codes in the 400 series were used the reported PPV was 83%; however, the reported PPV for the ICD-9 600 series (specific postpartum VTE) was only 30%. When either the ICD-9 400 or 600 series were utilized excluding codes 671.31 (Deep phlebothrombosis with antepartum delivery), 671.42 (Deep phlebothrombosis postpartum with delivery), and 671.9xx (Unspecified venous complication in pregnancy and the puerperium), the reported PPV was 65%. However, when specific ICD-9 codes were used (415.1, 451.1, 453.8, 671.33, 673.2) the reported PPV increased to 77%.

Patient Race. No study reported on differences in the validity of claims for VTE by race. The study based on the Atherosclerosis Risk in Communities Study (with 4,226 African Americans among the 15,792 enrollment total) and The Cardiovascular Health Study (with 924 African Americans among the 5,888 enrollment total) reported a combined PPV of 72% for PE and 74% for DVT. [9]

Time Period of Data Collection. This report includes populations studied between 1980 and 2004. Only 3 studies were conducted between 1980 and 1990. Of those studies, the reported PPV ranged from 42% to 54%. Eleven studies were conducted between 1990 and 2000. Of those studies, the reported PPV ranged from 35% to 96%. Seven studies were conducted after the year 2000 and reported PPV ranging from 24% to 96%.

Incident vs Prevalent Outcome Validation. No study reported on prevalent cases. All studies reported on incident VTE. Two studies reported on both incident and recurrent VTE. The first,[12] a study of the Worcester standardized metropolitan statistical area, validated ICD-9 codes 415.1x, 451.x, 453.x, 671.x, 673.x, 996.x, 997.x and reported a 96% PPV for DVT and 27% PPV for PE for both incident and recurrent VTE. The second,[8] a study of a commercial health plan using ICD-9 codes 451.x and 415.1x, reported an 11% false positive rate for recurrent VTE events.

Principal vs Secondary Diagnosis. Four studies[8, 17, 19, 25] reported on the performance of the ICD-9 codes in the principal position as a discharge diagnosis of VTE. The first included subjects from local commercial health plans and used ICD-9 codes 451.x and/or 415.1x in the primary or secondary position; it found a PPV of 93%. The second included subjects after orthopedic procedures and reported a PPV of 100% if an ICD-9 code for DVT or PE was found as the principal diagnosis after readmission following orthopedic surgery. The third study evaluated ICD-9 codes in the 400 or 600 series in the principal position at Kaiser Permanente Hospitals and reported a PPV of 97% when these codes were combined with a 2 day hospital stay and a code for a VTE test.

The fourth study[25] evaluated individual VTE codes and combined ICD-9 codes from 3 different institutions. When codes were found in the principal position for pulmonary embolism (either 415.11 or 415.19) the PPV ranged from 96 to 98%, compared to 75 to 81% when found in the secondary position. When only code 415.11 was used in the principal position, the PPV range (89-96%) was similar as compared to when used in the secondary position (91-93%). However, when only code 415.19 was used, there was a large difference when used in the principal vs. the secondary position, with a range of PPV between 96-99% for the principal position.

For any DVT codes (453.xx) in the principal position, the range of PPV was 80-94% compared to 40-74% in the secondary position. Individual 453.xx codes for DVT had higher PPV in the principal position compared to the secondary position.

G. SUMMARY OF EXCLUDED POPULATIONS AND DIAGNOSES

As described above, only two studies excluded males.[6, 21] One study included only young women within the Medicaid population who used oral contraceptives. In addition, several studies that included Medicare populations excluded those aged less than 65 years. One study excluded subjects with suspected DVT who were not candidates for anticoagulant therapy and those who had hypercoagulable states.[16]

H. EVIDENCE TABLE

Table 4. Positive Predictive Values by Algorithm

Citation	Study Population and Time Period	Description of Outcome Studied	Algorithm	Validation/Adjudication Procedure and Operational Definition Validation Statistics
Gertsman et al. 1990 [6]	The Computerized Online Medicaid Pharmaceutical Analysis and Surveillance System (COMPASS) for Medicaid in the state of Michigan. The study included women between the ages of 15 and 44 years who had received at least one oral contraceptive between 1980 and 1986 (N=234,218).	Clinical definition of inpatient incident venous thromboembolism within 56 days of oral contraceptive prescription.	ICD-9 codes PE code 415.1 VTE code 451-453 PE and VTE ICD-9 codes and pharmacy codes for outpatient anticoagulants within 6 months of hospitalizations	Medical records were retrieved by two internists who independently rendered a diagnosis of either probable deep vein thrombosis or possible deep venous thromboembolism. Probable cases were required to have objective diagnostic test confirmation of disease. 132 medical record based diagnosis for inpatient DVT *with and without* evidence of subsequent outpatient anticoagulant use. 42% (n=56) of all cases with inpatient claims consistent with deep venous thromboembolism were classified as probable cases. 80 medical record based diagnosis for inpatient DVT *with* evidence of subsequent anticoagulant use. 65% (n=52) of all cases with outpatient anticoagulant prescription codes following inpatient claims consistent with DVT were classified as probable cases.
Henderson et al. 2009 [10]	Barnes Jewish Hospital from September 1 through November 30, 2004. The study included a sample of postsurgical discharge records (n=3278)	Incident inpatient deep vein thrombosis and pulmonary embolism	AHRQ Patient Safety Indicator (PSI) software algorithm: -Includes all surgical discharges defined by specific DRG's Excludes: -Younger than 18 years -Obstetric patients -IVC filter	Records (n=3,278) were classified as positive or negative by the algorithm and dictated free text. If subjects were negative in the prior two steps, evaluations for anticoagulation (pharmacy) and IVC filters (billing) were performed. Medical records were reviewed for algorithm positive subjects, (n=263), random sample (n=59) of the negative group. (n=322) PPV 54% (95% CI 45-63) NPV 99% (95% CI 99-99) Sensitivity 87% Specificity 98%
Kniffin et al. 1994 [13]	Five percent sample of Medicare enrollees between 1986-and 1989 over 65 years of age. Excluded <65 years, not enrolled	Incidence of pulmonary embolism and deep vein thrombosis from a hospitalization, outpatient or emergency room	Pulmonary embolism: ICD-9 code 415.1 and CPT codes 33910 or 33915 (embolectomy) Deep vein thrombosis ICD-9	Charts were reviewed for subjects during November and December 1986 and November and December 1989. Pulmonary embolism: The PPV was 92% (84/91) for the coded cases. . DVT: The PPV was 84% (32/38) for cases for DVT when using specific codes and the PPV

	in both hospital and physician insurance in Medicare (n=7174 PE and n=8923 DVT).	visit in which the appropriate PE and specific DVT code diagnosis was preceded by hospitalization within 2 months and followed by at least 2 claims for prothrombin times (PT) during the 2 months after diagnosis. For less specific DVT codes case was accepted if code came from hospitalization followed by PT measurement within 90 days	specific codes: 451.1, 451.11, 451.19, 451.81, 453.2. Deep vein thrombosis ICD-9 non-specific codes: 451.2, 453.8, 453.9. Both PE and DVT codes had to be followed by prothrombin time claims.	was 79% (169/215) for non-specific codes.
Leibson et al. 2008 [11]	All inpatient encounters at Mayo Clinic-affiliated hospitals in Olmstead County, Minnesota between 1995-1998 (n=37,845)	Objectively confirmed hospital acquired incident venous thromboembolism events	<u>Exclusion rule approach:</u> Needleman/Buerhaus algorithm (encounters with at least 1 secondary diagnosis of VTE that did not meet any exclusion criteria were included and were defined as positive for hospital acquired.) <u>Indicator rule approach:</u> Needleman/Buerhaus algorithm (encounters with 1 secondary diagnosis of VTE claims) plus an indicator for hospital acquired conditions. VTE present on admission was defined as negative.	Rochester Epidemiology Project: cases status based on review of complete hospital and ambulatory medical records classified as positive if confirmed by computer tomography, magnetic resonance imaging, or pathological examination. <u>Exclusion rule results:</u> NPV 100% (99.9%, 37,611/37,637) Specificity 100% (99.6%, 37,611/37,747) PPV 35% (34.6%, 72/208) Sensitivity 74% (73.5%, 72/98) <u>Indicator variable results:</u> NPV 100% (99.8%, 28,311/28,358) Specificity 100% (99.9%, 28,311/28,321) PPV 74% (74.4%, 29/39) Sensitivity 38% (38.2%, 29/76)
Spencer at al. 2006[14]	Worcester (MA) Statistical Metropolitan Area (12 hospitals) in 1999. N= 2,249.	Incident recurrent venous thromboembolism classified as definite cases in	ICD-9 codes: PE 415.11 and 415.19 DVT:	The medical records of all identified subjects were reviewed by trained abstractors. Validation of records for VTE events was done with prespecified criteria (confirmed by venography,

