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Discretionary Thrombophilia Test Acquisition and Outcomes in Patients With Venous Thromboembolism in a Real-World Clinical Setting

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Background—The value of thrombophilia test acquisition in improving risk prediction beyond clinical presentation remains unknown. We investigated the effect of thrombophilia test acquisition on venous thromboembolism (VTE) outcomes.

Methods and Results—We performed a retrospective cohort study of adult patients over a 15-year period (September 2001 and May 2016) with first diagnosis of VTE in a single academic medical center. Participants were identified by *International Classification of Diseases, Ninth Revision* (*ICD-9*), *Current Procedural Terminology* (*CPT*) codes and medication history. Participants with thrombophilia testing were matched to control participants without thrombophilia testing using a propensity model. Primary outcomes included recurrent VTE, anticoagulant use 12 months after the index VTE event, bleeding-related hospitalization, and death. From 3590 unique patients who met the inclusion criteria, 747 participants with VTE who underwent thrombophilia testing were matched to a control participant without testing. Tested participants were more likely to have a recurrent event (46.1% versus 28.5%; *P*<0.001) and an anticoagulant prescription 12 months from the index event (53.9% versus 37.1%; *P*<0.001) but had no significant difference in bleeding-related hospitalization (11.4% versus 11.8%; *P*=0.81) compared with untested participants. An abnormal thrombophilia test result, per se, did not predict recurrent VTE (47.8% versus 44.1%; *P*=0.13), longer duration anticoagulation (53.2% versus 54.8%; *P*=0.51), bleeding (11.5% versus 11.3%; *P*=0.70), or mortality (12.2% versus 16.1%; *P*=0.18) compared with participants who had normal test results.

Conclusions—The decision to perform thrombophilia testing, but not the test result, is associated with a high risk of recurrent VTE despite a greater likelihood of long-duration anticoagulation. (***J Am Heart Assoc***. 2019;8:e013395. DOI: 10.1161/JAHA.119. 013395.)

Key Words: deep vein thrombosis • recurrent event • thrombophilia testing

Venous thromboembolism (VTE), including deep-vein thrombosis and pulmonary embolism, affects ≈300 000 to 600 000 individuals annually in the United States.[1] Patients with VTE are at increased risk for future thromboembolism, with recurrence rates as high as 30% at 10 years.[2,3] Anticoagulants serve as the backbone of VTE therapy to prevent thromboembolism progression and recurrence.[4–7] According to current guidelines, the duration of anticoagulant therapy depends on the identification of a provoking factor. VTE events in patients without instigating factors are labeled as *unprovoked*, and prolonged treatment (eg, >6 months) is suggested.[5] The failure to identify a VTE precipitant may indicate the possibility of an underlying predisposition to thrombosis, also known as *thrombophilia*.

Thrombophilia testing is used to identify factors that contribute to a VTE event, to refine the estimated risk of recurrent VTE, and to guide decision-making regarding the duration of anticoagulant therapy in patients without an instigating factor.[8,9] Currently, there is no consensus concerning the value of thrombophilia testing in VTE, and its use

Clinical Perspective

What Is New?

- Discretionary testing for thrombophilia was associated with a higher risk of recurrent venous thromboembolism, longer duration of anticoagulation, lower risk of death, and no difference in bleeding-related hospitalization compared with matched untested participants, but the results of testing did not identify patients at increased risk of clinical or treatment-related outcomes.
- The presence of cancer exerts an outsize effect on the risk of death after venous thromboembolism.

What Are the Clinical Implications?

- The decision to perform thrombophilia testing, rather than the test result, is associated with a high risk for recurrent venous thromboembolism despite a greater likelihood of long-duration anticoagulation.
- The results of discretionary testing do not provide additional prognostic information when performed in inappropriate settings.

in clinical practice is highly variable. Indeed, thrombophilia testing is commonly obtained in the absence of an indication, ordered in the setting of anticoagulation, and frequently not repeated for confirmation.[10] Consequently, the usefulness of discretionary thrombophilia testing in current clinical practice to predict recurrence and direct treatment beyond clinical presentation remains unknown.[10–16]

Accordingly, we performed a retrospective analysis of all patients diagnosed with VTE during a 15-year period in a tertiary care medical center to investigate the effect of discretionary testing for thrombophilia in an unrestricted environment. We did not study the test characteristics of any individual thrombophilia test. We hypothesized that unrestricted thrombophilia testing would not be associated with improved clinical outcomes for tested participants compared with matched control participants who did not undergo thrombophilia testing.

Methods

Anonymized data that support the findings of this study are available from the corresponding author on reasonable request.

Study Design Statement and Setting

We performed a retrospective cohort study of adult patients with a first diagnosis of VTE at Vanderbilt University Medical Center (VUMC) between September 2001 and May 2016. This study was approved by the institutional review board of Vanderbilt University and exempted from the requirement for informed consent.

Participants

Patients were identified from electronic health records using combinations of *International Classification of Diseases, Ninth Revision* (*ICD-9*) codes for deep-vein thrombosis and acute pulmonary embolism[17]; *Current Procedural Terminology* (*CPT*) codes for relevant diagnostic imaging; and anticoagulant use (Table S1). Inclusion in the final cohort required all of the following criteria: qualifying *ICD-9* diagnosis code, qualifying *CPT* code, and anticoagulant use between 1 and 12 months after the date of the initial diagnosis code. The delayed timing of the anticoagulant use requirement was to avoid inclusion of patients who received prophylactic anticoagulants during hospitalization without evidence of a VTE by imaging study. Inclusion criteria were validated by physician review of a sample of records, with >90% of patients meeting the aforementioned criteria having documentation of VTE in the electronic health record. From those included, tested participants were defined as those who had undergone some or all of the following testing for thrombophilia: lupus anticoagulant, anticardiolipin antibodies, β2-glycoprotein antibodies, antithrombin deficiency, factor V Leiden, and protein C and S activity. Based on local laboratory practices, these assays are grouped as a thrombophilia panel, although components may be ordered individually. The prothrombin 20210 gene polymorphism is not routinely included in the local thrombophilia testing panel and was excluded from this analysis. There was no maximum or minimum time limit between VTE event and subsequent testing, which reflects real-world practice. Untested control participants were defined as patients with VTE who did not undergo any of the aforementioned testing. Tested and untested participants were matched in a 1:1 manner using propensity score matching to reduce risk of bias caused by confounding variables that may have disposed participants to having been tested for thrombophilia.[18]

