Published in final edited form as:

Thromb Res. 2015 December ; 136(6): 1160–1164. doi:10.1016/j.thromres.2015.10.019.

Thrombophilia Testing Patterns among Patients with Acute Venous Thromboembolism

Melissa R. Meyer, PharmD¹, Daniel M. Witt, PharmD^{1,2}, Thomas Delate, PhD^{1,3}, Samuel G. Johnson, PharmD^{1,3}, Margaret Fang, MD, MPH⁴, Alan Go, MD^{5,6}, and Nathan P. Clark, PharmD^{1,3}

¹ Kaiser Permanente Colorado, Pharmacy Department, Aurora, CO

² University of Utah College of Pharmacy, Department of Pharmacotherapy, Salt Lake City, UT

³ University of Colorado Denver Skaggs School of Pharmacy and Pharmaceutical Sciences, Aurora, CO

⁴ University of California San Francisco, Division of Hospital Medicine, San Francisco, CA

⁵ Kaiser Permanente Northern California, Division of Research, Oakland, CA

⁶ Stanford University School of Medicine, Department of Health Research and Policy, Stanford, CA

Abstract

Background—Thrombophilia testing has limited value in determining the selection and duration of anticoagulation therapy for venous thromboembolism (VTE), yet is commonly performed. This study describes the patterns and appropriateness of thrombophilia testing in a large cohort of patients with acute VTE.

Materials and methods—This was a retrospective study of a random sample of patients with a validated diagnosis of acute VTE diagnosed between January 1, 2004 and December 31, 2010. Events were identified from administrative data and verified via manual review. Patients were grouped by thrombophilia testing status and compared on patient characteristics and thrombophilia testing results and appropriateness.

Corresponding Author: Nathan P. Clark, PharmD, 16601 East Centretech Parkway, Aurora, CO 80011, Ph: (303) 739-4901, FAX: (303) 739-3574, nathan.clark@kp.org.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

This study was presented in part at the International Society of Thrombosis and Haemostasis (ISTH) Scientific Standardization Committee (SSC) annual meeting in Milwaukee, WI on June 23, 2014.

Authorship Contributions

M.R.M., T.D., S.G.J., N.P.C. and D.M.W. designed the research with input from A.G. and M.F; M.R.M., T.D. and D.M.W. extracted information from medical records; T.D. performed the statistical analysis; M.R.M., T.D., S.G.J., N.P.C., A.G., M.F. and D.M.W. interpreted the analysis and revised the manuscript; M.R.M. wrote the initial draft of the manuscript; all authors approved the final version of the manuscript.

Disclosure of Conflicts of Interest

M.R.M., D.M.W., T.D., S.G.J., N.P.C., M.F., and A.G. have no conflicts of interest to disclose.

Results—Of 1,314 patients with validated VTE, 315 (24%) underwent thrombophilia testing, 62 (20%) of whom had 1 positive test. Tested patients were younger and more likely to have had a family history of VTE. Factor V Leiden (17%) and prothrombin *G20210A* mutation (4%) were the most commonly detected thrombophilias. Only 31 (10%) of tested patients met eligibility criteria for thrombophilia testing (i.e., at least one strong thrombophilic risk factor present) and were tested at least 90 days following unprovoked index VTE.

Conclusions—Thrombophilia is commonly evaluated in patients without a clear indication for testing and during times where results may be unreliable. Future studies are needed to assess interventions aimed at reducing inappropriate thrombophilia testing without adversely affecting patient outcomes.

Keywords

thrombophilia; thrombophilia, hereditary; thrombosis; venous thrombosis; genetic testing; multiphasic screening

Introduction

Thrombophilia is an inherited or acquired disorder of hemostasis resulting in increased risk for venous thromboembolism (VTE) [1]. Deficiencies of natural anticoagulants, antithrombin (AT), protein C, or protein S, homozygous gene mutations, presence of multiple thrombophilic traits, or antiphospholipid antibodies (APLA) occur infrequently but confer a high risk for first VTE [2-4]. Heterozygous factor V Leiden (FVL) and the prothrombin (PT) *G20210A* mutation are more commonly found, but are relatively weak risk factors [2]. Thrombophilia status rarely influences acute VTE management and, in most cases, has limited value in determining the duration of anticoagulation therapy [3,5-11].