	Baseline characteristics not reported.	the outpatient and inpatient setting.	451,451.11,451.19 ,451.2,451.81, 451.83,451.89,451 .9,453.1,453.2, 453.8,453.9,671.3 0, 671.31, 671.33,671.40, 671.42, 671.44 ,671.90, 671.91, 671.92, 671.93, 671.94,673.20, 673.21, 673.22, 673.23, 673.24, 996.73,996.74,997 .2	ultrasonography, CT scan, MRI or autopsy). Recurrent cases were defined as new occurrence of thrombosis in a previously uninvolved venous or pulmonary segment. 2,249 subjects were identified as possible cases using ICD-9 codes. 587 subjects were classified as having possible, probable, or definite venous thromboembolism. Of the 142 PE cases 27% were classified as definite. PPV=27% Of the 445 DVT cases 96% were classified as definite. PPV=96%.
Spencer et al. 2007 [15]	Worcester (MA) Statistical Metropolitan Area (12 hospitals) in 1999, 2001 and 2003. N= 7,222. The majority of the validated cases were 65 years and older with an even gender distribution between male and female.	Incident venous thromboembolism classified as definite cases in the outpatient and inpatient setting if confirmed by venography, ultrasonography, CT scan, MRI or autopsy.	VTE ICD-9 codes : 415.1 (1,9), 451,451.11,,451.1 9,451.2,451.81,45 1.83,451.89,451.9, 453.1,453.2, 453.8,453.9, 671.30, 671.31, 671.33,671.40, 671.42, 671.44 ,671.90, 671.91, 671.92, 671.93, 671.94,673.20, 673.21, 673.22, 673.23, 673.24, 996.73,996.74,997 .2	The medical records of all identified subjects were reviewed by trained abstractors. Validation of records for VTE events was done with prespecified criteria A total of 7222 medical records that might be VTE (2333 for 1999, 2462 for 2001, and 2427 for 2003) were identified using ICD-9 codes. 1897 validated cases of VTE were classified as definite VTE (PPV=26%).
Spyropoul-os et al. 2002 [16]	Lovelace Health System, an integrated health maintenance organization serving New Mexico from 1995-1998. Included subjects eligible for heparin or warfarin therapy. Exclusions were bleeding disorders, severe HTN, catheter induced DVT, morbid obesity.	DVT diagnosed as acute, proximal diagnosed with ultrasound and that oral anticoagulant therapy was planned for at least 3 months.	ICD-9 code for DVT 453.8	Medical records (n=354) reviewers examined patient charts to verify DVT status Of 354 records evaluated 129 had confirmed clinical events (PPV=34%).
White et al. 2000	Medicare inpatient claims of 25,388 fee for	Objective documentation of inpatient incident	VTE ICD-9 codes 451.11,451.18,451 .2,451.81,451.9,45	Trained physicians unaware of the hypothesis used a computerized tool to

[17]	service patients 65 years of age or older who underwent total hip arthroplasty between 1993-1996	VTE required positive findings on pulmonary arteriography, V/Q scan, venography, venous ultrasonography, or impedance plethysmography.	3.1,453.2,453.8,453.9,415.1	abstract data Of 297 patients who were hospitalized with postoperative venous thromboembolism 285 were objectively confirmed with VTE (PPV 96%).
Willey et al. 2004 [8]	Databases from 2 health plans located in the Southeastern and Western United States from 1997-2001. N= 2,090. Average age was 61.7 years. 53.4 % were female. Excluded VTE or anticoagulants 3 months before index date.	Inpatient incident and recurrent DVT and PE	VTE ICD-9 codes 451.x and/or 415.1x in either the primary or secondary diagnostic field. More than 1 outpatient pharmacy claim for anticoagulants (warfarin, heparin, or low-weight molecular heparin).	A random sample (n=225) of charts from patients' primary care physicians generated electronically from the computerized database was abstracted from one health plan. 6.7% (15/225) of charts did not have objective documentation of VTE event (PPV=93%). For recurrent VTE events there was 11% false positive rate (PPV=89%).
Zhan, C. et al. 2007 [20]	The Medicare Patient Safety Monitoring System 2002-2004 (CMS). N= 20,868 eligible surgical hospitalizations.	Confirmed postsurgical DVT or PE	ICD-9 codes for DVT: 451.11,451.19,451.2,451.81,451.9,453.40,453.41,453.42,453.8,453.9 ICD-9 codes for PE: 415.1,451.11,451.19	Annual random samples of medical records (2002-2004) abstracted by the Medicare Patient Safety Monitoring System operated by CMS. Data abstraction carried out by the Clinical Data Abstraction Center. Of 20,868 eligible hospitalizations, 232 DVT cases and 95 PE cases were identified by ICD-9 codes, 72 of the DVT cases and 23 of the PE cases confirmed by medical chart abstraction: DVT PPV 31% PE PPV 24% PE/DVT combined PPV 29% DVT sensitivity 67% PE sensitivity 74% PE/DVT sensitivity 68%
White et al. 1998 [19]	California hospital discharge records after unilateral primary total hip (n=19,586; mean age 66.5 yrs., 60% female, 89% white) and knee (n=24,059; mean age 69.6 yrs., 62% female, 84% white)	Incident DVT and PE	ICD-9 codes for DVT: 451.11,451.18,451.2,451.81,451.9,453.1,453.2,453.8,453.9, 997.2 ICD-9 codes for PE: 415.1	DVT and PE Sensitivity: 100% (4/4 cases) DVT or PE PPV: 67% (4/6 cases) DVT or PE PPV if principal diagnosis at the time of readmission after orthopedic surgery: 100% (17/17 cases) DVT or PE PPV for cases treated with an IVC filter: 98% (64/65 cases) DVT PPV for cases admitted for 3 or more days with a principal diagnosis of DVT: 92%

	arthroplasty.			183/198 cases)
Cushman et al. 2004 [9]	Cardiovascular Health Study (1989-1997) and the Atherosclerosis Risk in Communities Study (1987-1996) (n=756) Those identified with idiopathic thrombosis averaged 63 years of age, 46% were male and 26% were nonwhite. Those with secondary thrombosis averaged 63.6 years of age, 48% were male and 27% were nonwhite.	Incident DVT and PE	ICD-9 codes: PE 451.1x Phlebitis of the deep veins 451.1x Phlebitis of the lower extremities, unspecified 451.2 Phlebitis other sites 451.8 Phlebitis unspecified sites 451.9 Budd Chiari syndrome 453.0 Thrombophlebitis migrans 453.1 Thrombosis of the vena cava 453.2 Thrombosis of other specified veins 453.8 Thrombosis of unspecified site 453.9 Placement of vena cava filter 38.7	Hospital records were reviewed within 3 months of hospitalization independently by two investigators. Definite DVT was defined as positive duplex or venogram and PE was defined by ventilation perfusion scan and/or angiogram. PPV for all codes was 47% and for individual codes were as follows: PE 415.1x (n=153; PPV 72%) Phlebitis of the deep veins 451.1x (n=74; PPV 74%) Phlebitis of the lower extremities, unspecified 451.2 (n=20; PPV 20%) Phlebitis other sites 451.8 (n=15; PPV 13%) Phlebitis unspecified sites 451.9 (n=9; PPV 11%) Budd Chiari syndrome 453.0 (n=1; PPV 100%) Thrombophlebitis migrans 453.1 (n=2; PPV 50%) Thrombosis of the vena cava 453.2 (n=6; PPV 50%) Thrombosis of other specified veins 453.8 (n=195; PPV 80%) Thrombosis of unspecified site 453.9 (n=7; PPV 29%) Placement of vena cava filter 38.7(n=7; PPV 57%)
White et al.2004 [21]	UC Davis Medical Center and Kaiser Permanente hospitals (11) female patients before and after childbirth between 1990 and 1998 N=214.	Pregnancy associated VTE	ICD-9 VTE codes 400 codes: 451.11,451.2,451.8,451.11,453.8, 600 codes: 671.30, 671.31, 671.33, 671.42, 671.44,671.91,671.92, 671.93, 671.94, 673.21 ,673.22,673.23,673.24,673.83	Charts were reviewed by three physicians. Each case had to have: (1) objectively confirmed DVT using an objective test; or (2) objectively confirmed PE. The PPV and corresponding 95% CI are as follows: 400 codes only - 83% (67-94%) 600 codes only - 30% (23-37%) 400 or 600 codes as principal diagnosis, hospital stay for 2 days and a code for a VTE test - 97% (85-99%) 400 or 600 codes plus VTE test code and hospital stay for more than 3 days - 76% (64-85%) 400 or 600 codes but excluding 671.31, 671.42, and 671.9x – 65% (56-74%)

				Codes as principal diagnosis alone – 73% (61-82%) Codes as principal diagnosis plus stay for 2 days or more - 79% (67-87%) Codes as principal diagnosis plus stay for 2 days or more and VTE test code – 97% (85%-99%) 415.1x, 451.1 453.8, 671.33 and 673.2 -77 % (66-86%) Codes as principal diagnosis alone - 87 % (73%-95%) Codes as principal diagnosis plus stay for 2 days or more - 95% (83%-99%) Codes as principal diagnosis plus stay for 2 days or more and VTE test code - 100% (85%-100%)
Spencer et al. 2009 [12]	Worcester (MA) Standard Metropolitan Statistical area in 1999, 2001, and 2003. N=7,500. Mean age for validated cases was 64.4 years. 55.8% were female.	Incident and recurrent VTE	Specific ICD-9 VTE codes were not reported	Medical records were independently validated and reviewed by trained abstractors. After screening more than 7,500 potential cases of VTE a total of 1,567 were validated as a first time episode of possible, probable or definite VTE (208 patients had both DVT and PE). 97.3% of the DVT (1310) cases were classified as definite (PPV=97.3%) 52.1% of the PE (465) cases were classified as definite (PPV=52.1%).
Anderson et al. 1991 [24]	Worcester (MA) Standard Metropolitan Statistical area population discharged with a diagnosis of DVT or PE from 1985-1986 (n=405). Average age of DVT patients was 65 years. 47% were male. 98% were white. Average age of PE patients was 66 years. 51% were male. 97% were white.	Incident initial hospital discharge of VTE	ICD-9 codes for VTE 415.1,451.11,451.19,451.2,451.81, 453.2, 453.8,453.9,639.6, 671.30, 671.31,671.33,671.40,671.42,671.44, 671.91(0-4),997.2,999.2,996.7	230 of 274 patients had objectively confirmed DVT (by venography, impedance plethysmosgraphy, or ultrasound) (PPV=84%) 71 of 131 patients had objectively confirmed PE (by pulmonary angiography and/or lung scan). The PPV was 54%
McCarthy et al. [18]	Medicare hospital discharge data	Incident VTE after a medical or	ICD-9 codes for VTE	Four nurses at each site in CA and CT conducted the reviews. Randomly sampled