Variables

Recurrent events were defined by presence of a qualifying *ICD-9* diagnosis code and a qualifying *CPT* code at least 1 month after the initial VTE event. This 1-month time period and the requirement for a new imaging study were implemented to reduce the chance of incorrectly attributing codes referring to the index VTE event as recurrent events. Long-term anticoagulation use was defined as use of warfarin, dabigatran, apixaban, rivaroxaban, dalteparin, or enoxaparin for at least 12 months following the index VTE event. The 12-month period was chosen because guidelines define a

standard treatment period as 3 to 6 months.[5,19] Bleeding events were defined using an adaptation of a previously validated algorithm for bleeding-related hospitalization.[20] Provoked events were defined as the presence of ≥1 of the following conditions: hospitalization (medical or surgical) within 90 days of VTE, leg trauma within 90 days of VTE, preexisting thrombophilia diagnosis preceding the index event, and malignancy.

Data Collection

Data were obtained from the Research Derivative, a clinical research database derived from the VUMC electronic health records. The Research Derivative contains patient data generated during clinical care including demographics, billing and procedure codes, clinical notes and documentation (eg, problem lists, procedural reports), medication data, laboratory data, death data, and encounter and visit data. The last year of our study data collection overlapped with a transition to *ICD-10* coding; accordingly, a feature in this research database allows cross-over between equivalent *ICD-9* and *ICD-10* codes.

Statistical Analysis

Comparisons between case and control subjects were made using the Wilcoxon rank sum test for continuous variables and the Pearson χ^2 test for categorical variables. $P<0.05$ was considered to be significant. A propensity model was fitted to the probability of being classified as a case (ie, having thrombophilia testing). Clinical variables used in the model were age, race, sex, body mass index, malignant disease, unstable cardiac disease, HIV status, hepatic failure, pregnancy, hypertension, chronic coronary disease, chronic cerebrovascular disease, diabetes mellitus, heart failure, and smoking status. These variables were identified using *ICD-9* codes and electronic health record demographic data. *ICD-9* definitions are presented in Table S1. We calculated the empirical difference between the quartile–quartile functions of the tested and untested participants after matching to show the balance between the groups after matching. The relative importance of each variable to the propensity score was calculated using a χ^2 minus degree of freedom statistic. The primary analysis included all participants, including those with a malignancy diagnosis, and sensitivity analyses excluding subjects with malignancy were performed.[21] Subgroup analyses were performed to investigate outcomes among participants depending on the results of thrombophilia testing (*normal* or *abnormal*) and provoked versus unprovoked index VTE event status. The log-rank test was used to compare curves for survival analysis, and subjects without observed events during the study period were censored at the last follow-up date (March 22, 2017). Multivariable analysis was also performed to investigate the effect of baseline

characteristics including age, sex, and era on the outcomes of interest. Survival, logistic regression, and ordinal logistic regression were performed to compare the 2 groups on the outcomes of interest adjusting for prespecified covariates. For continuous covariates, spline was used to capture the nonlinear relationship.

Results

We identified 3590 unique patients who met our inclusion criteria (Figure S1). The number of patients meeting inclusion criteria per year increased over time from 2002 to 2008 and remained steady thereafter (Figure S2). The number of patients with thrombophilia testing remained between ≈100 and ≈200 tests annually until the medical center began discouraging testing in 2014 and ultimately prohibited in-hospital thrombophilia testing at the end of 2015. The mean time from index VTE event to the most recent healthcare contact was 29.6 months (SD: 38.9 months). Within the whole population, 793 patients underwent thrombophilia testing. Subjects who underwent testing were younger and less likely to be male, to have hypertension, to have chronic coronary disease, and to have a malignancy (Table 1).

Among all patients, those who were tested were more likely to have a recurrent VTE event (45.3% versus 25.4%,

Table 1. Baseline Characteristics Before Propensity Matching

	Tested (n=793)	Untested (n=2797)	*P* Value
Age, y	44	54	<0.001
Male sex, %	49	55	0.003
White race, %	77	80	0.21
Body mass index	31	30	0.02
HIV, %	1	2	0.62
Hepatic failure, %	4	5	0.36
Unstable cardiovascular disease, %	5	3	0.05
Pregnancy, %	1	0	0.002
Hypertension, %	46	51	0.02
Chronic coronary disease, %	12	17	<0.001
Chronic cerebrovascular disease, %	9	6	0.01
Chronic heart failure, %	2	2	0.30
Diabetes mellitus, %	14	17	0.04
Smoking, %	2	3	0.32
Provoked event, %	86	86	0.85
Malignancy, %	27	44	<0.001

P<0.001) and to receive extended anticoagulation at 12 months (52.8% versus 34.5%, *P*<0.001) but less likely to die (15.0% versus 34.1%, *P*<0.001) compared with untested patients (Table 2 and Figure 1). There was no difference in bleeding-related hospitalization (11.2% versus 10.3%, *P*=0.45) between groups.

Propensity-Matched Groups

Because of the imbalance in risk factors for recurrent events, anticoagulation use, and mortality, we used propensity matching to account for these factors. Age, sex, and body mass index were the most significant contributing variables to the propensity model (Figure S3). There were 747 patients with VTE who underwent thrombophilia testing and were propensity matched to a control participant with VTE who did not have thrombophilia testing (Figure S1). The postmatching improvement in the balance of clinical characteristics of tested and control subjects is shown in Table S2.

Among propensity-matched participants, those who were tested were more likely to have a recurrent VTE event (46.1% versus 28.5%, *P*<0.001) and to receive extended anticoagulation at 12 months (53.9% versus 37.1%, *P*<0.001) but less likely to die (14.1% versus 25.7%, *P*<0.001) compared with untested participants. There was no difference in the bleeding-related hospitalization (11.4% versus 11.8%, *P*=0.81) between groups (Table 3).