Most VTE management guidelines suggest limiting thrombophilia testing to specific clinical scenarios where test results will materially influence anticoagulation therapy treatment decisions [12-15]. Routine or indiscriminate testing in patients with VTE or in asymptomatic family members of patients with VTE may identify test positivity resulting in needless anxiety without clear clinical or therapeutic significance. Similarly, negative results may provide false reassurance [16,17]. Additionally, some thrombophilia tests are less accurate when obtained during acute VTE or while taking anticoagulants. Our study describes the patterns and appropriateness of thrombophilia testing in a large cohort of patients with acute VTE.

Materials and methods

Study Design and Setting

This retrospective study was conducted at Kaiser Permanente Colorado (KPCO), an integrated healthcare delivery system providing care to over 565,000 members in Colorado. The majority of patients with acute VTE are treated in KPCO outpatient clinics or referred to contract facilities (e.g., hospitals, emergency departments [ED]) where they are treated by KPCO physicians. Information (e.g., date of testing, test type, result) from laboratory tests

performed at KPCO outpatient clinics and contract facilities are available in KPCO administrative databases and its electronic medical record (EMR).

Providers at KPCO have access to organization-specific thrombophilia laboratory evaluation clinical guidelines last updated in 2010. The guideline recommended thrombophilia testing be limited to patients with at least one strong thrombophilic risk factor which included personal history of VTE before age 50 years, recurrent VTE, or family history of VTE. Thrombophilia testing results are recorded in the EMR and an electronic anticoagulation patient tracking system (DAWN AC, 4S Information Systems, Ltd., Cumbria, UK). All study activities were reviewed and approved by the KPCO Institutional Review Board. A waiver of patient informed consent was obtained due to the retrospective nature of the study.

Study Population

Patients in this study 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 who had ≥ 180 consecutive days of health plan membership prior to presenting with an acute VTE discharge diagnosis (defined as a primary or secondary International Classification of Diseases Ninth Revision Clinical Modification [ICD-9] diagnosis code recorded during an inpatient or outpatient encounter) between January 1, 2004 and December 31, 2010. Events were categorized as pulmonary embolism (PE), upper and lower extremity deep venous thrombosis (DVT), or other venous thrombosis (diagnosis codes available upon request).

A random sample of 2,500 KPCO patients identified administratively with acute VTE for the CVRN VTE study underwent EMR review using a structured data collection form to confirm the validity of their VTE. To be considered valid, an acute event required objective confirmation by contrast venography or ultrasonography for suspected DVT or ventilation-perfusion (VQ) scanning, pulmonary angiography, or helical computed tomography for suspected PE or other VTE types (e.g. portal or mesenteric vein thrombosis). Superficial venous thromboses were excluded from this evaluation. All validated VTEs were categorized as either provoked or unprovoked by the reviewer. Unprovoked VTE was defined as an event not associated with transient thromboembolic risk factors (see below) or active malignancy.

Clinical data collected during EMR review included: (1) the type and location of VTE (lower extremity DVT, upper extremity DVT, PE, or other thrombosis); (2) provoking VTE risk factors (documented prolonged immobility or non-surgical trauma at the VTE site in the 7 days preceding the event; surgery or recent hospitalization in the 30 days preceding the event; or pregnancy, hormonal therapy, or presence of an indwelling venous catheter present at the time of the event); (3) medical comorbidities (heart failure, inflammatory bowel disease, lung disease, active cancer, and sepsis); and (4) anticoagulant use status. Active cancer was defined as the receipt of chemotherapy or other cancer-related treatment, cancer-related surgery, or cancer-related radiation therapy during the 180 days prior to the index event. Thrombophilia testing and results were identified from KPCO administrative laboratory databases and confirmed via EMR review if result interpretation was unclear or

missing. Blood for thrombophilia testing was drawn during hospitalization/ED visits or at KPCO outpatient clinic laboratories.

