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Assessment of Algorithms to Identify Patients with Thrombophilia following Venous Thromboembolism

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Abstract

Introduction—Routine testing for thrombophilia following venous thromboembolism (VTE) is controversial. The use of large datasets to study the clinical impact of thrombophilia testing on patterns of care and patient outcomes may enable more efficient analysis of this practice in a wide range of settings. We set out to examine how accurately algorithms using International

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Classification of Diseases 9th Revision (ICD-9) codes and/or pharmacy data reflect laboratory-confirmed thrombophilia diagnoses.

Materials and Methods—A random sample of adult Kaiser Permanente Colorado patients diagnosed with unprovoked VTE between 1/2004 and 12/2010 underwent medical record abstraction of thrombophilia test results. Algorithms using "ICD-9" (positive if a thrombophilia ICD-9 code was present), "Extended anticoagulation (AC)" (positive if AC therapy duration was >6 months), and " ICD-9 & Extended AC" (positive for both) criteria to identify possible thrombophilia cases were tested. Using positive thrombophilia laboratory results as the gold standard, the sensitivity, specificity, positive predictive value (PPV), and negative predictive value of each algorithm were calculated, along with 95% confidence intervals (CIs).

Results—In our cohort of 636 patients, sensitivities were low (<50%) for each algorithm. "ICD-9" yielded the highest PPV (41.5%, 95% CI 26.3–57.9%) and a high specificity (95.9%, 95% CI 94.0–97.4%). "Extended AC" had the highest sensitivity but lowest specificity, and "ICD-9 & Extended AC" had the highest specificity, but the lowest sensitivity.

Conclusions—ICD-9 codes for thrombophilia are highly specific for laboratory-confirmed cases, but all algorithms had low sensitivities. Further development of methods to identify thrombophilia patients in large datasets is warranted.

Keywords

Thrombophilia; venous thromboembolism; dataset; algorithms; sensitivity; specificity

Introduction

Routine testing for thrombophilia following venous thromboembolism (VTE) is controversial [1, 2]. Randomized clinical trials or observational studies to-date have not demonstrated a reduced risk of recurrent VTE associated with thrombophilia testing [3, 4]. Current guidelines recommend thrombophilia testing only if the results are likely to influence treatment decisions and usually only in the setting of unprovoked VTE [5, 6].

Analysis of thrombophilia testing in large VTE datasets may enable evaluation of quality of care and clarification of issues surrounding thrombophilia testing (e.g., clinical utility, impact on outcomes). The only large, prospective, observational VTE cohort studies evaluating thrombophilia testing come from the RIETE initiative [7–13], which utilized detailed inpatient and outpatient medical record abstraction not easily replicated in other settings. Utilization of administrative datasets to assess the impact of thrombophilia offers the ability to study real-world patterns of care and patient outcomes in large numbers. Positive predictive values (PPVs) of approximately 95% have been achieved using International Classification of Diseases 9th Revision (ICD-9) codes to identify patients with VTE in a large dataset [14]. However, ICD-9 codes have not been evaluated similarly to identify patients with thrombophilia. The goal of this study was to evaluate whether patients with unprovoked VTE and laboratory-confirmed thrombophilia can be efficiently identified in a large dataset with high sensitivity and specificity (>90%) using algorithms based on ICD-9 codes and/or electronic pharmacy records.

Materials and Methods

Patients and Study Period

Kaiser Permanente Colorado (KPCO) patients were identified as part of the Cardiovascular Research Network Venous Thromboembolism (CVRN VTE) Study. The CVRN VTE Study identified all patients ≥ 21 years of age with an ICD-9 primary or secondary diagnosis code of VTE in the time period between January 1, 2004 and December 31, 2010 who had at least 180 consecutive days of health plan membership prior to the event (index VTE). Index VTE events were categorized as pulmonary embolism (PE), upper or lower extremity deep vein thrombosis (DVT), or other venous thrombosis (codes available upon request). Both inpatient and outpatient events were included. For this study, patients with atrial fibrillation, prior VTE or warfarin prescription <3 years prior to index VTE event, and recurrent VTE during the study period were excluded to ensure selection of patients who received anticoagulation (AC) for their initial VTE event. Patients with <1 month of continuous health plan enrollment and prescription drug benefit after index VTE were also excluded, as complete data regarding patients' AC treatment for their VTE event was desired. Finally, patients with provoked VTE (active cancer, surgery <1 month prior to index VTE event, or pregnancy <1 year prior to index VTE event) were excluded as these patients were less likely to undergo thrombophilia testing. We included patients who had non-surgical trauma in the month prior to their VTE diagnosis based on the previous finding that this risk factor independently predicted having had a positive thrombophilia test result (Meyer—submitted). Patients were followed for up to 1 year after their index VTE. This study was reviewed and all aspects approved by the KPCO Institutional Review Board.