Propensity Matching Without Malignancy

Thrombophilia testing is not recommended for patients with malignancy. Accordingly, we next evaluated the propensity-matched groups after excluding participants with malignancy. Baseline characteristics before matching are shown in Table S3. There were 536 participants with VTE without malignancy who underwent thrombophilia testing and were propensity matched to a control participant with VTE without malignancy who did not have thrombophilia testing (Table 3).

Among propensity-matched subjects without malignancy, those who were tested were more likely to have a recurrent

Table 2. Clinical Outcomes by Testing Status Before Propensity Matching

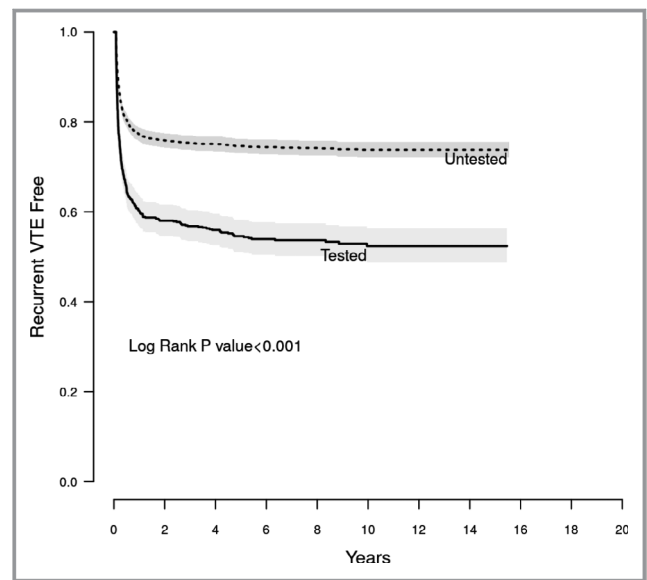| Outcome	Tested (n=793), %	Untested (n=2797), %	*P* Value
Recurrent event	45	25	<0.001
Extended anticoagulation	53	35	<0.001
Bleeding-related hospitalization	11	10	0.45
Death	15	34	<0.001

Figure 1. Long-term venous thromboembolism (VTE) recurrence following index VTE event by thrombophilia test status. Kaplan–Meier survival curves for recurrent VTE events are stratified by thrombophilia testing status of all subjects.

VTE event (44.0% versus 25.4%, *P*<0.001) and to receive extended anticoagulation at 12 months (52.4% versus 41.6%, *P*<0.001), but there was no difference in mortality (11.4% versus 14.4%, *P*=0.15) or bleeding-related hospitalization (9.9% versus 10.6%, *P*=0.69) compared with untested subjects (Table 3).

Impact of Provoked/Unprovoked Status in Propensity-Matched Participants Without Cancer

Among the 1072 patients without malignancy in the propensity matched cohort, 888 (83%) were categorized as having a provoked VTE event and 184 as having an unprovoked VTE. Among propensity-matched subjects without malignancy, those with a provoked VTE were less likely to have a recurrent VTE event (32.7% versus 41.3%, *P*<0.001), to receive extended anticoagulation at 12 months (41.6% versus 54.9%, *P*<0.001), and to die (12.3% versus 16.3%, *P*<0.001) but were more likely to have a bleeding-related hospitalization (10.4% versus 7.6%, *P*<0.001) compared with patients with an unprovoked VTE (Table S4).

Among participants with either provoked or unprovoked status in the propensity matched groups, those who underwent testing were more likely to have a recurrent event, extended anticoagulation treatment, and no difference in bleeding-related hospitalizations (Table S5). For those with a provoked event, there was no difference in mortality. In the small subgroup of participants with an unprovoked VTE without malignancy, those who underwent testing were less

Table 3. Clinical Outcomes by Testing Status in Propensity-Matched Participants

Outcome	All Participants			Participants Without Malignancy		
	Tested (n=747), %	Matched Untested Controls (n=747), %	*P* Value	Tested (n=536), %	Matched Untested Controls (n=536), %	*P* Value
Recurrent event	46	29	<0.001	44	25	<0.001
Extended anticoagulation	54	37	<0.001	52	42	<0.001
Bleeding-related hospitalization	11	12	0.81	10	11	0.69
Death	14	26	<0.001	11	14	0.15

likely to die (10.9% versus 21.7%, *P*=0.046) compared with participants who were not tested (Table S5).

Impact of Testing Results in Propensity-Matched Participants

There were no differences in recurrent VTE events (47.8% versus 44.1%, *P*=0.13), frequency of extended anticoagulation at 12 months (53.2% versus 54.8%, *P*=0.51), mortality (12.2% versus 16.1%, *P*=0.18), and bleeding related hospitalization (11.5% versus 11.3%, *P*=0.69) among propensity-matched participants by test result (Figure 2). These relationships were maintained when patients with malignancy were excluded (Table S6).

Sensitivity Analysis and Multivariable Modeling

To investigate the impact of timing on testing, we performed a sensitivity analysis limited to those with thrombophilia testing within the first 180 days of the index VTE event (n=393). There was no change in the outcomes of interest in this sensitivity analysis compared with primary analysis.

Likewise, there was no change to the conclusions when using 3 months instead of 1 month as the "blanking period" before counting a recurrent VTE event. We investigated whether repeated hospitalizations with attendant follow-up studies of chronic deep-vein thrombosis were responsible for differences in recurrent events, but we did not see a significant difference in hospitalizations between the matched tested and untested subjects when using a 1- or 3-month blanking period for repeated hospitalization (*P*>0.2). Multivariable modeling was performed to assess for significant interaction between the baseline characteristics of age, sex, race, and era (before or after 2008), and there was no significant effect of these baseline characteristics (all *P*>0.1) on the outcomes of interest. This result suggests that thrombophilia testing has an association with the outcomes that is not completely explained by baseline differences in the tested subjects.