Study Outcomes

Primary outcomes included the proportion of patients with acute VTE who had thrombophilia testing performed and the proportion of tested patients who had at least one positive test for thrombophilia. Patients were categorized into 'tested' and 'not tested' groups based on whether thrombophilia testing was performed anytime during the year following the index VTE event. Thrombophilia testing consisted of qualitative assays for deficiencies of protein C, protein S, and AT; genotyping for FVL and PT G20210A; and APLA assays (serum anticardiolipin and anti- β_2 glycoprotein I antibody assays and testing for lupus anticoagulant). Positive APLA results required serum anti- β_2 glycoprotein I IgG and/or anticardiolipin IgG antibody titers to be $>99^{\text{th}}$ percentile (medium-high positive range) or confirmation of lupus anticoagulant. Except for genetic test results, initially positive thrombophilia tests required confirmation at least six weeks later. Positive test results were categorized by thrombophilia type (protein C deficiency, protein S deficiency, AT deficiency, FVL, PT G20210A, or APLA syndrome).

Secondary outcomes included the proportions of patients: (1) with at least one strong thrombophilic risk factor according to KPCO guidelines; (2) tested during the acute VTE episode (i.e., within seven days of the index event); and (3) tested during anticoagulant therapy (i.e., within 90 days of the index event). Patients were considered to have met eligibility criteria for thrombophilia testing if testing was performed following unprovoked VTE consistent with guideline recommendations as described above. In the absence of a universally accepted definition of provoked VTE, subgroup analyses were performed to assess eligibility for testing based on defining provoked VTE strictly (i.e., associated with the presence of surgery within 30 days of VTE) or less strictly (i.e., associated with any of the aforementioned provoked VTE risk factors).

Data Analysis

Patient and VTE event characteristics were summarized using descriptive statistics (e.g., mean or median and standard deviation [SD] or interquartile range [IQR] for continuous variables and percentages for categorical variables). Continuous variable distributions were assessed for normality. Appropriate parametric (e.g., t-test, ANOVA) and non-parametric (e.g., chi-square tests of association, Wilcoxon rank sum test) were used to compare variables between tested and not tested groups and across test positive, test negative, and not tested groups with post-hoc analysis to determine differences between test positive and other groups. Multivariable logistic regression modeling was used to identify patient-specific factors associated with having had any thrombophilia testing and a positive test for thrombophilia amongst patients with at least one thrombophilia test. All factors with a $p < 0.2$ in the bivariate analysis were included in each logistic regression model. Statistical analysis was completed using SAS v 9.2 (SAS, Cary, NC).

Results

We identified 1,314 patients with confirmed acute VTE. Patients tested for thrombophilia were younger than those who were not tested (**Table I**). Patients with a family history of VTE, use of hormone therapy, and pregnancy were more likely to have been tested for thrombophilia (all $p<0.05$). Patients with upper extremity DVT, cancer, heart failure, hospitalization in the preceding 30 days, indwelling venous catheters, and lung disease were more likely to have not been tested (all $p<0.05$).

Overall, 315 (24.0%) patients were tested for thrombophilia, 62 (19.7%) of whom tested positive, with heterozygous FVL (15.4%) and PT G20210A (4.3%) mutations the most commonly detected types (**Table II**). Of the patients not tested, 217 (21.7%) and 122 (12.2%) met the eligibility and alternate eligibility criteria for thrombophilia testing, respectively (**Table I**). Deficiencies of endogenous anticoagulants, homozygous FVL, and APLA syndrome were found less frequently. Of the tested patients, 35.2% and 50.5% were tested within 7 and 90 days, respectively. Patients testing positive for thrombophilia had a numerically longer mean duration of anticoagulation therapy than those testing negative, but this did not reach statistical significance (1266 vs. 1145 days, $p=0.142$).

Patients who tested positive for thrombophilia were more likely to have been younger, had a positive family history of VTE, recent non-surgical trauma, and recent prolonged immobility than patients who tested negative for thrombophilia (all $p<0.05$) (**Table III**). On the other hand, patients who tested positive were less likely to have had cancer and a recent hospitalization compared to patients who tested negative (both $p<0.05$). Patients who tested positive were more likely to have been younger, had a positive family history of VTE, pregnancy, recent non-surgical trauma, and recent prolonged immobility and received hormone therapy than patients who were not tested (all $p<0.05$). Conversely, patients who tested positive were less likely to have had an upper extremity DVT, cancer, heart failure, indwelling catheter, and lung disease than patients who were not tested (all $p<0.05$).