Data Collection

A random sample of KPCO CVRN VTE patients underwent medical record review using a structured data collection form to determine whether the events were valid, acute VTE events. Thrombophilia laboratory test results were extracted from KPCO's electronic laboratory database and confirmed with manual chart review as necessary. Tests included factor V Leiden, prothrombin gene mutation, antithrombin activity, protein C activity, protein S activity, and antiphospholipid antibody syndrome (APS) tests (lupus anticoagulant [hexagonal phase and Russell's viper venom time], Cardiolipin immunoglobulin [Ig]G, and β-2 glycoprotein IgG). Testing for APS was considered positive if there were two positive APS results separated by at least 6 weeks. Patients were considered "positive" for laboratory-confirmed thrombophilia if ≥1 test was positive, "negative" if no tests were positive, and "not tested" if none of the abstracted thrombophilia laboratory tests were performed. Because guidelines recommend that providers who do not suspect thrombophilia should not order thrombophilia testing for their patients [15], we chose to combine patients who tested negative for thrombophilia with those who did not undergo testing ("no thrombophilia") for our analyses. Duration of AC was determined from electronic pharmacy records.

Thrombophilia Identification Algorithms

The study cohort was subjected to "ICD-9" (positive: ≥1 ICD-9 code for primary [289.81] or secondary hypercoagulable state [289.82], negative otherwise) and "extended AC" criteria

(positive: received AC >6 months duration after index VTE, negative otherwise) individually and in combination ("ICD-9 & extended AC") to identify possible thrombophilia cases (Figure 1).

Statistical Analyses

Using positive thrombophilia laboratory test results as the gold standard, sensitivities, specificities, PPVs, and negative predictive values (NPVs) of ICD-9, extended AC, and ICD-9 & extended AC identification strategies were calculated along with binomial proportion 95% confidence intervals (CIs). Patient characteristics were analyzed overall and by thrombophilia test result and testing statuses. Differences in proportions and means were assessed between groups using the chi-square or Fisher's exact test, as appropriate, or independent sample t-test, respectively. Analyses were performed with SAS 9.2 (SAS Institute Inc., Cary, NC).

Results

Patient Characteristics

There were 1314 patients with confirmed index VTE. We excluded 678 patients who had recurrent VTE, atrial fibrillation, cancer, surgery, pregnancy, or <1 month enrollment after VTE during the study period, leaving 636 patients to be included in the analysis (Figure 2). Of these patients, 206 (32.4%) were tested for thrombophilia; 48 (7.5%) had at least one positive thrombophilia test result, 158 (24.8%) tested negative, and 430 (67.6%) were not tested (588 [92.5%] patients were considered to have "no thrombophilia"; Table 1).

The overall cohort had a mean (standard deviation) age of 62.7 (17.0) years, 49.5% were male, and 55.2% and 54.4% had a lower extremity DVT and PE, respectively. After applying the various algorithms, 6.5% percent had at least one ICD-9 thrombophilia code while 47.6% received extended AC following VTE. Seventeen of 48 (35.4%) thrombophilia-positive patients versus 15 of 158 thrombophilia-negative (9.5%) and 9 of 430 (2.1%) not tested patients had at least one ICD-9 thrombophilia code ($p<0.001$). The percentage of patients receiving extended AC was slightly less than 50%, regardless of their thrombophilia test status or results (Table 1).

There were statistically significant differences in the mean age ($p=0.001$), proportion with family history of VTE ($p=0.001$), proportion with at least one thrombophilia test ordered ($p<0.001$), and proportion with presence of at least one ICD-9 thrombophilia code ($p<0.001$) between the thrombophilia-positive and no thrombophilia groups. Patients who received thrombophilia testing were younger, had a family history of VTE, were taking hormone therapy at the time of index VTE event, and had at least one ICD-9 thrombophilia code (all $p<0.001$) compared to non-tested patients (Table 1). Such differences were also seen between patients who tested negative versus those who were not tested (Table 1).