	from California and Connecticut for persons 65 and older in 1994 (n=78)	surgical hospitalization	415.1,451.11,451.19,451.2,451.81,453.8	25 cases for re-abstraction by another nurse at each study site. Also sent 5 randomly chosen cases at each site for re-abstraction at another site. For postsurgical cases (n=36) the PPV was 67% when objective clinical evidence of VTE was used as the gold standard and the PPV was 8% when physician notes were used as the gold standard. For medical cases (n=42) the PPV was 55% when objective clinical evidence was used as the gold standard and the PPV was 12% when physician notes were used.
Weingart et al. [22]	Medicare hospital discharge data from California and Connecticut for persons 65 and older in 1994 (n=1,025)	Incident VTE after a medical or surgical hospitalization	ICD-9 codes for VTE 415.1,451.11,451.19,451.2,451.81,453.8	Cases were reviewed at each site by 4 nurses and 6 physicians. For patients with a suspected in-hospital VTE (n=40) the PPV was 70%. For patients with a suspected medical case of VTE (n=71) the PPV was 28%.
Lawthers et al. [23]	Medicare hospital discharge data from California and Connecticut for persons 65 and older in 1994 (n=1298; 813 were surgical cases, mean age was 76 yrs., 53% were female, 8% were non-white; 485 were medical cases, mean age was 78 yrs., 68% were female, 15% were non-white)	Incident VTE after medical or surgical hospitalization	ICD-9 codes for VTE 415.1,451.11,451.19,451.2,451.81,453.8	For surgical cases (n=813): PPV 90% NPV 98% For medical cases (n=485): PPV 76% NPV 99%
Smith et al. [7]	Large HMO (Group Health Cooperative) in Washington state included perimenopausal or post-menopausal female aged 30 to 89 years from 1995-2001.	Inpatient and outpatient VTE	No specific codes were detailed. ICD-9 codes (not supplied) were abstracted from GHC hospitalization records over 6 years to identify first DVT or PE.	Trained medical record abstractors reviewed the medical records of all potential cases to verify the diagnosis of VTE. 586 incident cases were identified. VTE cases were diagnosed with imaging documentation. 92% of cases had a positive diagnostic imaging test (PPV=92%)
White et al. 2010 [25]	3456 cases hospitalized between 2005 and 2007 that had a discharge	Inpatient VTE	**1. Predictive value of ICD9-CM codes in the principal**	At UDMC 2 abstractors (2 of the study authors) reviewed all records and entered data into a preconfigured Excel spreadsheet. UHC abstractors were trained by study staff via teleconference and

	diagnosis for VTE. Three sample populations included: single academic hospital (University of California, Davis Medical Center - UCDMC, 33 University Healthsystem Consortium hospitals (UHSC), and 35 community hospitals (The Joint Commission - TJC). Demographics: UCMDC: n=413, Mean Age 54, 53% male, 52% Caucasian, 13 % African American, 11% Hispanic, Asian/Pacific 5% TJC: n=2052, Mean Age 64, 47% male, race not available. UNHSC (medical-length of stay two days or more) n=501 Mean Age 56, 52% male, 59% Caucasian, 29 % African American, 7% Hispanic, Asian/Pacific 2% UNHSC (surgical-underwent valid operating room procedure) n=490 Mean Age 56, 55% male, 64% Caucasian, 24 % African American, 7% Hispanic, Asian/Pacific 2%		**position** *415 codes: pulmonary embolism* 415.11 PE and infarction, 'iatrogenic' 415.19 PE and infarction, other *451 codes: thrombophlebitis* 451.11 Phlebitis, femoral vein 451.19 Phlebitis, other deep vein 451.2 Phlebitis, leg, unspecified 451.9 Phlebitis, unspecified site *453 codes: venous thrombosis* 453.1 Thrombophlebitis migrans 453.2 Vena cava 453.40 Lower extremity DVT, not specified 453.41 Lower extremity DVT, proximal 453.42 Lower extremity DVT, distal 453.8 Thrombosis, other specified vein 453.9 Thrombosis, of unspecified vein Prox or Distal DVT: 453.41 or 453.42 Other DVT codes: 453.1, 453.2, 453.9 **2. ICD9-CM codes in a secondary**	entered data into web-based application. TJC also developed electronic abstraction tool and trained RNs to abstract the medical records. At all 3 locations objectively confirmed VTE required a report stating that VTE was found using compression/duplex ultrasound, chest computerized tomographic angiogram, pulmonary arteriogram, pulmonary scan (high probability) or venography. Superficial venous thrombosis could be documented by compression ultrasound or by clinical diagnosis alone. **Analysis stratified by code in principal or secondary position.** **1. Predictive value of ICD9-CM codes in the principal position** *(2 reference standard measures: any acute VTE or acute PE or lower extremity DVT)* All VTE Codes (Any Acute VTE: 1096 cases/1043 events, PPV 95%; acute PE or lower extremity DVT: 164/150, PPV 91%). *415 codes: pulmonary embolism* 415.11 PE and infarction, 'iatrogenic' (Any acute VTE: 52/50, PPV 96%; acute PE or lower extremity DVT: 9/8, PPV 89%) 415.19 PE and infarction, other (Any acute VTE: 632/608, PPV 96%; acute PE or lower extremity DVT: 94/93, 99%) All pulmonary embolism codes (Any acute VTE: 684/658, PPV 96%; acute PE or lower extremity DVT: 103/101, 98%) *451 codes: thrombophlebitis (1 reference standard measure: any acute VTE).* 451.11 Phlebitis, femoral vein (4/4, PPV 100 %) 451.19 Phlebitis, other deep vein (7/6, PPV 86 %) 451.2 Phlebitis, leg, unspecified (2/1, PPV 50 %) 451.9 Phlebitis, unspecified site (1/1, PPV 100 %) All thrombophlebitis codes (14/12, PPV 86 %) *453 codes: venous thrombosis (2 reference standard measures: any acute VTE and acute PE or lower extremity DVT)* 453.1 Thrombophlebitis migrans (Any acute

			position *415 codes: pulmonary embolism* 415.11 PE and infarction, 'iatrogenic' 415.19 PE and infarction, other *451 codes: thrombophlebitis* 451.11 Phlebitis, femoral vein 451.19 Phlebitis, other deep vein 451.2 Phlebitis, leg, unspecified 451.9 Phlebitis, unspecified site *453 codes: venous thrombosis (for 453.1 and 453.40)* 453.1 Thrombophlebitis migrans 453.2 Vena cava 453.40 Lower extremity DVT, not specified 453.41 Lower extremity DVT, proximal 453.42 Lower extremity DVT, distal 453.8 Thrombosis, other specified vein 453.9 Thrombosis, of unspecified vein Prox or Distal DVT: 453.41 or 453.42 Other DVT codes: 453.1, 453.2, 453.9 **Group 1 Only:** (Group 1 includes	VTE: 1/1, PPV 100%; acute PE or lower extremity DVT: 1/1, PPV 100%) 453.2 Vena cava (Any acute VTE: 12/8, PPV 67%; acute PE or lower extremity DVT: 1/0, PPV 0%) 453.40 Lower extremity DVT, not specified (Any acute VTE: 57/53, PPV 93%; acute PE or lower extremity DVT: 1/1, 100%) 453.41 Lower extremity DVT, proximal (Any acute VTE: 179/170, PPV 95%; acute PE or lower extremity DVT: 19/17, PPV % 89) 453.42 Lower extremity DVT, distal (Any acute VTE: 78/74, PPV 95%; acute PE or lower extremity DVT: 9/7, PPV 78%) 453.8 Thrombosis, other specified vein (Any acute VTE: 70/66, PPV 94%; acute PE or lower extremity DVT: 30/23, PPV 77%) 453.9 Thrombosis, of unspecified vein (Any acute VTE: 1/1, PPV 100%; acute PE or lower extremity DVT; not calculated) Prox or Distal DVT: 453.41 or 453.42 (Any acute VTE: 257/245, PPV 95%; acute PE or lower extremity DVT: 28/24, PPV 86%) Other DVT codes: 453.1, 453.2, 453.9 (Any acute VTE: 14/9, PPV 64%; acute PE or lower extremity DVT; not calculated) All venous thrombosis codes (Any acute VTE: 398/373, PPV 94%; acute PE or lower extremity DVT: 61/49, PPV 80%) **2. Predictive value of ICD9-CM codes in a secondary position** All VTE Codes (Any Acute VTE: 2360 cases/1779 events, PPV 75%; acute PE or lower extremity DVT: 1240/671, PPV 50%). *415 codes: pulmonary embolism (2 reference standard measures any acute VTE and acute PE or lower extremity DVT)* 415.11 PE and infarction, 'iatrogenic' (Any acute VTE: 126/117, PPV 93%; acute PE or lower extremity DVT: 57/52, PPV 91%) 415.19 PE and infarction, other (Any acute VTE: 644/509, PPV 79%; acute PE or lower extremity DVT: 311/225, 72%) Any PE codes (Any acute VTE: 770/626, PPV 81%; acute PE or lower extremity DVT: 368/277, 75%) *451 codes: thrombophlebitis (2 reference standard measures any acute VTE and acute*