Thrombophilia tests were ordered for 142 (45.1%) eligible patients (i.e., at least one strong thrombophilic criteria present) using the strict definition of provoked VTE (surgery during the previous 30 days) (**Table I**). Of these, 55 (38.7%) and 73 (51.4%) were tested within 7 and 90 days of index VTE, respectively. Testing was ordered for 79 (25.1%) eligible patients using the expanded definition of provoked VTE; with 39 (49.4%) and 48 (60.8%) of these tested within 7 and 90 days of index VTE, respectively. Only 31 (9.8%) patients meeting eligibility criteria were tested at least 90 days after the index VTE using the expanded definition of provoked VTE. Patients who tested positive for thrombophilia were more likely to have met both eligibility criteria than patients not tested (both $p<0.001$) (**Table III**).

Patient-specific factors independently associated with having been tested for thrombophilia included family history of VTE (odds ratio [OR]: 3.62; 95% confidence interval [CI]: 2.17-6.02), age <50 years (OR: 2.73; CI: 1.98-3.75), and hormone use (OR: 1.69; CI: 1.09-2.63) (**Table IV**). History of heart failure (OR: 0.20, CI: 0.07-0.57), cancer (OR: 0.31, CI: 0.19-0.48), and lung disease (OR: 0.54, CI: 0.30-0.95) were independently associated

with not having been tested. Factors independently associated with having had a positive test for thrombophilia included recent non-surgical trauma (OR: 2.92; CI: 1.13-7.58) and recent prolonged immobility (OR: 2.18; CI: 1.08-4.41) (**Table V**).

Discussion

We found that nearly one in four patients with acute VTE were tested for thrombophilia during the following year, and of those tested, one in five tested positive. When compared to KPCO guidelines available during the study period, three-quarters of tested patients did not meet eligibility criteria for thrombophilia testing. Patients were often tested in the absence of strong thrombophilia risk factors or following provoked VTE. In addition, thrombophilia testing was often performed in situations known to increase the potential for inaccurate results (e.g., during the acute VTE period and/or anticoagulation therapy). Our findings raise important questions regarding clinical utility and resource utilization associated with thrombophilia testing [18,19].

Our results do not support using the presence of strong thrombophilic risk factors to determine when to perform thrombophilia testing, as suggested by some thrombophilia testing consensus recommendations [12,20-21], as more than half of thrombophilia positive patients lacked strong thrombophilic risk factors. It may be preferable to perform thrombophilia testing only after patients have completed a treatment course for VTE and when uncertainty exists regarding discontinuing anticoagulation therapy [14]. More than half of patients tested for thrombophilia in our study were likely tested before anticoagulation therapy completion (i.e., within 90 days of acute VTE).

Other researchers also have found that a significant proportion of patients with VTE receive inappropriate thrombophilia testing [18,22-23]. One study found that implementing an evidence-based, clinical decision flowchart to help guide inpatient thrombophilia testing reduced orders for FVL and PT G20210A mutation testing by 79.4% (95% CI 71.2%-87.6%) [18]. Another study identified that more than half of thrombophilia tests were ordered during acute thrombotic episodes and that nearly two-thirds of abnormal protein C and S test results were attributable to the presence of anticoagulation therapy [22]. These observations underscore the importance of appropriate timing for thrombophilia testing and the need for confirming abnormal results for non-genetic tests in order to avoid falsely diagnosing and unnecessarily alarming patients [18,22].

Our study has limitations that merit consideration. Misclassification was possible with our retrospectively collected data. We attempted to minimize this potential bias by objectively confirming VTE events and ambiguities in administratively collected thrombophilia testing results via manual review of medical records. Although we included 1,314 validated VTE events in the analysis, rare thrombophilia traits were infrequently identified; thus, comparison between thrombophilia types was not possible. Homocysteine and factor VIII were not included in KPCO guidelines and, therefore, were not available routinely for analysis. Hyperhomocysteinemia does not appear to predict VTE recurrence [24]; however, recent research has suggested factor VIII may have a role in future VTE prediction models [25]. We were unable to verify whether family history of VTE involved a first-degree

relative in all cases. We required at least six weeks to elapse between confirmatory follow-up tests for initially positive non-genetic thrombophilia tests [26] but acknowledge that other recommendations suggest at least 12 weeks elapse between tests to minimize the risk of APLA syndrome misclassification [27]. The optimal interval between confirmatory thrombophilia tests has not been universally agreed upon; therefore, we used the six-week retesting time frame suggested by the existing KPCO testing guideline for confirming thrombophilia in our study. We were unable to determine what type of provider (e.g. specialist vs. generalist) ordered thrombophilia testing. Details regarding the specific methodology used to perform thrombophilia tests for non-KPCO laboratories (e.g., hospitals) were unavailable.