Algorithm Performance Results

Negative predictive values were high but sensitivities and PPVs were low in all three algorithms. Applying thrombophilia ICD-9 codes only yielded the numerically highest PPV

(41.5%, 95% CI 26.3–57.9%) and a high specificity (95.9%, 95% CI 94.0–97.4%). The extended AC algorithm had the numerically highest sensitivity (45.8%, 95% CI 31.4–60.8%) but the lowest specificity (52.2%, 95% CI 48.1–56.3%). The ICD-9 & extended AC algorithm had the numerically highest specificity (97.1%, 95% CI 95.4–98.3%) and a high NPV (93.6%, 95% CI 91.4–95.4%), but the lowest sensitivity (18.8%, 95% CI 9.0–32.6%) (Table 2).

Discussion

In this study of 636 patients with unprovoked VTE, approximately one-third of the patients were tested for thrombophilia. The high specificity of our ICD-9 algorithm suggests that the presence of thrombophilia ICD-9 codes can be used to rule in patients with laboratory-confirmed thrombophilia. Unfortunately, all algorithms had limited ability to capture the entire VTE population who underwent thrombophilia testing based on the observed low sensitivities and PPVs.

That there was no significant difference in proportions of patients who received extended AC after VTE between the thrombophilia-positive and no thrombophilia groups could suggest that thrombophilia test results were not associated with differences in treatment decisions regarding duration of AC, though we were not able to obtain data on all confounding factors. Because so few patients in our cohort had laboratory-confirmed thrombophilia, we were unable to distinguish whether any one type of thrombophilia was associated with extended AC duration following an unprovoked VTE event. Providers likely choose extended AC for patients with unprovoked VTE because of the associated higher risk for VTE recurrence. Therefore, it appears that the decision to extend the duration of AC is not related to the presence or absence of a positive thrombophilia result and may instead be based on clinical grounds as guidelines recommend [16].

The low sensitivities of all three algorithms support that medical record/laboratory record abstraction captures more thrombophilia-positive patients than the tested algorithms. On the other hand, the high NPVs indicate that providers are not assigning thrombophilia ICD-9 codes or continuing AC beyond six months if the patient does not have laboratory-confirmed thrombophilia. It may be that providers are relying on the presence of a laboratory-confirmed diagnosis of thrombophilia to label their patient as such, although just over a third of thrombophilia-positive patients had a corresponding ICD-9 code for thrombophilia. Of note, our algorithm results are comparable to other studies investigating the use of administrative data to identify patients with related conditions, such as heart failure [17] and obesity [18].

There are several limitations to this study. Laboratory evidence of APS was considered to be met if there were two positive APS test results separated by at least six weeks, according to the original Sapporo criteria published in 1999 [19], instead of by at least 12 weeks, as published in 2006 in the revised Sapporo criteria [20]. The original criteria were used because a significant proportion of the study population was diagnosed with unprovoked VTE from 2004 to 2006, prior to the dissemination of the revised Sapporo criteria. Also, given that we had so few patients who met the diagnostic laboratory criteria of APS, our

overall results are unlikely to be affected significantly by the selection of this definition. IgM results for the Cardiolipin and β-2 glycoprotein tests were not included, as these were not required by the original Sapporo criteria. Some patients may have been incorrectly determined as thrombophilia-negative, although again, this likely impacts a very small number of patients in our study. Also, some patients did not undergo testing of all thrombophilia tests. Therefore, the proportion of unprovoked VTE patients who have a positive thrombophilia result is likely to be higher than what we are able to report, as thrombophilia testing by clinicians is oftentimes incomplete. We combined patients who were not tested with thrombophilia-negative patients. Although these two groups differed in baseline characteristics similar to how tested versus not tested patients differed, there is strong clinical rationale to group thrombophilia-negative and not tested patients together as neither can be considered to have thrombophilia based on the gold standard of positive test results. In addition, guidelines recommend that providers who do not suspect thrombophilia should not order thrombophilia testing for such patients [15], which further support this grouping.