			PE codes 415.11, 415.19) **Group 1 and 2:** Group 1 and Group 2 (Group 2 includes specific lower extremity DVT codes 453.41, 453.42) **Groups 1-3:** Group 1, Group 2, and Group 3 (Group 3 includes non-specific lower extremity DVT code 453.40) **Groups 1-4:** Group 1, Group 2, Group 3, and Group 4 (Group 4 includes thrombosis of other specified vein: 453.8) **Groups 1-5:** Group 1, Group 2, Group 3, Group 4, and Group 5 (Group 5 includes other venous thrombosis codes: 453.1, 453.2, 453.9) **Groups 1-6:** Group 1, Group 2, Group 3, Group 4, Group 5, and Group 6 (Group 6 includes thrombophlebitis codes: 451.11, 451.19, 451.2, 451.9)	*PE or lower extremity DVT).* 451.11 Phlebitis, femoral vein (Any acute VTE: 3/1, PPV 33%; acute PE or lower extremity DVT: 2/0, PPV 0%) 451.19 Phlebitis, other deep vein (Any acute VTE: 9/6, PPV 67%; acute PE or lower extremity DVT: 4/2, PPV 50%) 451.2 Phlebitis, leg, unspecified (Any acute VTE: 5/3, PPV 60%; acute PE or lower extremity DVT: 2/0, PPV 0%) 451.9 Phlebitis, unspecified site (Any acute VTE: 17/7, PPV 41%; acute PE or lower extremity DVT: 14/2, PPV 14%) All thrombophlebitis codes (Any acute VTE: 34/17, PPV 50%; acute PE or lower extremity DVT: 22/4, PPV 18%) *453 codes: venous thrombosis (for 453.1 and 453.40 - 2 reference standard measures and acute VTE and acute PE or lower extremity DVT)* 453.1 Thrombophlebitis migrans (Any acute VTE: 1/1, PPV 100%; acute PE or lower extremity DVT: not calculated) 453.2 Vena cava (Any acute VTE: 29/18, PPV 62%; acute PE or lower extremity DVT: 7/3, PPV 43%) 453.40 Lower extremity DVT, not specified (Any acute VTE: 236/144, PPV 61%; acute PE or lower extremity DVT: 126/48, 38%) 453.41 Lower extremity DVT, proximal (Any acute VTE: 355/306, PPV 86%; acute PE or lower extremity DVT: 158/115, PPV % 73) 453.42 Lower extremity DVT, distal (Any acute VTE: 184/152, PPV 83%; acute PE or lower extremity DVT: 74/48, PPV 65%) 453.8 Thrombosis, other specified vein (Any acute VTE: 709/495, PPV 70%; acute PE or lower extremity DVT: 458/119, PPV 26%) 453.9 Thrombosis, of unspecified vein (Any acute VTE: 42/20, PPV 48%; acute PE or lower extremity DVT: 27/3, PPV 11%) Prox or Distal DVT: 453.41 or 453.42 (Any acute VTE: 539/458, PPV 85%; acute PE or lower extremity DVT: 232/163, PPV 70%) Other DVT codes: 453.1, 453.2, 453.9 (Any acute VTE: 72/39, PPV 54%; acute PE or lower extremity DVT: 22/4, PPV 18%) All venous thrombosis codes (Any acute VTE: 1556/1136, PPV 74%; acute PE or

				lower extremity DVT: 850/336, PPV 40%) **Effect of selecting specific secondary position ICD9-CM VTE codes on the proportion of cases identified and the positive predictive value** **Group 1 Only:** (PE codes 415.11, 415.19) **Results:** Any acute VTE (33% of cases) PPV 81%; acute PE or lower extremity DVT (30% of cases) PPV 75%. **Group 1 and 2:** Group 1 and Group 2 (specific lower extremity DVT codes 453.41, 453.42) **Results:** Any acute VTE (53% of cases) PPV 83%; acute PE or lower extremity DVT (49% of cases) PPV 73%. **Groups 1-3:** Group 1, Group 2, and Group 3 (non-specific lower extremity DVT code 453.40) **Results:** Any acute VTE (65% of cases) PPV 80%; acute PE or lower extremity DVT (59% of cases) PPV 67%. **Groups 1-4:** Group 1, Group 2, Group 3, and Group 4 (thrombosis of other specified vein: 453.8) **Results:** Any acute VTE (96% of cases) PPV 76%; acute PE or lower extremity DVT (96% of cases) PPV 51%). **Groups 1-5:** Group 1, Group 2, Group 3, Group 4, and Group 5 (other venous thrombosis codes: 453.1, 453.2, 453.9) **Results:** Any acute VTE (99% of cases) PPV 76%; acute PE or lower extremity DVT (98% of cases) PPV 50%. **Groups 1-6:** Group 1, Group 2, Group 3, Group 4, Group 5, and Group 6 (thrombophlebitis codes: 451.11, 451.19, 451.2, 451.9) **Results:** Any acute VTE (100% of cases) PPV 75%; acute PE or lower extremity DVT (100% of cases) PPV 50%.

I. CLINICIAN OR TOPIC EXPERT CONSULTATION

For pulmonary embolism, the performance of ICD-9 code 415.1x consistently reported a PPV in the 70-96% range. However, when procedure codes for pulmonary embolectomy were added the PPV increased to 92%. For deep vein thrombosis, the performance of multiple ICD-9 codes (451.x and 453.x) ranged from 31 to 84%. When a single ICD-9 code was used to evaluate, the results were dependent on the code used; for example, if ICD-9 code 453.8 was used the reported PPV was 34%, however when only ICD-9 code 451.1 was used the reported PPV was 74%.

For VTE, the performance of multiple PE and/or DVT ICD-9 codes (415.1x, 451.x, and 453.x) reported PPVs that ranged from 26% to 93%.

The addition of pharmacy claims for anticoagulants after an incident episode of VTE or procedure claims for diagnostic tests or therapeutic procedures (pulmonary embolectomy) improved the PPV; however, the use of procedure codes for inferior vena cava filters reported a lower PPV. The rationale for this finding could be the fact that inferior vena cava filters could be used as prophylaxis for VTE.

Several studies included subjects at higher risk for VTE. The PPV was lowest for the lower risk patients (women using oral contraceptives), followed by intermediate risk patients after surgical or medical admissions. The highest PPV's were seen for those estimated to be at the highest risk following a knee or hip replacement.

The distinction between the criteria for validation is a fundamental issue that will need to be addressed. Specifically, it will be important to specify at the outset of a study which type of diagnosis is made: ultrasound and/or venogram for DVT, angiogram/CT or V/Q scan for PE. This is of particular importance in PE since several studies did not have clear standardization of the objective criteria for diagnosis.

Few studies determined how the use of procedure, pharmacy, and DRG codes as part of the algorithm affected the PPV. For example, how does the presence of a code indicating the evaluation of risk factors for thrombophilia, the completion of specific testing for DVT or PE, or the prolonged use of warfarin impact the PPV if included in the algorithm?

VI. SUMMARY AND CONCLUSIONS

A. RECOMMENDATIONS FOR ALGORITHMS

The combined use of ICD-9 codes 415.1x (pulmonary embolism), 451.x, and 453.x (deep vein thrombosis) as a VTE event consistently yielded the highest PPV. This was particularly true when the Medicare population was used to evaluate the ICD-9 codes.

If a specific event like DVT or PE was evaluated, the PPV was lower than when the combined events were examined. The code for pulmonary embolism yielded particularly high PPVs and codes for deep vein thrombosis performed better when code 451.x was used than when code 453.x was used.

The addition of CPT procedure codes (33910 and 33915) for embolectomy and evaluation of prothrombin tests during follow-up improved the PPVs; however, ICD-9 procedure codes indicating the placement of inferior vena cava filters (ICD-9 procedure code 387) did not.

The addition of outpatient pharmacy claims for anticoagulant to DVT ICD-9 codes improved the PPV when compared to the use of DVT ICD-9 codes alone in patients suspected of having a DVT after a hospitalization.

The performance of VTE ICD-9 codes was dependent on the population. ICD-9 codes evaluated in higher risk subjects like postsurgical patients or Medicare patients consistently reported the highest PPV.

The use of ICD-9 codes that indicate VTE in pregnant women (ICD-9 codes in the 600 range) yielded lower PPV than codes normally used for all patients (ICD-9 codes in the 400 range).

The performance of VTE codes differed importantly by the position where the code was located. Individual or combined codes in the principal position yielded much higher PPVs when compared to those codes in the secondary position.

B. SUGGESTIONS FOR FUTURE RESEARCH BASED ON EVIDENCE GAPS

The most important gap is the inconsistent reporting of the objective criteria used for the diagnosis of VTE. Other important gaps include the lack of use of the other data commonly included in administrative files like pharmacy, procedure, and DRG codes. Also, there is a dearth of knowledge of the influence of prevalence on the performance of the positive predictive value in high risk patients (e.g., orthopedic patients). In addition, no validation studies have been conducted on ICD-10 codes or in patients of different races/ethnicities in whom the criteria published to date may have varying sensitivities and specificities.

VII. REFERENCES

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VIII. APPENDICES

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

Gerstman BB, Freiman JP, Hine LK. Use of subsequent anticoagulants to increase the predictive value of medicaid deep venous thromboembolism diagnoses. *Epidemiology*. 1990; 1: 122-127.

Linked data bases that derive their information from health care administrative sources are increasingly being used to conduct pharmacoepidemiologic research. Computerized case ascertainment using these data would be highly advantageous in terms of time and cost considerations. For a study of oral-contraceptive-associated deep venous thromboembolism, we evaluated the utility of using anticoagulant treatment codes to validate diagnostic codes suggestive of deep venous thrombosis and pulmonary embolism. By requiring evidence of outpatient anticoagulant use within six months of hospitalization, the predictive value of case ascertainment increased from 42% to 65% for "probable" deep venous thromboembolism and from 70% to 97% for "possible" deep venous thromboembolism. In addition, use of anticoagulant treatment codes as a second marker of disease resulted in nondifferential outcome misclassification when the study base was restricted to current oral-contraceptive users. Use of confirmatory treatment claims may provide a rapid, cost-effective alternative to medical-record-based case ascertainment for pharmacoepidemiologic studies of selected outcomes conducted in Medicaid and other linked universal health care coverage populations.