Discussion

We report 3 main observations from this study. First, the clinical decision to perform thrombophilia testing in an
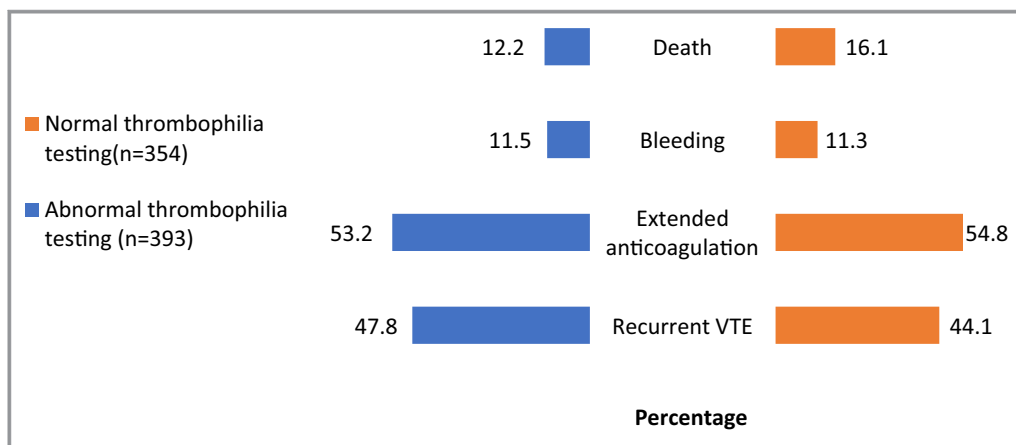

Figure 2. Clinical outcomes following venous thromboembolism (VTE) event in all tested subjects, stratified by test status. Clinical outcomes are shown by testing status. There were no significant differences in clinical outcomes by normal or abnormal test result.

unrestricted environment is associated with a higher risk of recurrent VTE despite a greater likelihood of long-duration anticoagulation. Second, the cohort of subjects with unprovoked index events is at higher risk of recurrent VTE events. Third, among patients who underwent testing, the results of thrombophilia testing do not further discriminate within this higher risk cohort. This outcome pattern was maintained when patients with malignancy were excluded. It is notable that excluding malignancy eliminated the difference in mortality, highlighting the particular importance of malignancy in VTE-related death. The effect persisted despite matching on a wide range of clinical features, suggesting that the clinical decision to test captures risk in a way that is incompletely explained by the clinical features and comorbidities used in our model.

Bayesian risk assessment is commonly performed in settings of intermediate risk to better discriminate patients who may benefit from treatments that may cause adverse events. Uncommonly, the decision to perform a test, rather than its results, identifies the high-risk group. For example, the Multicenter Unsustained Tachycardia Trial showed that investigators correctly identified high-risk patients with the criteria to undergo electrophysiology studies; however, the results of the electrophysiology studies did not further risk-stratify patients, as the 5-year mortality was quite high in both positive and negative study groups.[22] Such instances highlight the complex and integrative nature of clinical decision-making and the value of clinical "gestalt."

The results of this study do not support the value of discretionary thrombophilia testing in subjects with VTE because the results of testing did not aid in clinical decision-making. Because recurrent VTE rates were higher in tested patients, regardless of test results, future studies should investigate the decision to perform thrombophilia testing. Understanding the clinical features that lead to testing could define findings or patterns of findings that, when present, identify patients at higher risk for recurrent VTE. Analysis of our propensity-matching model showed that age and malignant disease were the most significant clinical variables associated with testing. Sensitivity analysis limiting testing to the acute setting (within 180 days of the index event) did not alter the outcomes, suggesting that the decision to test at any time is marker of risk. Patient characteristics that are not well captured by our propensity matching may be relevant in this regard, such as frailty, severity of underlying illness, family history of thrombosis, and perceived ability to tolerate or comply with anticoagulation. For now, we believe that the clinical context of the VTE event should guide risk stratification and duration of anticoagulation until the use of testing in the proper setting is studied prospectively. The cost of inappropriate testing is significant, and spurious results from indiscriminate testing may lead to inappropriate therapy.[10,23,24]

The impact of malignancy on mortality in patients with VTE is clear from clinical trials. Thromboembolism is the second-leading cause of death in cancer patients, and recurrence is common despite anticoagulation.[25–27] In large randomized direct oral anticoagulant trials in VTE that excluded cancer patients, 12-month mortality was 1% to 3%, whereas 12-month mortality in cancer-associated thrombosis was 38% in a study of direct oral anticoagulant versus low-molecular-weight heparin.[28–33] Because current guidelines recommend indefinite anticoagulation for malignancy-associated VTE in patients with active cancer or ongoing anticancer therapy, thrombophilia testing would be unlikely to alter clinical management in this population.[5,34] However, thrombophilia test acquisition (but not necessarily the results) is associated with a lower risk of death in participants with malignancy. We surmise that testing is less likely to be performed in patients with advanced stages of cancer, but further investigation of this observation is warranted.

The results of our study should be interpreted within the limitations of its design. Although we refined our definition of VTE events by using the presence of imaging studies and anticoagulant therapy to refine identification by *ICD-9* codes, there may have been incomplete ascertainment and/or misclassification of cases and controls.[35] Given the retrospective design, we cannot exclude residual confounding from factors (eg, those discussed earlier) not included in the propensity model. We considered that detected recurrent events may have been higher in the tested population because of longer follow-up in our system. However, >90% of events occurred by 18 months. Our study had a high percentage of provoked VTE, which limits interpretation of the results from the smaller number of patients with unprovoked VTE. This limitation may reflect VTE events occurring before hospital arrival being incorrectly deemed provoked if diagnostic imaging was performed after the admission order. However, such misclassification would be expected to occur with roughly the same frequency in both tested cases and untested controls. The small number of patients with unprovoked VTE in our cohort suggests a high rate of inappropriate testing. As a single-center study, outcomes outside of our medical center may be incompletely ascertained; index events may have occurred before 2002, rendering some early events as recurrent; VTE events outside of our medical center may not be recorded correctly; and VTE events may have occurred at other medical centers. Although we classified thrombophilia testing as either normal or abnormal, further investigation is needed to determine whether components of the thrombophilia workup, when tested prospectively in the right setting, may be predictive of outcomes and provide information to substantiate continuation or cessation of anticoagulation.