Conclusions

This is the first study, to our knowledge, to evaluate if algorithms using ICD-9 codes and/or pharmacy claims data can accurately identify laboratory-confirmed cases of thrombophilia in a large cohort of unprovoked VTE patients. We found that thrombophilia test results were not associated with differences in the proportion of patients who received extended AC. There appeared to be a lack of concordance between thrombophilia laboratory test result and ICD-9 codes, but ICD-9 codes for primary and secondary hypercoagulable state accurately identified individuals who had positive thrombophilia test results. In our thrombophilia identification algorithms, the low sensitivities and PPVs of algorithms using ICD-9 codes and/or pharmacy claims data suggest that medical record abstraction is still required to capture all cases of laboratory-confirmed thrombophilia. If the use of administrative data to investigate the implications of thrombophilia testing in large VTE cohorts is to be optimized, further development of methods to identify thrombophilia status in large datasets is warranted.

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Abbreviations

AC anticoagulation

APS antiphospholipid antibody syndrome

CIs confidence intervals

CVRN VTE Cardiovascular Research Network Venous Thromboembolism

DVT	deep vein thrombosis
ICD-9	International Classification of Diseases 9th Revision
Ig	immunoglobulin
KPCO	Kaiser Permanente Colorado
NPV(s)	negative predictive value(s)
PE	pulmonary embolism
PPV(s)	positive predictive value(s)
RIETE	Registro Informatizado de Enfermedad TromboEmbolica
VTE	venous thromboembolism

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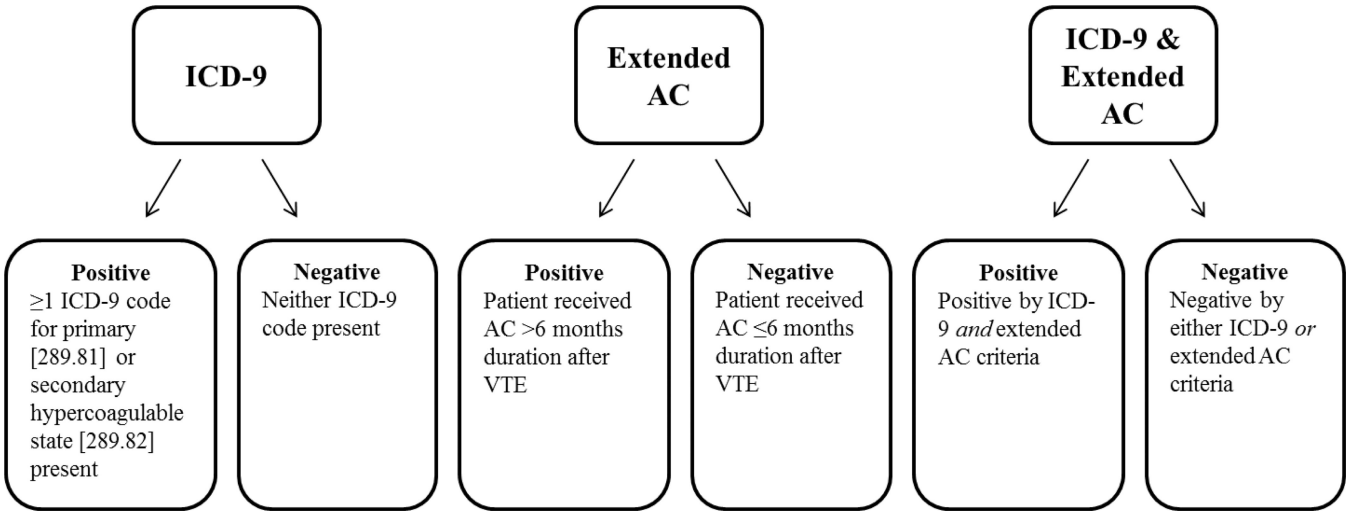

Figure 1. Criteria for Thrombophilia Status by Thrombophilia Identification Algorithms

Abbreviations: AC, anticoagulation; ICD-9, International Classification of Diseases 9th Revision; VTE, venous thromboembolism.