Henderson KE, Recktenwald A, Reichley RM, et al. Clinical validation of the AHRQ postoperative venous thromboembolism patient safety indicator. *Jt Comm J Qual Patient Saf*. 2009; 35: 370-376.

BACKGROUND: The Agency for Healthcare Research and Quality (AHRQ) patient safety indicators (PSIs) screen for potentially preventable complications in hospitalized patients using hospital administrative data. The PSI for postoperative venous thromboembolism (VTE) relies on International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes for deep vein thrombosis (DVT) or pulmonary embolism (PE) in secondary diagnoses fields. In a clinical validation study of the PSI for postoperative VTE, natural language processing (NLP), supplemented by pharmacy and billing data, was used to identify VTE events missed by medical records coders. METHODS: In a retrospective review of postsurgical discharges, charts were processed using the AHRQ PSI software. Cases were identified as possible false negatives by flagging charts for possible VTEs using pharmacy and billing data to identify all patients who were therapeutically anticoagulated or had placement of an inferior vena caval filter. All charts were reviewed by a physician blinded to screening results. Physician interpretation was considered the gold standard for VTE classification. RESULTS: The AHRQ PSI had a positive predictive value (PPV) of .545 (95% confidence interval [CI], .453-.634) and a negative predictive value (NPV) of .997 (95% CI, .995-.999). Sensitivity was .87 and specificity was .98. Secondary coding review suggested that all 9 false-negative results were miscoded; if they had been properly coded, the sensitivity would increase to 1.00. Most false-positive cases resulted from superficial venous clots identified by the PSI due to coding ambiguity. DISCUSSION: The VTE PSI performed well as a screening tool but generated a significant number of false-positive cases, a problem that could be substantially reduced with improved coding methods.

Kniffin WD Jr, Baron JA, Barrett J, Birkmeyer JD, Anderson FA Jr. The epidemiology of diagnosed pulmonary embolism and deep venous thrombosis in the elderly. *Arch Intern Med*. 1994; 154: 861-866.

BACKGROUND: There are no studies that define the basic epidemiology of pulmonary embolism (PE) and deep venous thrombosis (DVT) in the elderly. This project was undertaken to provide that information. METHODS: We obtained all Medicare claims during the period 1986 through 1989 from a random 5% sample of US Medicare enrollees. By selecting codes used for diagnoses and treatment, we identified 7174 cases of PE and 8923 cases of DVT. These cohorts were analyzed to provide incidence by age, race, sex, and geographic location; frequency of invasive treatment; frequency of PE after treatment for DVT; frequency of recurrence of PE; and survival after diagnosis. RESULTS: Annual incidence rates per 1000 at age 65 to 69 years for PE and DVT were 1.3 and 1.8, respectively. Both rates increased steadily with age to 2.8 and 3.1 by age 85 to 89 years. For PE, women had lower rates than men (adjusted relative risk, 0.86; 95% confidence interval, 0.82 to 0.90), and blacks had higher rates than whites (adjusted relative risk, 1.25; 95% confidence interval, 1.15 to 1.36). For DVT, the associations with gender and race were weaker and in the opposite direction. Pulmonary embolectomy was done in 0.2% of cases of PE; interruption of the vena cava was done in 4.4% of cases of PE and in 2% of cases of DVT. Thrombectomy was done in 0.3% of all cases. Pulmonary embolism occurred in 1.7% of patients with DVT within 1 year of hospital discharge for initial treatment. The 1-year recurrence rate for PE was 8.0%. In-hospital mortality associated with PE and DVT was 21% and 3%, respectively. One-year mortality was 39% and 21%, respectively. CONCLUSIONS: Pulmonary embolism and DVT are common problems in the elderly. Both increase with age, but the effects of race and sex are small. Current treatment patterns appear to be effective in preventing both PE after DVT and recurrence of PE. Both are associated with substantial 1-year mortality, suggesting the need to understand the role of associated conditions as well as the indications for prophylaxis and the methods of treatment.

Leibson CL, Needleman J, Buerhaus P, et al. Identifying in-hospital venous thromboembolism (VTE): A comparison of claims-based approaches with the Rochester Epidemiology Project VTE cohort. *Med Care*. 2008; 46: 127-132.

BACKGROUND: Efforts to identify hospital-acquired complications from claims data by applying exclusion rules to discharge diagnosis codes exhibit low positive predictive value (PPV). The PPV improves when a variable is added to each secondary diagnosis to indicate whether the condition was "present-on-admission" (POA) or "hospital-acquired". Such indicator variables will soon be required for Medicare reimbursement. No estimates are available, however, of the proportion of hospital-acquired complications that are missed (sensitivity) using either exclusion rules or indicator variables. We estimated sensitivity, specificity, PPV, and negative predictive value (NPV) of claims-based approaches using the Rochester Epidemiology Project (REP) venous thromboembolism (VTE) cohort as a "gold standard." METHODS: All inpatient encounters by Olmsted County, Minnesota, residents at Mayo Clinic-affiliated hospitals 1995-1998 constituted the at-risk-population. REP-identified hospital-acquired VTE consisted of all objectively-diagnosed VTE among County residents 1995-1998, whose onset of symptoms occurred during inpatient stays at these hospitals, as confirmed by detailed review of County residents' provider-linked medical records. Claims-based approaches used billing data from these hospitals. RESULTS: Of 37,845 inpatient encounters, 98 had REP-identified hospital-acquired VTE; 47 (48%) were medical encounters. NPV and specificity were >99% for both claims-based approaches. Although indicator variables provided higher PPV (74%) compared with exclusion rules (35%), the sensitivity for exclusion rules was 74% compared with only 38% for indicator variables. Misclassification was greater for medical than surgical encounters. CONCLUSIONS: Utility and accuracy of claims data for identifying hospital-acquired conditions, including POA indicator variables, requires close attention be paid by clinicians and coders to what is being recorded.

Spencer FA, Emery C, Lessard D, et al. The Worcester Venous Thromboembolism study: A population-based study of the clinical epidemiology of venous thromboembolism. *J Gen Intern Med*. 2006; 21: 722-727.

BACKGROUND: While there have been marked advances in diagnostic and therapeutic strategies for venous thromboembolism, our understanding of its clinical epidemiology is based on studies conducted more than a decade ago. OBJECTIVE: The purpose of this observational study was to describe the incidence and attack rates of venous thromboembolism in residents of the Worcester Statistical Metropolitan Area in 1999. We also describe demographic and clinical characteristics, management strategies, and associated hospital and 30-day outcomes. DESIGN AND MEASUREMENTS: The medical records of all residents from Worcester, MA (2000 census=477,800), diagnosed with International Classification of Diseases, 9th revision (ICD-9) codes consistent with possible venous thromboembolism during 1999 were independently validated, classified, and reviewed by trained abstractors. RESULTS: A total of 587 subjects were enrolled with validated venous thromboembolism. The incidence and attack rates of venous thromboembolism were 104 and 128 per 100,000 population, respectively. Three quarters of patients developed their venous thromboembolism in the outpatient setting - a substantial proportion of these patients had undergone recent surgery or had a recent prior hospitalization. Less than half of the patients received anticoagulant prophylaxis during high-risk periods before their venous thromboembolism. Thirty-day rates of venous thromboembolism recurrence, major bleeding, and mortality were 4.8%, 7.7%, and 6.6%, respectively. CONCLUSION: These data provide insights into recent incidence and attack rates, changing patient profiles, management strategies, and subsequent outcomes in patients with venous thromboembolism. The underutilization of prophylaxis before venous thromboembolism, and relatively high 30-day recurrence rates, suggest a continued need for the improvement of venous thromboembolism prophylaxis and management in the community.

Spencer FA, Lessard D, Emery C, Reed G, Goldberg RJ. Venous thromboembolism in the outpatient setting. *Arch Intern Med*. 2007; 167: 1471-1475.

BACKGROUND: There has been great interest in optimizing prophylaxis against venous thromboembolism (VTE) in the hospital setting. However, data from earlier studies suggest that most VTEs occur in the outpatient setting. The purposes of this observational study were to describe the frequency of VTEs occurring in the outpatient setting, characterize the prevalence of previously identified risk factors for VTE, and identify previous use of VTE prophylaxis. METHODS: The medical records of residents from the Worcester metropolitan area diagnosed as having International Classification of Diseases, Ninth Revision codes consistent with possible VTE during 1999, 2001, and 2003 were independently validated and reviewed by trained abstractors. RESULTS: A total of 1897 subjects had a confirmed episode of VTE. In all, 73.7% of patients developed VTE in the outpatient setting; a substantial proportion of these patients had undergone surgery (23.1%) or hospitalization (36.8%) in the preceding 3 months. Among these patients, 67.0% experienced VTE within 1 month of the preceding hospital encounter. Other major risk factors for VTE in the outpatient setting included active malignant neoplasm (29.0%) or previous VTE (19.9%). Among 516 patients with a recent hospitalization who subsequently developed VTE, less than half (42.8%) had received anticoagulant prophylaxis for VTE during that visit. CONCLUSIONS: More VTEs were diagnosed in the 3 months following hospitalization than during hospitalization. Efforts to improve in-hospital use of VTE prophylaxis may help decrease the incidence of outpatient VTE. However, given the shortening of hospital stays, studies of extended VTE prophylaxis following hospital discharge are warranted.

Spyropoulos AC, Hurley JS, Ciesla GN, de Lissovoy G. Management of acute proximal deep vein thrombosis: Pharmacoeconomic evaluation of outpatient treatment with enoxaparin vs inpatient treatment with unfractionated heparin. *Chest*. 2002; 122: 108-114.

