Thrombosis Research xxx (2015) xxx–xxx

Contents lists available at ScienceDirect

Thrombosis Research

journal homepage: www.elsevier.com/locate/thromres

Full Length Article

Assessment of algorithms to identify patients with thrombophilia following venous thromboembolism☆

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ARTICLE INFO

Article history:
Received 31 October 2014
Received in revised form 5 November 2015
Accepted 6 November 2015
Available online xxxx

Keywords:
Thrombophilia
Venous thromboembolism
Dataset
Algorithms
Sensitivity
Specificity

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 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 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.

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1. 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

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.

☆ Presented as a poster at the 56th American Society of Hematology Annual Meeting and Exposition, San Francisco, CA, December 6–9, 2014.

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http://dx.doi.org/10.1016/j.thromres.2015.11.009
0049-3848/© 2015 Published by Elsevier Ltd.

Please cite this article as: T. Delate, et al., Assessment of algorithms to identify patients with thrombophilia following venous thromboembolism, Thromb Res (2015), http://dx.doi.org/10.1016/j.thromres.2015.11.009

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.

2. Materials and methods

2.1. 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 [15]. 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.

2.2. Data collection

A random sample of 2500 KPCO CVRN VTE patients underwent medical record review using a structured data collection form to determine whether the events were valid, acute VTE events based on confirmed imaging results (i.e., contrast venography or ultrasonography to diagnose DVT or ventilation–perfusion scanning, pulmonary angiography, or helical computed tomography to diagnose PE or other VTE, such as portal or mesenteric vein thrombosis). Of note, superficial venous thromboses were excluded for the purposes of this study. Details regarding the clinical data that were abstracted from KPCO's electronic medical record to support the selection of the study population and conduct of the analyses have been previously described [15]. 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 [16], 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.

2.3. 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 (Fig. 1).

2.4. Statistical analyses

Using positive thrombophilia laboratory test results as the gold standard, sensitivities, specificities, PPVs, and negative predictive values

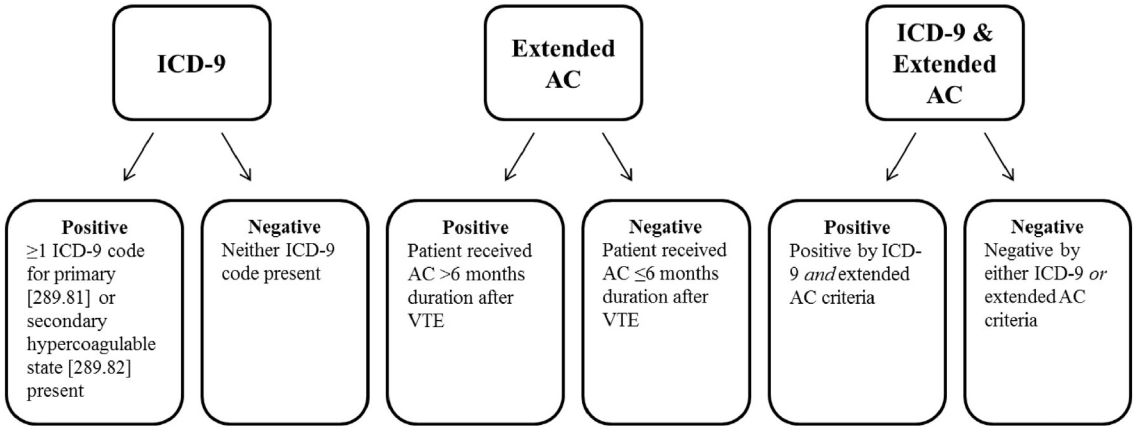

Fig. 1. Criteria for thrombophilia status by thrombophilia identification algorithms. Abbreviations: AC, anticoagulation; ICD-9, International Classification of Diseases 9th Revision; and VTE, venous thromboembolism.

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