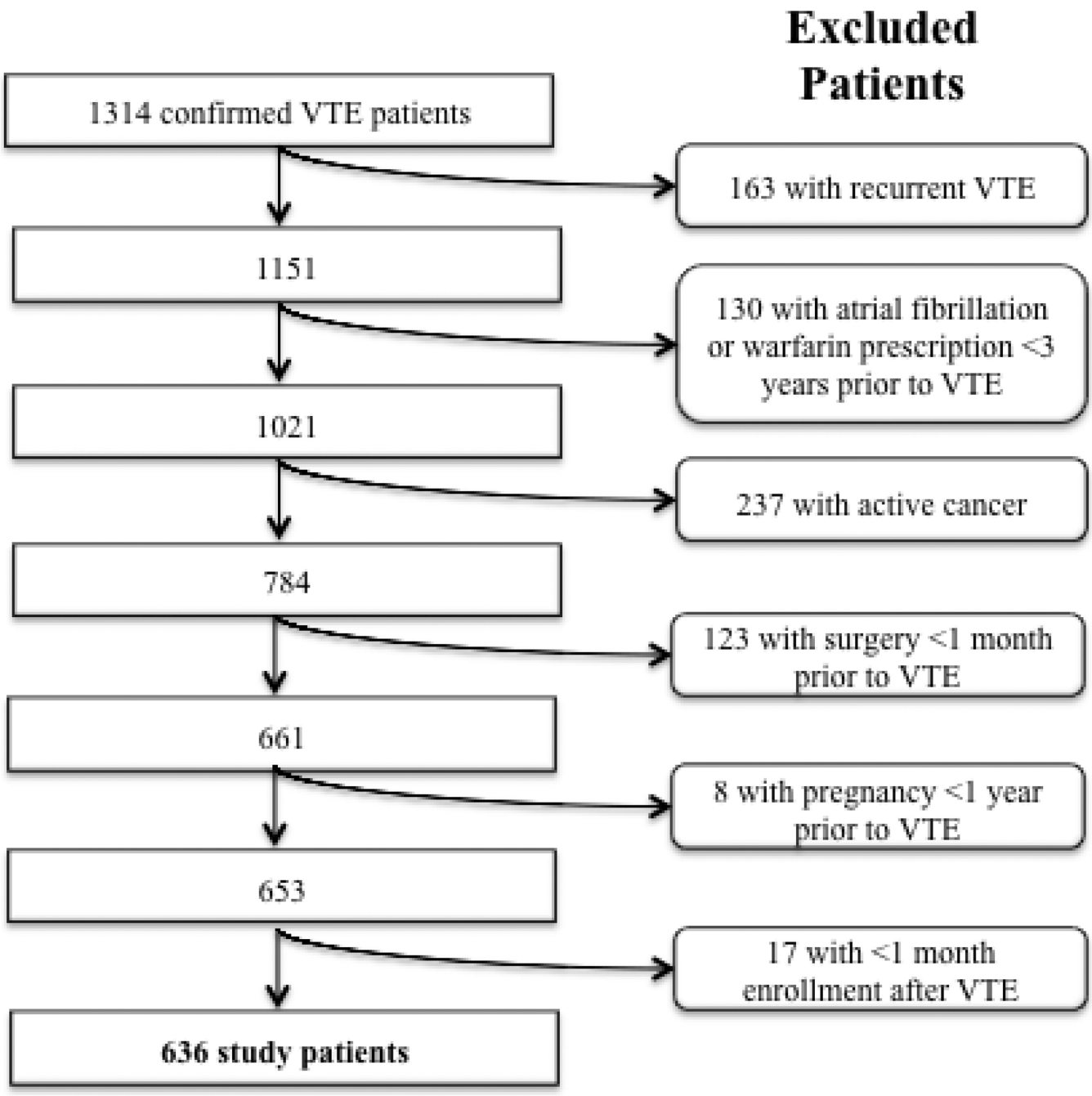

Figure 2. Analytic Cohort Selection
Abbreviations: VTE, venous thromboembolism.