OBJECTIVES: A landmark Canadian randomized controlled clinical trial compared treatment of acute proximal vein thrombosis via low-molecular-weight heparin (LMWH) [enoxaparin] administered primarily at home with IV unfractionated heparin (UH) in the hospital. Results demonstrated equivalent safety and efficacy for home care with enoxaparin with a reduction in cost. Our objective was to validate these findings in the routine practice setting of a US health maintenance organization. DESIGN: Retrospective analysis of medical and administrative records of health-plan members meeting inclusion-exclusion criteria of the Canadian trial during the period from 1995 to 1998. SETTING: Staff-model health maintenance organization serving New Mexico. PATIENTS: Persons presenting as outpatients from 1995 to 1996 or from 1997 to 1998 with acute, proximal deep vein thrombosis (DVT) diagnosed by duplex ultrasonography. INTERVENTIONS: Initial anticoagulant therapy of IV UH administered in the hospital (from 1995 to 1996 group, n = 64) or subcutaneous LMWH (enoxaparin) administered primarily at home (from 1997 to 1998 group, n = 65), followed by warfarin therapy. RESULTS: No statistically significant differences were observed in the number of recurrent venous thromboembolic events (p = 0.36) or bleeding events (p = 1.0). Mean +/- SD cost per patient was 9,347 dollars +/- 8,469 in the enoxaparin group compared with 11,930 dollars +/- 10,892 in the UH group, a difference of - 2,583 dollars (95% bootstrap-adjusted asymmetrical confidence interval, - 6,147 dollars, + 650 dollars). CONCLUSIONS: Retrospective replication of the Canadian study in a US routine (managed) care setting found similar clinical and economic outcomes. Treatment of acute proximal DVT with enoxaparin in a primarily outpatient setting can be accomplished safely and yields savings through avoidance or minimization of inpatient stays.

White RH, Gettner S, Newman JM, Trauner KB, Romano PS. Predictors of rehospitalization for symptomatic venous thromboembolism after total hip arthroplasty. *N Engl J Med*. 2000; 343: 1758-1764.

BACKGROUND: Recent studies have shown that symptomatic venous thromboembolism after total hip arthroplasty most commonly develops after the patient is discharged from the hospital. Risk factors associated with these symptomatic thromboembolic events are not well defined. METHODS: Using administrative data from the California Medicare records for 1993 through 1996, we identified 297 patients 65 years of age or older who were rehospitalized for thromboembolism within three months after total hip arthroplasty. We compared demographic, surgical, and medical variables potentially associated with the development of thromboembolism in these patients and 592 unmatched controls. RESULTS: A total of 89.6 percent of patients with thromboembolism and 93.8 percent of control patients were treated with pneumatic compression, warfarin, enoxaparin, or unfractionated heparin, alone or in combination. In addition, 22.2 percent and 29.7 percent, respectively, received warfarin after discharge. A body-mass index (the weight in kilograms divided by the square of the height in meters) of 25 or greater was associated with rehospitalization for thromboembolism, with an odds ratio of 2.5 (95 percent confidence interval, 1.8 to 3.4). In a multivariate model, the only prophylactic regimens associated with a reduced risk of thromboembolism were pneumatic compression in patients with body-mass indexes of less than 25 (odds ratio, 0.3; 95 percent confidence interval, 0.2 to 0.6) and warfarin treatment after discharge (odds ratio, 0.6; 95 percent confidence interval, 0.4 to 1.0). CONCLUSIONS: In patients who underwent total hip arthroplasty, a body-mass index of 25 or greater was associated with subsequent hospitalization for thromboembolism. Pneumatic compression in patients with a body-

mass index of less than 25 and prophylaxis with warfarin after discharge were independently protective against thromboembolism.

Willey VJ, Bullano MF, Hauch O, et al. Management patterns and outcomes of patients with venous thromboembolism in the usual community practice setting. *Clin Ther*. 2004; 26: 1149-1159.

OBJECTIVE: The objectives of this study were to observe a commercially insured sample diagnosed with a venous thromboembolism (VTE) event and treated postevent with warfarin and to detail the thromboembolic and bleeding outcomes in the time periods during warfarin therapy and after discontinuation of such therapy. METHODS: This retrospective, observational cohort study used medical, pharmacy, and eligibility data from 2 US health plans. Study inclusion required an inpatient diagnosis of deep venous thrombosis (DVT) or pulmonary embolism (PE) between January 1, 1998, and December 31, 2000; warfarin, heparin, or low-molecular-weight heparin within 30 days after diagnosis; no VTE diagnosis; and no anticoagulant use for 3 months preceding diagnosis. A random sample of medical charts was abstracted to validate VTE events and collect prothrombin time/international normalized ratio (INR) result data. Recurrent VTE events, bleeding events, and proportion of time within INR range were captured in the postindex VTE event time period. Univariate and multivariate statistical techniques were used to assess outcomes. RESULTS: A total of 2,090 patients were identified with a newly diagnosed VTE event (DVT only, 1450; PE with or without DVT, 640). Mean (SD) age was 61.7 (16) years; mean (SD) follow-up time after the index diagnosis was 21.3 (10) months. Overall mean (SD) length of warfarin therapy was 6.6 (6) months. During the follow-up period, 224 patients (10.7%) experienced a recurrent VTE event and 122 patients (5.8%) experienced a bleeding event requiring hospitalization. The cumulative incidence of recurrent VTE events over 3 and 6 months was 9.0% and 10.9%, respectively. Using the chart abstraction subset, patients were within the appropriate INR range 37.7% of the time while receiving warfarin. CONCLUSIONS: Negative outcomes associated with warfarin therapy-recurrent VTE events and bleeding requiring hospitalization-were experienced by 10.7% and 5.8% of patients, respectively. These data suggest that negative outcomes may be more prevalent in usual community medical practice compared with rates observed in the controlled environment of the clinical trial or specialized anticoagulation clinic.

Zhan C, Battles J, Chiang YP, Hunt D. The validity of ICD-9-CM codes in identifying postoperative deep vein thrombosis and pulmonary embolism. *Jt Comm J Qual Patient Saf*. 2007; 33: 326-331.

BACKGROUND: Deep vein thrombosis and pulmonary embolism (DVT/PE) are common complications after surgery and are associated with substantial excess mortality and length of stay. International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes recorded in hospital claims have been used to identify and study DVT/PE, but the validity of this method is not well studied. METHODS: Identification of postoperative DVT/PE events were compared using ICD-9-CM codes and medical record abstraction in random samples of hospital discharges of Medicare beneficiaries in 2002-2004. RESULTS: Among 20,868 eligible surgical hospitalizations, 232 DVT cases and 95 PE cases were identified by ICD-9-CM codes; 108 DVT cases and 31 PE cases by medical record abstraction; 72 DVT cases and 23 PE cases by both methods. The resulting estimates of PPV of ICD9-CM coding were 31% (72/232 cases) for DVT, 24% (23/95) for PE, and 29% (90/308) for DVT/PE combined. The resulting sensitivity estimates were 67% (72/108 cases) for DVT, 74% (23/31) for PE, and 68% (90/133) for DVT/PE combined. DISCUSSION: ICD-9-CM codes in Medicare claims are sensitive but have limited predictive validity in identifying postoperative DVT/PE. Improvements in the validity are needed before the indicator can be used for safety performance assessment.

White RH, Romano PS, Zhou H, Rodrigo J, Bargar W. Incidence and time course of thromboembolic outcomes following total hip or knee arthroplasty. *Arch Intern Med.* 1998 Jul 27; 158(14): 1525-31.

BACKGROUND: Little is known about the incidence and time course of clinical thromboembolic events after total hip or knee arthroplasty, particularly after hospital discharge. METHODS: We used a linked hospital discharge database provided by the State of California to identify cases diagnosed as having deep vein thrombosis or pulmonary embolism within 3 months of unilateral total hip or knee arthroplasty. Also, we surveyed orthopedic surgeons to estimate the frequency of postoperative thromboprophylaxis during July 1991 through June 1993. Medical charts were audited to determine the accuracy of the coded records. RESULTS: Among 19,586 primary hip and 24,059 primary knee arthroplasties, the cumulative incidence of deep vein thrombosis or pulmonary embolism within 3 months of surgery was 556 (2.8%) after hip arthroplasty and 508 (2.1%) after knee arthroplasty. The diagnosis of thromboembolism was made after hospital discharge in 76% and 47% of the total hip and total knee arthroplasty cases, respectively (P<.001), with a median time of diagnosis of 17 days and 7 days after surgery, respectively (P<.001). Questionnaire results indicated that 95% of all cases received thromboprophylaxis and that the frequency, type, and duration of thromboprophylaxis were virtually identical after hip and knee arthroplasty. CONCLUSIONS: There is a difference in the temporal patterns of clinically symptomatic thromboembolic complications after total hip and total knee arthroplasty, suggesting differences in pathogenesis or natural history. The findings suggest that to further reduce thromboembolic outcomes, earlier, more intense prophylaxis may be needed for total knee arthroplasty, and more prolonged prophylaxis may be required after total hip arthroplasty.

Cushman M, Tsai AW, White RH, Heckbert SR, Rosamond WD, Enright P, Folsom AR. Deep vein thrombosis and pulmonary embolism in two cohorts: the longitudinal investigation of thromboembolism etiology. *Am J Med.* 2004 Jul 1; 117(1): 19-25.

PURPOSE: To determine the incidence of deep vein thrombosis and pulmonary embolism in two cohorts representing regions of the United States. METHODS: The sample comprised 21,680 participants of the Atherosclerosis Risk in Communities study and the Cardiovascular Health Study. Subjects were aged >/=45 years, resided in six communities, and were followed for 7.6 years. All hospitalizations were identified and thromboses were validated by chart review. RESULTS: The age-standardized incidence of first-time venous thromboembolism was 1.92 per 1000 person-years. Rates were higher in men than women, and increased with age in both sexes. There was no antecedent trauma, surgery, immobilization, or diagnosis of cancer for 48% (175/366) of events. The 28-day case-fatality rate was 11% (29/265) after a first venous thromboembolism and 25% (17/67) for cancer-associated thrombosis. The recurrence rate 2 years after a first venous thromboembolism was 7.7% per year (95% confidence interval [CI]: 4.5% to 10.9% per year). Cancer was the only factor independently associated with 28-day fatality (relative risk [RR] = 5.2; 95% CI: 1.4 to 19.9) or recurrent thrombosis (RR = 9.2; 95% CI: 2.0 to 41.7). CONCLUSION: The incidence of venous thromboembolism in this cohort of middle- and older-aged subjects was similar to that observed in more geographically homogeneous samples. Half of cases were idiopathic. Short-term mortality and 2-year recurrence rates were appreciable, especially among subjects with cancer. Based on this study we estimate that 187,000 cases of first-time venous thromboembolism are diagnosed yearly in the United States among those aged 45 years or older.