Conclusion

Approximately one in four randomly sampled patients with acute VTE were tested for thrombophilia but only one in ten of these tests were ordered for patients meeting testing eligibility criteria. Future studies are needed to assess whether interventions, such as strict avoidance of thrombophilia testing during the first 90 days of anticoagulation therapy and/or reserving testing to situations where uncertainty regarding continuing anticoagulation therapy exists, will reduce inappropriate thrombophilia testing without adversely affecting patient outcomes.

Acknowledgement

T.D. had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

The authors would like to acknowledge the assistance of Aubrey E. Jones with data collection for this study.

Financial Disclosure Statement

This study was funded in part by the National Heart Lung and Blood Institute of the National Institutes of Health-sponsored Cardiovascular Research Network grants: U19 HL091179 (PI: Go) and R01 HL103820 (PI: Fang) and by Kaiser Permanente Colorado Pharmacy Department.

References

- [1]. Machin SJ. Pros and cons of thrombophilia testing: cons. *J Thromb Haemost.* 2003; 1:412–413. [PubMed: 12871439]
- [2]. De Stefano V, Rossi E. Testing for inherited thrombophilia and consequences for antithrombotic prophylaxis in patients with venous thromboembolism and their relatives. A review of the Guidelines from Scientific Societies and Working Groups. *Thromb Haemost.* 2013; 110:697–705. [PubMed: 23846575]
- [3]. De Stefano V, Martinelli I, Mannucci PM, et al. 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. [PubMed: 10477778]
- [4]. Segal JB, Brotman DJ, Necochea AJ, et al. 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. [PubMed: 19531787]
- [5]. Christiansen SC, Cannegieter SC, Koster T, Vandenbroucke JP, Rosendaal FR. Thrombophilia, clinical factors, and recurrent venous thrombotic events. *JAMA.* 2005; 293:2352–2361. [PubMed: 15900005]

- [6]. Prandoni P, Lensing AW, Cogo A, et al. The long-term clinical course of acute deep venous thrombosis. *Ann Intern Med.* 1996; 125:1–7. [PubMed: 8644983]
- [7]. Miles JS, Miletich JP, Goldhaber SZ, Hennekens CH, Ridker PM. G20210A mutation in the prothrombin gene and the risk of recurrent venous thromboembolism. *J Am Coll Cardiol.* 2001; 37:215–218. [PubMed: 11153741]
- [8]. Baglin T, Luddington R, Brown K, Baglin C. Incidence of recurrent venous thromboembolism in relation to clinical and thrombophilic risk factors: prospective cohort study. *Lancet.* 2003; 362:523–526. [PubMed: 12932383]
- [9]. Eichinger S, Weltermann A, Mannhalter C, et al. 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. [PubMed: 12418950]
- [10]. De Stefano V, Martinelli I, Mannucci PM, et al. The risk of recurrent venous thromboembolism among heterozygous carriers of the G20210A prothrombin gene mutation. *Br J Haematol.* 2001; 113:630–635. [PubMed: 11380448]
- [11]. Simioni P, Prandoni P, Lensing AW, et al. Risk for subsequent venous thromboembolic complications in carriers of the prothrombin or the factor V gene mutation with a first episode of deep-vein thrombosis. *Blood.* 2000; 96:3329–3333. [PubMed: 11071624]
- [12]. Baglin T, Gray E, Greaves M, et al. Clinical guidelines for testing for heritable thrombophilia. *Br J Haematol.* 2010; 149:209–220. [PubMed: 20128794]
- [13]. Evaluation of Genomic Applications in P, Prevention Working G. Recommendations from the EGAPP Working Group: routine testing for Factor V Leiden (R506Q) and prothrombin (20210G>A) mutations in adults with a history of idiopathic venous thromboembolism and their adult family members. *Genet Med.* 2011; 13:67–76. [PubMed: 21150787]
- [14]. Langford N, Stansby G, Avital L. The management of venous thromboembolic diseases and the role of thrombophilia testing: summary of NICE Guideline CG144. *Acute Med.* 2012; 11:138–142. [PubMed: 22993743]
- [15]. Kearon C, Akl EA, Comerota AJ, et al. Antithrombotic therapy for VTE disease: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest.* 2012; 141(2 Suppl):e419S–494S. [PubMed: 22315268]
- [16]. van Sluis GL, Sohne M, El Kheir DY, Tanck MW, Gerdes VE, Buller HR. Family history and inherited thrombophilia. *J Thromb Haemost.* 2006; 4:2182–2187. [PubMed: 16999851]
- [17]. Mazzolai L, Duchosal MA. Hereditary thrombophilia and venous thromboembolism: critical evaluation of the clinical implications of screening. *Eur J Vasc Endovasc Surg.* 2007; 34:483–488. [PubMed: 17588784]
- [18]. Smith TW, Pi D, Hudoba M, Lee AY. Reducing inpatient heritable thrombophilia testing using a clinical decision-making tool. *J Clin Pathol.* 2014; 67:345–349. [PubMed: 24170209]
- [19]. Favaloro EJ, McDonald D, Lippi G. Laboratory investigation of thrombophilia: the good, the bad, and the ugly. *Semin Thromb Hemost.* 2009; 35:695–710. [PubMed: 20013536]
- [20]. Pernod G, Biron-Andreani C, Morange PE, et al. Recommendations on testing for thrombophilia in venous thromboembolic disease: a French consensus guideline. *J Mal Vasc.* 2009; 34:156–203. [PubMed: 19645086]
- [21]. European Genetics F, Cardiovascular Disease E, Research T. et al. Thrombophilia and venous thromboembolism. International consensus statement. Guidelines according to scientific evidence. *Int Angiol.* 2005; 24:1–26. [PubMed: 15876995]
- [22]. Somma J, Sussman II, Rand JH. An evaluation of thrombophilia screening in an urban tertiary care medical center: A "real world" experience. *Am J Clin Pathol.* 2006; 126:120–127. [PubMed: 16753592]
- [23]. Mahajerin A, Obasaju P, Eckert G, Vik TA, Mehta R, Heiny M. Thrombophilia testing in children: a 7 year experience. *Pediatr Blood Cancer.* 2014; 61:523–527. [PubMed: 24249220]
- [24]. Moll S, Varga EA. Homocysteine and MTHFR mutations. *Circulation.* 2015; 132:e6–e9. [PubMed: 26149435]