The rate of abnormal results may also reflect false-positive results related to the testing of inpatients during the acute event or later when patients are treated with anticoagulants at the time of testing. Furthermore, thrombophilia testing may not have sufficient discriminatory power to aid in risk assessment. As testing improves, by becoming more accurate and removing conditions that affect the test, new tests such as exome sequencing and polygenic risk scores may provide direction and be independent of the timing of test acquisition.[36] Our finding that more than half of testing occurred within 180 days of a VTE event is consistent with the findings of others.[10,37] It is important to note that this study is not designed to assess the value of any specific component of the thrombophilia panel. The study was performed to assess the impact on outcomes of indiscriminate use of thrombophilia testing by clinicians and their response to the results; therefore, we included all testing, including possible false-positive or inappropriately timed thrombophilia testing, in the analysis to reflect the real-world use of these tests.

Conclusions

The decision to perform thrombophilia testing, rather than the test result, was associated with a high risk of recurrent VTE despite a greater likelihood of long-duration anticoagulation. We cannot draw causal inference, given potential confounding factors in the study of clinical care.

We reinforce the observation that unprovoked VTE events are associated with a higher rate of recurrent VTE events and long-duration anticoagulation. Further investigation is needed to identify the factors used by clinicians in identifying this high-risk cohort.

Disclosures

Dr Beckman reports consulting with AstraZeneca, Bristol Myers Squibb, Amgen, Merck, Sanofi, Antidote Pharmaceutical, and Boehringer Ingelheim. He serves on the Data and Safety Monitoring Committee (DSMC) for Bayer and Novartis. The remaining authors have no disclosures to report.

References

1. Beckman MG, Hooper WC, Critchley SE, Ortel TL. Venous thromboembolism: a public health concern. *Am J Prev Med*. 2010;38:S495–S501.

2. Heit JA. Epidemiology of venous thromboembolism. *Nat Rev Cardiol*. 2015;12:464–474.

3. Kyrle PA, Kammer M, Eischer L, Weltermann A, Minar E, Hirschl M, Heinze G, Eichinger S. The long-term recurrence risk of patients with unprovoked venous thromboembolism: an observational cohort study. *J Thromb Haemost*. 2016;14:2402–2409.

4. Vedantham S, Piazza G, Sista AK, Goldenberg NA. Guidance for the use of thrombolytic therapy for the treatment of venous thromboembolism. *J Thromb Thrombolysis*. 2016;41:68–80.

5. Kearon C, Akl EA, Ornelas J, Blaivas A, Jimenez D, Bounameaux H, Huisman M, King CS, Morris TA, Sood N, Stevens SM, Vintch JR, Wells P, Woller SC, Moores L. Antithrombotic therapy for VTE disease: CHEST guideline and expert panel report. *Chest*. 2016;149:315–352.

6. Wells PS, Forgie MA, Rodger MA. Treatment of venous thromboembolism. *JAMA*. 2014;311:717–728.

7. Eichinger S, Heinze G, Jandeck LM, Kyrle PA. Risk assessment of recurrence in patients with unprovoked deep vein thrombosis or pulmonary embolism: the Vienna prediction model. *Circulation*. 2010;121:1630–1636.

8. Di Minno MN, Dentali F, Lupoli R, Ageno W. Mild antithrombin deficiency and risk of recurrent venous thromboembolism: a prospective cohort study. *Circulation*. 2014;129:497–503.

9. Segal JB, Brotman DJ, Necochea AJ, Emadi A, Samal L, Wilson LM, Crim MT, Bass EB. Predictive value of factor V Leiden and prothrombin G20210A in adults with venous thromboembolism and in family members of those with a mutation: a systematic review. *JAMA*. 2009;301:2472–2485.

10. Shen YM, Tsai J, Taiwo E, Gavva C, Yates SG, Patel V, Frenkel E, Sarode R. Analysis of thrombophilia test ordering practices at an academic center: a proposal for appropriate testing to reduce harm and cost. *PLoS One*. 2016;11: e0155326.

11. De Stefano V, Martinelli I, Mannucci PM, Paciaroni K, Chiusolo P, Casorelli I, Rossi E, Leone G. The risk of recurrent deep venous thrombosis among heterozygous carriers of both factor V Leiden and the G20210A prothrombin mutation. *N Engl J Med*. 1999;341:801–806.

12. Eichinger S, Weltermann A, Mannhalter C, Minar E, Bialonczyk C, Hirschl M, Schonauer V, Lechner K, Kyrle PA. The risk of recurrent venous thromboembolism in heterozygous carriers of factor V Leiden and a first spontaneous venous thromboembolism. *Arch Intern Med*. 2002;162:2357–2360.

13. Chong LY, Fenu E, Stansby G, Hodgkinson S. Management of venous thromboembolic diseases and the role of thrombophilia testing: summary of NICE guidance. *BMJ*. 2012;344:e3979.

14. Hicks LK, Bering H, Carson KR, Kleinerman J, Kukreti V, Ma A, Mueller BU, O'Brien SH, Pasquini M, Sarode R, Solberg L Jr, Haynes AE, Crowther MA. The ASH Choosing Wisely(R) campaign: five hematologic tests and treatments to question. *Blood*. 2013;122:3879–3883.

15. Baglin T, Gray E, Greaves M, Hunt BJ, Keeling D, Machin S, Mackie I, Makris M, Nokes T, Perry D, Tait RC, Walker I, Watson H. Clinical guidelines for testing for heritable thrombophilia. *Br J Haematol*. 2010;149:209–220.

16. Coppens M, Reijnders JH, Middeldorp S, Doggen CJ, Rosendaal FR. Testing for inherited thrombophilia does not reduce the recurrence of venous thrombosis. *J Thromb Haemost*. 2008;6:1474–1477.

17. Huang W, Goldberg RJ, Cohen AT, Anderson FA, Kiefe CI, Gore JM, Spencer FA. Declining long-term risk of adverse events after first-time community-presenting venous thromboembolism: the population-based Worcester VTE Study (1999 to 2009). *Thromb Res*. 2015;135:1100–1106.

18. Austin PC. An introduction to propensity score methods for reducing the effects of confounding in observational studies. *Multivariate Behav Res*. 2011;46:399–424.