White RH, Brickner LA, Scannell KA. ICD-9-CM codes poorly indentified venous thromboembolism during pregnancy. *J Clin Epidemiol.* 2004 Sep; 57(9): 985-8.

OBJECTIVE: There is little data regarding the accuracy of pregnancy-specific ICD-9-CM codes used to identify patients with venous thromboembolism (VTE). STUDY DESIGN AND SETTING: We identified a large cohort of pregnant patients in whom there were one or more pregnancy-specific (600 codes) or standard ICD-9-CM codes (400 codes) for VTE. Charts of these cases were abstracted to determine the presence of objectively documented VTE. RESULTS: A total of 214 cases had a code for VTE either during pregnancy or the 6-week postpartum period; 82% had a pregnancy-specific code and 18% a standard code. Overall, 84 (39%, 95% CI=33-46%) had objectively documented VTE. A pregnancy-specific ICD-9-CM for VTE had a positive predictive value (PPV) of 54/174=31% (95% CI=24-38%), whereas standard VTE codes had a PPV of 30 of 38=80% (95% CI=63-99%). A PPV in the range of 95-100% could be attained using other criteria, at the expense of detecting only 28 to 45% of all VTE cases. CONCLUSIONS: Pregnancy-specific ICD-9-CM codes for VTE have low PPV. Other criteria must be applied to select cases with a high probability of having objectively documented VTE.

Spencer FA, Emery C, Joffe SW, Pacifico L, Lessard D, Reed G, Gore JM, Goldberg RJ. Incidence rates, clinical profile, and outcomes of patients with venous thromboembolism. The Worcester VTE study. *J Thromb Thrombolysis.* 2009 Nov; 28(4): 401-9.

While there have been advances in prophylaxis and management of venous thromboembolism (VTE), there are a dearth of data from the perspective of a community-wide study, on the epidemiology, management, and outcomes of patients with a first episode of deep vein thrombosis (DVT) or pulmonary embolism (PE). The purpose of this population-based observational study was to describe trends in the incidence rates, clinical profile, management, and outcomes for patients with VTE. The medical records of Worcester (MA) metropolitan area residents with ICD-9 codes consistent with possible VTE during 1999, 2001, and 2003 were independently validated and reviewed by trained abstractors. A total of 1,567 persons with first-time VTE were identified. Incidence rates (per 100,000) of VTE were stable between 1999 (109) and 2003 (117). A considerable proportion of patients treated for VTE had events of unclear clinical significance (e.g., isolated calf DVT, unconfirmed "possible" PE). By 2003, low-molecular-weight heparin was increasingly utilized as acute therapy and more than 25% of patients with VTE were managed as outpatients. Cumulative rates of recurrent VTE and major bleeding following initial VTE were high (approximately 16% and 12%, respectively, mean follow-up 1,216 days) and did not change significantly between 1999 and 2003. Our data suggest that while the incidence rates of VTE remain high, and outcomes suboptimal, there have been marked changes in its management. Whether these changes will result in future declines in VTE incidence and/or improved outcomes in the community setting will require further surveillance.

Anderson FA Jr, Wheeler HB, Goldberg RJ, Hosmer DW, Patwardhan NA, Jovanovic B, Forcier A, Dalen JE. A population-based perspective of the hospital incidence and case-fatality rates of deep vein thrombosis and pulmonary embolism. The Worcester DVT Study. *Arch Intern Med.* 1991 May; 151(5): 933-8.

A community-wide study was conducted in 16 short-stay hospitals in metropolitan Worcester, Mass, to examine the incidence and case-fatality rates of deep vein thrombosis and pulmonary embolism in patients hospitalized between July 1, 1985, and December 31, 1986. The average annual incidence of deep vein thrombosis alone was 48 per 100,000, while the incidence of pulmonary embolism with or without deep vein thrombosis was 23 per 100,000. The incidence rates of deep vein thrombosis and pulmonary embolism increased exponentially with age. The in-hospital case-fatality rate of venous thromboembolism was 12%. Among patients discharged from the hospital, the long-term case-fatality rates were 19%, 25%, and 30% at 1, 2, and 3 years after hospital

discharge. Extrapolation of the data from this population-based study suggests that there are approximately 170,000 new cases of clinically recognized venous thromboembolism in patients treated in short-stay hospitals in the United States each year, and 99,000 hospitalizations for recurrent disease. Because of the silent nature of this disease and the low rate of autopsy in the United States, the total incidence, prevalence, and mortality rates of venous thromboembolism remain elusive.

McCarthy EP, Iezzoni LI, Davis RB, Palmer RH, Cahalane M, Hamel MB, Mukamal K, Phillips RS, Davies DT Jr. Does clinical evidence support ICD-9-CM diagnosis coding of complications? *Med Care*. 2000 Aug; 38(8): 868-76.

BACKGROUND: Hospital discharge diagnoses, coded by use of the International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM), increasingly determine reimbursement and support quality monitoring. Prior studies of coding validity have investigated whether coding guidelines were met, not whether the clinical condition was actually present. OBJECTIVE: To determine whether clinical evidence in medical records confirms selected ICD-9-CM discharge diagnoses coded by hospitals. RESEARCH DESIGN AND SUBJECTS: Retrospective record review of 485 randomly sampled 1994 hospitalizations of elderly Medicare beneficiaries in Califomia and Connecticut. MAIN OUTCOME MEASURE: Proportion of patients with specified ICD-9-CM codes representing potential complications who had clinical evidence confirming the coded condition. RESULTS: Clinical evidence supported most postoperative acute myocardial infarction diagnoses, but fewer than 60% of other diagnoses had confirmatory clinical evidence by explicit clinical criteria; 30% of medical and 19% of surgical patients lacked objective confirmatory evidence in the medical record. Across 11 surgical and 2 medical complications, objective clinical criteria or physicians' notes supported the coded diagnosis in >90% of patients for 2 complications, 80% to 90% of patients for 4 complications, 70% to <80% of patients for 5 complications, and <70% for 2 complications. For some complications (postoperative pneumonia, aspiration pneumonia, and hemorrhage or hematoma), a large fraction of patients had only a physician's note reporting the complication. CONCLUSIONS: Our findings raise questions about whether the clinical conditions represented by ICD-9-CM codes used by the Complications Screening Program were in fact always present. These findings highlight concerns about the clinical validity of using ICD-9-CM codes for quality monitoring.

Weingart SN, Lezzoni LI, Davis RB, Palmer RH, Cahalane M, Hamel MB, Mukamal K, Phillips RS, Davies DT Jr, Banks NJ. Use of administrative data to find substandard care: validation of the complications screening program. *Med Care.* 2000 Aug; 38(8): 796-806.

OBJECTIVE: The use of administrative data to identify inpatient complications is technically feasible and inexpensive but unproven as a quality measure. Our objective was to validate whether a screening method that uses data from standard hospital discharge abstracts identifies complications of care and potential quality problems. DESIGN: This was a case-control study with structured implicit physician reviews. SETTING: Acute-care hospitals in California and Connecticut in 1994. PATIENTS: The study included 1,025 Medicare beneficiaries greater than 265 years of age. METHODS: Using administrative data, we stratified acute-care hospitals by observed-to-expected complication rates and randomly selected hospitals within each state. We randomly selected cases flagged with 1 of 17 surgical complications and 6 medical complications. We randomly selected controls from unflagged cases. MAIN OUTCOME MEASURE: Peer-review organization physicians' judgments about the presence of the flagged complication and potential quality-of-care problems. RESULTS: Physicians confirmed flagged complications in 68.4% of surgical and 27.2% of medical cases. They identified potential quality problems in 29.5% of flagged surgical and 15.7% of medical

cases but in only 2.1% of surgical and medical controls. The rate of physician-identified potential quality problems among flagged cases exceeded 25% in 9 surgical screens and 1 medical screen. Reviewers noted several potentially mitigating circumstances that affected their judgments about quality, including factors related to the patients' illness, the complexity of the case, and technical difficulties that clinicians encountered. CONCLUSIONS: For some types of complications, screening administrative data may offer an efficient approach for identifying potentially problematic cases for physician review. Understanding the basis for physicians' judgments about quality requires more investigation.

Lawthers AG, McCarthy EP, Davis RB, Peterson LE, Palmer RH, Iezzoni LI. Identification of in-hospital complications from claims data. Is it valid? *Med Care*. 2000 Aug; 38(8): 785-95.

OBJECTIVES: This study examined the validity of the Complications Screening Program (CSP) by testing whether (1) ICD-9-CM codes used to identify a complication are coded completely and accurately and (2) the CSP algorithm successfully separates conditions present on admission from those occurring in the hospital. METHODS: We compared diagnosis and procedure codes contained in the Medicare claim with codes abstracted from an independent re-review of more than 1,200 medical records from Connecticut and California. RESULTS: Eighty-nine percent of the surgical cases and 84% of the medical cases had their CSP trigger codes corroborated by re-review of the medical record. For 13% of the surgical cases and 58% of the medical cases, the condition represented by the code was judged to be present on admission rather than occurring in-hospital. The positive predictive value of the claim was greater than 80% for the surgical risk pool, suggesting the value of the CSP as a screening tool. CONCLUSIONS: The CSP has validity as a screen for most surgical complications but only for 1 medical complication. The CSP does not have addition of an indicator to the Medicare claim to capture the timing of secondary diagnoses would improve validity as a "stand-alone" tool to identify more than a few in-hospital surgery-related events. The validity of the CSP for identifying both surgical and medical in-hospital events.