- [25]. Timp JF, Lijfering WM, Flinterman LE, et al. Predictive value of factor VIII levels for recurrent venous thrombosis: results from the MEGA follow-up study. *J Thromb Haemost.* Aug 13.2015 doi:10.1111/jth.13113. [Epub ahead of print].
- [26]. Wilson WA, Gharavi AE, Koike T, et al. International consensus statement on preliminary classification criteria for definite antiphospholipid syndrome: report of an international workshop. *Arthritis Rheum.* 1999; 42:1309–1311. [PubMed: 10403256]
- [27]. Miyakis S, Lockshin MD, Atsumi T, et al. International consensus statement on an update of the classification criteria for definite antiphospholipid syndrome (APS). *J Thromb Haemost.* 2006; 4:295–306. [PubMed: 16420554]

Highlights

- Thrombophilia testing occurred in 24% of patients with VTE in this study
- Tested patients often did not have an indication for a thrombophilia workup
- Testing was frequently performed during times where results were unreliable
- Thrombophilia results did not appear to influence duration of anticoagulation
- Methods to decrease inappropriate thrombophilia testing should be explored

Table I**Baseline Characteristics Overall and by Thrombophilia Testing Status**

Characteristic	Overall Cohort (n=1314)	Tested (n=315)	Not Tested (n=999)	p-value
Mean Age ^a (SD)	64.7 (15.9)	55.0 (15.5)	67.8 (14.7)	<0.001
Age < 50 years ^a	259 (19.7%)	120 (38.1%)	139 (13.9%)	<0.001
Male	657 (50.0%)	157 (49.8%)	500 (50.0%)	0.887
VTE Type ^b				
Lower Extremity DVT	630 (48.0%)	156 (49.5%)	474 (47.5%)	0.516
Upper Extremity DVT	107 (8.1%)	14 (4.4%)	93 (9.3%)	0.006
Pulmonary Embolism	704 (53.6%)	177 (56.2%)	527 (52.8%)	0.290
Other	60 (4.6%)	18 (5.7%)	42 (4.2%)	0.258
Thromboembolic Risk Factors				
Cancer	284 (21.6%)	24 (7.6%)	260 (26.0%)	<0.001
Family History of VTE	77 (5.9%)	47 (14.9%)	30 (3.0%)	<0.001
Heart Failure	91 (6.9%)	4 (1.3%)	87 (8.7%)	<0.001
Hormone Therapy at index VTE	119 (9.1%)	49 (15.6%)	70 (7.0%)	<0.001
Hospitalization in 30 days prior to index VTE	351 (26.7%)	47 (14.9%)	304 (30.4%)	<0.001
Indwelling Venous Catheter at index VTE	86 (6.5%)	7 (2.2%)	79 (7.9%)	0.002
Inflammatory Bowel Syndrome	10 (0.8%)	2 (0.6%)	8 (0.8%)	0.766
Lung Disease	144 (11.0%)	15 (4.8%)	129 (12.9%)	<0.001
Non-Surgical Trauma in 7 days prior to index VTE	77 (5.9%)	22 (7.0%)	55 (5.5%)	0.325
Pregnancy at index VTE	9 (0.7%)	7 (2.2%)	2 (0.2%)	<0.001
Prolonged Immobility in 7 days prior to index VTE	209 (15.8%)	55 (17.5%)	154 (15.4%)	0.572