19. Hirsh J, Dalen J, Anderson DR, Poller L, Bussey H, Ansell J, Deykin D. Oral anticoagulants: mechanism of action, clinical effectiveness, and optimal therapeutic range. *Chest*. 2001;119:8s–21s.

20. Cunningham A, Stein CM, Chung CP, Daugherty JR, Smalley WE, Ray WA. An automated database case definition for serious bleeding related to oral anticoagulant use. *Pharmacoepidemiol Drug Saf*. 2011;20:560–566.

21. Akl EA, Kahale L, Barba M, Neumann I, Labedi N, Terrenato I, Sperati F, Muti P, Schünemann H. Anticoagulation for the long-term treatment of venous thromboembolism in patients with cancer. *Cochrane Database Syst Rev*. 2014;8:CD006650.

22. Buxton AE, Lee KL, DiCarlo L, Gold MR, Greer GS, Prystowsky EN, O'Toole MF, Tang A, Fisher JD, Coromilas J, Talajic M, Hafley G. Electrophysiologic testing to identify patients with coronary artery disease who are at risk for sudden death. Multicenter Unsustained Tachycardia Trial Investigators. *N Engl J Med*. 2000;342:1937–1945.

23. Petrilli CM, Heidemann L, Mack M, Durance P, Chopra V. Inpatient inherited thrombophilia testing. *J Hosp Med*. 2016;11:801–804.

24. Gupta A, Sarode R, Nagalla S. Thrombophilia testing in provoked venous thromboembolism: a teachable moment. *JAMA Intern Med*. 2017;177:1195–1196.

25. Khorana AA, Francis CW, Culakova E, Kuderer NM, Lyman GH. Thromboembolism is a leading cause of death in cancer patients receiving outpatient chemotherapy. *J Thromb Haemost*. 2007;5:632–634.

26. Lee AYY, Kamphuisen PW, Meyer G, Bauersachs R, Janas MS, Jarner MF, Khorana AA. Tinzaparin vs warfarin for treatment of acute venous thromboembolism in patients with active cancer: a randomized clinical trial. *JAMA*. 2015;314:677–686.

27. Lee AY, Levine MN, Baker RI, Bowden C, Kakkar AK, Prins M, Rickles FR, Julian JA, Haley S, Kovacs MJ, Gent M; Randomized Comparison of Low-Molecular-

Weight Heparin versus Oral Anticoagulant Therapy for the Prevention of Recurrent Venous Thromboembolism in Patients with Cancer I. Low-molecular-weight heparin versus a coumarin for the prevention of recurrent venous thromboembolism in patients with cancer. *N Engl J Med*. 2003;349:146–153.

28. Buller HR, Prins MH, Lensin AW, Decousus H, Jacobson BF, Minar E, Chlumsky J, Verhamme P, Wells P, Agnelli G, Cohen A, Berkowitz SD, Bounameaux H, Davidson BL, Misselwitz F, Gallus AS, Raskob GE, Schellong S, Segers A. Oral rivaroxaban for the treatment of symptomatic pulmonary embolism. *N Engl J Med*. 2012;366:1287–1297.

29. Bauersachs R, Berkowitz SD, Brenner B, Buller HR, Decousus H, Gallus AS, Lensing AW, Misselwitz F, Prins MH, Raskob GE, Segers A, Verhamme P, Wells P, Agnelli G, Bounameaux H, Cohen A, Davidson BL, Piovella F, Schellong S. Oral rivaroxaban for symptomatic venous thromboembolism. *N Engl J Med*. 2010;363:2499–2510.

30. Agnelli G, Buller HR, Cohen A, Curto M, Gallus AS, Johnson M, Masiukiewicz U, Pak R, Thompson J, Raskob GE, Weitz JI. Oral apixaban for the treatment of acute venous thromboembolism. *N Engl J Med*. 2013;369:799–808.

31. Hokusai VTEI, Buller HR, Decousus H, Grosso MA, Mercuri M, Middeldorp S, Prins MH, Raskob GE, Schellong SM, Schwocho L, Segers A, Shi M, Verhamme P, Wells P. Edoxaban versus warfarin for the treatment of symptomatic venous thromboembolism. *N Engl J Med*. 2013;369:1406–1415.

32. Schulman S, Kearon C, Kakkar AK, Schellong S, Eriksson H, Baanstra D, Kvamme AM, Friedman J, Mismetti P, Goldhaber SZ; RE-MEDY Trial Investigators; RE-SONATE Trial Investigators. Extended use of dabigatran, warfarin, or placebo in venous thromboembolism. *N Engl J Med*. 2013;368:709–718.

33. Raskob GE, van Es N, Verhamme P, Carrier M, Di Nisio M, Garcia D, Grosso MA, Kakkar AK, Kovacs MJ, Mercuri MF, Meyer G, Segers A, Shi M, Wang TF, Yeo E, Zhang G, Zwicker JI, Weitz JI, Buller HR. Edoxaban for the treatment of cancer-associated venous thromboembolism. *N Engl J Med*. 2018;378:615–624.

34. Khorana AA, Carrier M, Garcia DA, Lee AYY. Guidance for the prevention and treatment of cancer-associated venous thromboembolism. *J Thromb Thrombolysis*. 2016;41:81–91.

35. O'Malley KJ, Cook KF, Price MD, Wildes KR, Hurdle JF, Ashton CM. Measuring diagnoses: ICD code accuracy. *Health Serv Res*. 2005;40:1620–1639.

36. Lee EJ, Dykas DJ, Leavitt AD, Camire RM, Ebberink E, Garcia de Frutos P, Gnanasambandan K, Gu SX, Huntington JA, Lentz SR, Mertens K, Parish CR, Rezaie AR, Sayeski PP, Cromwell C, Bar N, Halene S, Neparidze N, Parker TL, Burns AJ, Dumont A, Yao X, Chaar CIO, Connors JM, Bale AE, Lee AI. Whole-exome sequencing in evaluation of patients with venous thromboembolism. *Blood Adv*. 2017;1:1224–1237.

37. Gavva C, Sarode R, Zia A. A clinical audit of thrombophilia testing in pediatric patients with acute thromboembolic events: impact on management. *Blood Adv*. 2017;1:2386–2391.

SUPPLEMENTAL MATERIAL

Table S1. DVT/PE ICD-9 criteria.