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Table 1

Patient Characteristics Overall and by Thrombophilia and Testing Statuses

Characteristic	Overall Sample (n=636)	Tested		Not Tested	Tested (Positive or Negative) (n=206)	"No Thrombophilia" (Negative or Not Tested) (n=588)	*p*-value (Tested vs. Not Tested)	*p*-value (Pos vs. "No thrombo-philia)	*p*-value (Neg vs. Not Tested)
		Thrombophilia Result							
		Positive Thrombophilia Test (n=48)	Negative Thrombophilia Test (n=158)	Not Tested (n=430)					
Mean Age[a] (SD)	62.7 (17.0)	55.1 (15.0)	54.0 (16.2)	66.6 (16.1)	54.3 (15.9)	63.3 (17.0)	***<0.001***	***0.001***	***<0.001***
Age < 50 years[a]	163, 25.6%	15, 31.3%	64, 40.5%	84, 19.5%	79, 38.3%	148, 25.2%	***<0.001***	0.354	***<0.001***
Male (n, %)	315, 49.5%	28, 58.3%	80, 50.6%	207, 48.1%	108, 52.4%	287, 48.8%	0.237	0.205	0.471
Index VTE Type[b] (n, %)									
DVT	351, 55.2%	31, 64.6%	75, 47.5%	245, 57.0%	106, 51.5%	320, 54.4%	0.261	0.174	0.063
PE	346, 54.4%	23, 47.9%	99, 62.7%	224, 52.1%	122, 59.2%	323, 54.9%	0.060	0.348	***0.013***
Other	6, 0.9%	1, 2.1%	3, 1.9%	3, 0.7%	3, 1.5%	5, 0.9%	0.392	0.376	0.612
Thromboembolic Risk Factors (n, %)									
Family History of VTE	45, 7.1%	9, 18.8%	23, 14.6%	13, 3.0%	32, 15.5%	36, 6.1%	***<0.001***	***0.001***	***<0.001***
Heart Failure	36, 5.7%	1, 2.1%	1, 0.6%	34, 7.9%	2, 1.0%	35, 6.0%	***<0.001***	0.509	***<0.001***
Hormone Therapy[a]	74, 11.6%	8, 16.7%	29, 18.4%	37, 8.6%	37, 18.0%	66, 11.2%	***<0.001***	0.258	***<0.001***
Lung Disease	64, 10.1%	3, 6.3%	7, 4.4%	54, 12.6%	10, 4.9%	61, 10.4%	***0.003***	0.361	***0.005***
≥1 Thrombophilia Test[c]	206, 32.4%	48, 100%	0, 0%	0, 0.0%	206, 100%	158, 26.9%	n/a	***<0.001***	n/a
≥1 Positive Thrombophilia Test[c]	48, 7.6%	48, 100%	0, 0%	0, 0.0%	48, 23.3%	0, 0.0%	n/a	n/a	n/a
≥1 Thrombophilia Diagnosis Code[c]	41, 6.5%	17, 35.4%	15, 9.5%	9, 2.1%	32, 15.5%	24, 4.1%	***<0.001***	***<0.001***	***<0.001***
>6 months of AC	303, 47.6%	22, 45.8%	78, 49.4%	203, 47.2%	100, 48.5%	281, 47.8%	0.633	0.794	0.519

Abbreviations: AC, anticoagulation; DVT, deep vein thrombosis; PE, pulmonary embolism; n/a, not applicable; SD, standard deviation; VTE, venous thromboembolism.

[a] As of date of index VTE.

[b] A patient can have had more than one type of VTE.

[c] During the 365 days following index VTE.

Table 2

Algorithm Performance Results and Statistics[a]

	Sensitivity % (95% CI)	PPV % (95% CI)	Specificity % (95% CI)	NPV % (95% CI)
ICD-9	35.4 (22.2–50.5)	41.5 (26.3–57.9)	95.9 (94.0–97.4)	94.8 (92.7–96.4)
Extended AC	45.8 (31.4–60.8)	7.3 (4.6–10.8)	52.2 (48.1–56.3)	92.2 (88.8–94.8)
ICD-9 & Extended AC	18.8 (9.0–32.6)	34.6 (17.2–55.7)	97.1 (95.4–98.3)	93.6 (91.4–95.4)

Abbreviations: AC, anticoagulation; CI, confidence interval; ICD-9, International Classification of Diseases 9th Revision; NPV, negative predictive value; PPV, positive predictive value.

[a]Patients with a positive thrombophilia laboratory test result were considered truly positive for thrombophilia. Patients with a negative thrombophilia test result and patients who did not undergo thrombophilia testing were considered truly negative for thrombophilia.