Smith NL, Heckbert SR, Lemaitre RN, Reiner AP, Lumley T, Weiss NS, Larson EB, Rosendaal FR, Psaty BM. Esterified estrogens and conjugated equine estrogens and the risk of venous thrombosis*. JAMA.* 2004 Oct 6; 292(13): 1581-7.

CONTEXT: Clinical trial evidence indicates that estrogen therapy with or without progestins increases venous thrombotic risk. The findings from these trials, which used oral conjugated equine estrogens, may not be generalizable to other estrogen compounds. OBJECTIVE: To compare risk of venous thrombosis among esterified estrogen users, conjugated equine estrogen users, and nonusers. DESIGN, SETTING, AND PARTICIPANTS: This population-based, case-control study was conducted at a large health maintenance organization in Washington State. Cases were perimenopausal and postmenopausal women aged 30 to 89 years who sustained a first venous thrombosis between January 1995 and December 2001 and controls were matched on age, hypertension status, and calendar year. MAIN OUTCOME MEASURE: Risk of first venous thrombosis in relation to current use of esterified or conjugated equine estrogens, with or without concomitant progestin. Current use was defined as use at thrombotic event for cases and a comparable reference date for controls. RESULTS: Five hundred eighty-six incident venous thrombosis cases and 2268 controls were identified. Compared with women not currently using hormones, current users of esterified estrogen had no increase in venous thrombotic risk (odds ratio [OR], 0.92; 95% confidence interval [CI], 0.69-1.22). In contrast, women currently taking conjugated equine estrogen had an elevated risk (OR, 1.65; 95% CI, 1.24-2.19). When analyses were restricted to estrogen users, current users of conjugated equine estrogen had a higher risk than current users of esterified estrogen (OR,

1.78; 95% CI, 1.11-2.84). Among conjugated equine estrogen users, increasing daily dose was associated with increased risk (trend P value = .02). Among all estrogen users, concomitant progestin use was associated with increased risk compared with use of estrogen alone (OR, 1.60; 95% CI, 1.13-2.26). CONCLUSION: Our finding that conjugated equine estrogen but not esterified estrogen was associated with venous thrombotic risk needs to be replicated and may have implications for the choice of hormones in perimenopausal and postmenopausal women.

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

1. Studies Excluded Due to Poorly Defined Algorithms

Amin A, Stemkowski S, Lin J, Yang G. Appropriate thromboprophylaxis in hospitalized cancer patients. *Clin Adv Hematol Oncol*. 2008; 6: 910-920.

Amin A, Stemkowski S, Lin J, Yang G. Thromboprophylaxis rates in US medical centers: Success or failure? *J Thromb Haemost*. 2007; 5: 1610-1616.

Bernstein CN, Blanchard JF, Houston DS, Wajda A. The incidence of deep venous thrombosis and pulmonary embolism among patients with inflammatory bowel disease: A population-based cohort study. *Thromb Haemost*. 2001; 85: 430-434.

Ganz DA, Glynn RJ, Mogun H, Knight EL, Bohn RL, Avorn J. Adherence to guidelines for oral anticoagulation after venous thrombosis and pulmonary embolism. *J Gen Intern Med*. 2000; 15: 776-781.

Gomes JP, Shaheen WH, Truong SV, Brown EF, Beasley BW, Gajewski BJ. Incidence of venous thromboembolic events among nursing home residents. *J Gen Intern Med*. 2003; 18: 934-936.

Hershman DL, Buono DL, Malin J, McBride R, Tsai WY, Neugut AI. Patterns of use and risks associated with erythropoiesis-stimulating agents among medicare patients with cancer. *J Natl Cancer Inst*. 2009; 101: 1633-1641.

Kristinsson SY, Fears TR, Gridley G, et al. Deep vein thrombosis after monoclonal gammopathy of undetermined significance and multiple myeloma. *Blood*. 2008; 112: 3582-3586.

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Ray JG, Mamdani MM, Yeo EL. Antipsychotic and antidepressant drug use in the elderly and the risk of venous thromboembolism. *Thromb Haemost*. 2002; 88: 205-209.

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Stein PD, Hull RD, Ghali WA, et al. Tracking the uptake of evidence: Two decades of hospital practice trends for diagnosing deep vein thrombosis and pulmonary embolism. *Arch Intern Med*. 2003; 163: 1213-1219.

Tillman DJ, Charland SL, Witt DM. Effectiveness and economic impact associated with a program for outpatient management of acute deep vein thrombosis in a group model health maintenance organization. *Arch Intern Med*. 2000; 160: 2926-2932.

Van Walraven C, Oake N, Wells PS, Forster AJ. Burden of potentially avoidable anticoagulant-associated hemorrhagic and thromboembolic events in the elderly (ref art 575736). *Chest*. 2007; 131: 1508-1515.

Zhan C, Kaczmarek R, Loyo-Berrios N, Sangl J, Bright RA. Incidence and short-term outcomes of primary and revision hip replacement in the United States. *J Bone Joint Surg Am*. 2007; 89: 526-533.

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

Amin AN, Lin J, Lenhart G, Schulman KL. Clinical and economic outcomes in patients at risk of venous thromboembolism receiving appropriate enoxaparin or unfractionated heparin prophylaxis. *Thromb Haemost*. 2009; 102: 321-326.

Aujesky D, Long JA, Fine MJ, Ibrahim SA. African American race was associated with an increased risk of complications following venous thromboembolism. *J Clin Epidemiol*. 2007; 60: 410-416.

Aujesky D, Mor MK, Geng M, Stone RA, Fine MJ, Ibrahim SA. Predictors of early hospital readmission after acute pulmonary embolism. *Arch Intern Med*. 2009; 169: 287-293.

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Cole JA, Norman H, Doherty M, Walker AM. Venous thromboembolism, myocardial infarction, and stroke among transdermal contraceptive system users. *Obstet Gynecol*. 2007; 109: 339-346.

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Felcher AH, Mularski RA, Mosen DM, Kimes TM, DeLoughery TG, Laxson SE. Incidence and risk factors for venous thromboembolic disease in podiatric surgery. *Chest*. 2009; 135: 917-922.

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C. APPENDIX C: LIST AND DEFINITIONS OF ICD-9-CM, ICD-9 PROCEDURE, AND CPT CODES INCLUDED IN ALGORITHMS

Type of Code	Code	Description
ICD9-CM	415.1	Pulmonary Embolism and Infarction
ICD9-CM	415.11	Iatrogenic pulmonary embolism and infarction
ICD9-CM	415.19	Other Pulmonary Embolism and Infarction
ICD9-CM	451	Phlebitis and thrombophlebitis
ICD9-CM	451.1	Phlebitis and thrombophlebitis of deep veins of lower extremities
ICD9-CM	451.11	Phlebitis and thrombophlebitis of femoral vein (deep) (superficial)
ICD9-CM	451.19	Phlebitis and thrombophlebitis of other
ICD9-CM	451.2	Phlebitis and thrombophlebitis of lower extremities unspecified
ICD9-CM	451.8	Phlebitis and thrombophlebitis of other sites
ICD9-CM	451.81	Phlebitis and thrombophlebitis of Iliac vein
ICD9-CM	451.82	Phlebitis and thrombophlebitis of superficial veins of upper extremities
ICD9-CM	451.83	Phlebitis and thrombophlebitis of deep veins of upper extremities
ICD9-CM	451.84	Phlebitis and thrombophlebitis of upper extremities unspecified
ICD9-CM	451.89	Phlebitis and thrombophlebitis of other sites
ICD9-CM	451.9	Phlebitis and thrombophlebitis of unspecified site
ICD9-CM	453	Other venous embolism and thrombosis
ICD9-CM	453.1	Thrombophlebitis migrans
ICD9-CM	453.2	Embolism and thrombosis of vena cava
ICD9-CM	453.4	Venous embolism and thrombosis of deep vessels of lower extremity
ICD9-CM	453.40	Venous embolism and thrombosis of unspecified deep vessels of lower extremity
ICD9-CM	453.41	Venous embolism and thrombosis of deep vessels of proximal lower extremity
ICD9-CM	453.42	Venous embolism and thrombosis of deep vessels of distal lower extremity
ICD9-CM	453.8	Embolism and thrombosis of other specified veins
ICD9-CM	453.9	Venous embolism and thrombosis of unspecified site
ICD9-CM	671.xx	Venous complications in pregnancy and puerperium
ICD9-CM	671.3 (0,1,3)	Deep phlebothrombosis antepartum

ICD9-CM	671.4 (0,2,4)	Deep phlebothrombosis postpartum
ICD9-CM	671.9 (0-4)	Unspecified venous complication in pregnancy and the puerperium
ICD9-CM	673.2 (0-4)	Obstetrical blood clot embolism
ICD9-CM	673.8 (0-4)	Other obstetrical pulmonary embolism
ICD9-CM	996.7	Other complications of internal (biologic)(synthetic) prosthetic device implant and graft
ICD9-CM	996.73	Complication because of renal dialysis device implant and graft
ICD9-CM	996.74	Other complications due to vascular device implant and graft
ICD9-CM	997.2	Peripheral vascular complications not elsewhere classified
ICD9-CM	999.2	Other vascular complications of medical care not elsewhere specified
ICD9 Procedure Code	387	Interruption of the vena cava
CPT	33910	Pulmonary artery embolectomy; with cardiopulmonary bypass
CPT	33915	Pulmonary artery embolectomy; without cardiopulmonary bypass