ICD-9 Code	Description
Deep venous thrombosis	
451.1	Of deep vessels of lower extremities
451.11	Femoral vein phlebitis
451.19	Deep phlebitis-leg
451.81	Iliac thrombophlebitis
451.83	Of deep veins of upper extremities
453.2	Other inferior vena cava thrombosis
453.8	Acute venous embolism and thrombosis of other specified veins
453.9	Venous thrombosis, not otherwise specified
671.3	Deep phlebothrombosis antepartum
671.4	Deep phlebothrombosis postpartum
671.9	Unspecified venous complications
673.2	Obstetrical blood-clot embolism
673.24	Obstetrical blood-clot embolism
Pulmonary embolism	
415.1	Pulmonary embolism and infarction
415.11	Iatrogenic pulmonary embolism/infarction
415.19	Pulmonary embolism/infarction

Qualifying Imaging Study CPT Codes

CPT Code	Study Description
71275	CT angiogram of the chest
93568	Pulmonary artery angiogram
78582	Nuclear Medicine V/Q scan of the lungs
93970	Duplex ultrasound extremity veins, complete bilateral
93971	Duplex ultrasound extremity veins, unilateral or limited
75822	Venogram, extremity, bilateral
75820	Venogram, extremity, unilateral

ICD-9 codes for clinical variables

ICD-9 Code	Description
140-239	Malignant disease
410, 411, 428.21, 428.23, 428.31, 428.33, 428.41, 428.43, 427.5	Unstable cardiac disease
042	HIV infection
573.8, 571.1,070,20, 070.21,070.41, 070.51	Hepatic failure or active hepatitis
V22, V23	Pregnancy
401-405	Hypertension
414	Chronic coronary disease
430-438	Chronic cerebrovascular disease
250	Diabetes
428.22, 428.32, 428.42	Heart Failure
From EHR structured social history	Smoking Status

Table S2. Balancing of characteristics after propensity matching.

	Tested (n=747)	Untested Control (n=747)	eQ-Q mean[*]
Age (years)	44	44	1.04
Male sex (%)	48	51	0.03
Caucasian race (%)	78	78	0.01
BMI	31	31	0.31
HIV (%)	1	1	0.00
Hepatic failure (%)	4	4	0.00
Unstable cardiovascular disease (%)	5	5	0.00
Pregnancy (%)	1	0	0.01
Hypertension (%)	46	44	0.02
Chronic coronary disease (%)	12	12	0.00
Chronic cerebrovascular disease (%)	9	9	0.00
Chronic heart failure (%)	2	2	0.00
Diabetes (%)	14	13	0.01
Smoking (%)	2	3	0.01
Malignancy (%)	28	30	0.02

*Mean difference between empirical quartile-quartile functions of the tested and control groups

Table S3. Baseline Characteristics of Propensity Matched Subjects Without Malignancy.

	Tested (n=578)	Untested Control (n= 1,564)	P-value
Age (years)	41	51	<0.001
Male sex (%)	50	58	0.002
Caucasian race	75	78	0.59
BMI	30	31	0.56
HIV (%)	1	2	0.20
Hepatic failure (%)	2	3	0.74
Unstable cardiovascular disease (%)	5	4	0.42
Pregnancy (%)	1	0	0.002
Hypertension (%)	41	47	0.01
Chronic cardiovascular disease (%)	11	18	<0.001
Chronic cerebrovascular disease (%)	9	7	0.12
Chronic heart failure (%)	2	2	0.47
Diabetes (%)	13	16	0.04
Smoking (%)	2	3	0.32
Provoked event (%)	81	75	0.003

Table S4. Clinical Outcomes in All Propensity Matched Subjects Without Malignancy By Provoked Status.

Outcome (%)	Provoked (n=888)	Unprovoked (n=184)	p-value
Recurrent Event	32.7	41.3	<0.001
Extended anticoagulation	41.6	54.9	<0.001
Bleeding-related hospitalization	10.4	7.6	<0.001
Death	12.3	16.3	<0.001

Table S5. Clinical Outcomes by Testing and Provocation Status in Propensity Matched Subjects.

	Provoked index VTE			Unprovoked index VTE		
Outcome (%)	Tested (n=444)	Matched controls (n=444)	p-value	Tested (n=92)	Matched controls (n=92)	p-value
Recurrent event	42.6	22.7	<0.001	51.1	31.5	<0.001
Extended Anticoagulation	49.5	33.6	<0.001	66.3	43.5	0.002
Bleeding-related hospitalization	10.1	10.6	0.83	8.7	6.5	0.578
Death	11.5	13.1	.47	10.9	21.7	.046

Table S6. Clinical Outcomes in Propensity Matched Subjects Without Malignancy by Thrombophilia Test Outcome.

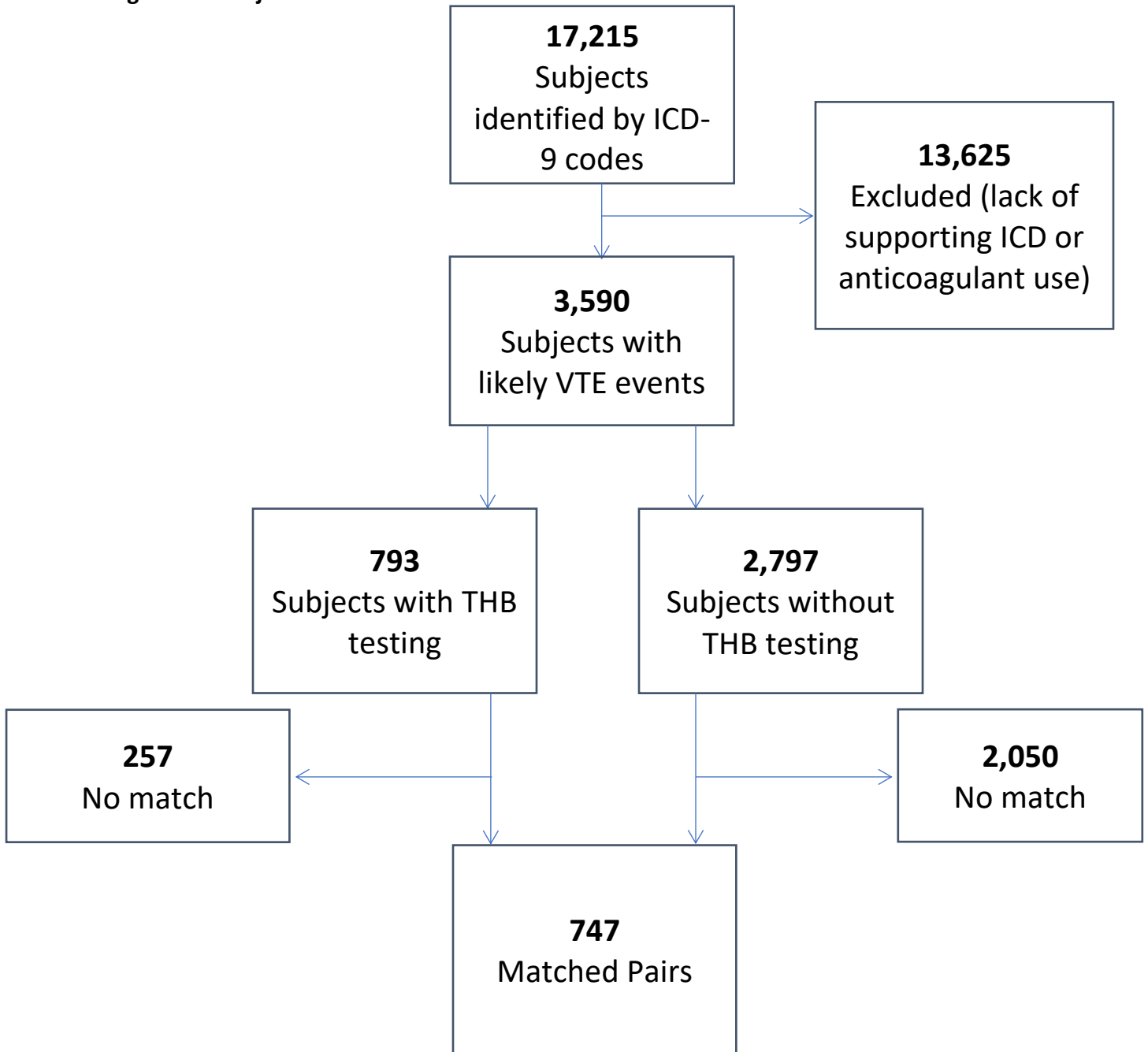|	Subjects With Testing		
Outcome (%)	Abnormal (n=285)	Normal (n=251)	p-value
Recurrent event	47	41	0.21
Extended anticoagulation	53	52	0.52
Bleeding-related hospitalization	9	11	0.20
Death	10	13	0.11

Figure S1. Subject Flow.

Figure S2. The annual incidence of subjects meeting criteria for venous thromboembolism and subjects undergoing thrombophilia testing.
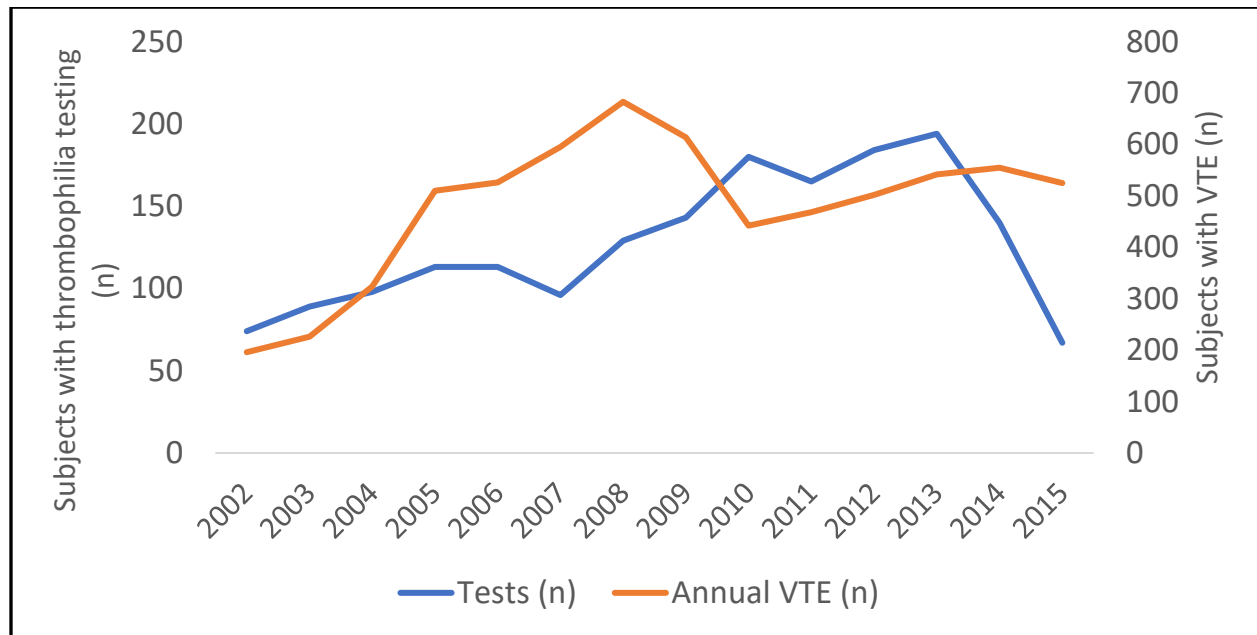

Figure S3. Chi Squared minus Degree of Freedom for each component of the propensity score showing the relative importance of each variable to the model.

	χ^2	P
race.factor	0.0	0.9788
chronic.cvd	0.0	0.8814
diabetes	0.0	0.8320
hepatic.failure	0.1	0.8197
heart.failure	0.9	0.3320
hiv.status	1.4	0.2340
pregnancy	1.7	0.1953
smoking	3.1	0.0766
hypertension	4.9	0.0269
unstable.cvd	5.1	0.0242
chronic.cerebrovascular	7.1	0.0079
bmi	10.8	0.0044
male	10.4	0.0013
age	212.7	0.0000