Recurrent VTE	163 (12.4%)	38 (12.1%)	125 (12.5%)	0.833
Sepsis	32 (2.4%)	4 (1.3%)	28 (2.8%)	0.119
Surgery in 30 days prior to index VTE	212 (16.1%)	44 (14.0%)	168 (16.8%)	0.231
Met Eligibility Criteria for Thrombophilia Testing ^c	359 (27.3%)	142 (45.1%) ^d	217 (21.7%)	<0.001
Met Eligibility Criteria for Thrombophilia Testing (alternate definition) ^d	201 (15.3%)	79 (25.1%) ^f	122 (12.2%)	<0.001

e - No surgery, no prolonged immobility, no non-surgical trauma, no hospitalization, no hormone therapy, no cancer, and no pregnancy AND a family history of VTE, VTE recurrence, or age <50 years at the time of index VTE

DVT - deep vein thrombosis; VTE - venous thromboembolism

^a - As of date of index VTE

^b - More than one type of VTE possible

^c - No surgery in the 30 days prior to index VTE date AND a family history of VTE, VTE recurrence, or age <50 years at the time of index VTE

^d - 55 (38.7%) and 73 (51.4%) of these patients had their testing performed within seven and 90 days of their index VTE, respectively

f - 39 (49.4%) and 48 (60.8%) of these patients had their testing performed within seven and 90 days of their index VTE, respectively

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

Table II

Testing Characteristics and Types of 315 Adult Patients with Acute VTE Tested for Thrombophilia

Characteristic	Value
Positive for At Least One Test	62 (19.7%)
Testing Performed within Seven Days of Index VTE	111 (35.2%)
Testing Performed within 90 Days of Index VTE	159 (50.5%)
Median Count of Unique Thrombophilia Tests Performed (IQR)	11 (7-14)

Test Type		
Test	Tested ^a	Positive ^b
Factor V Leiden	260 (82.5%)	43 (16.5%) ^c
Prothrombin G20210A	280 (88.9%)	12 (4.3%) ^d
Beta2-Glycoprotein I IgG	101 (32.1%)	3 (3.0%)
Antithrombin Deficiency	154 (48.9%)	4 (2.6%)
Protein S Deficiency	151 (47.9%)	2 (1.3%)
Lupus Anticoagulant	255 (81.0%)	2 (0.8%)
Protein C Deficiency	150 (47.6%)	1 (0.7%)
Anticardiolipin Ab IgG	299 (94.9%)	1 (0.3%)

IQR - interquartile range; VTE – venous thromboembolism

^a - Percent of the 315 patients with at least one test^b - Percent of the patients tested^c - 40 were heterozygous and 3 were homozygous^d - All patients are heterozygous

Table III

Characteristics of by Thrombophilia Testing Status

Characteristic	Thrombophilia Positive (n=62)	Thrombophilia Negative (n=253)	Not Tested (n=999)	p-value ^a
Mean Age ^b (SD)	54.9 (14.2) ^c	55.0 (15.8)	67.8 (14.7)	<0.001
Age < 50 years ^b	20 (32.3%) ^c	100 (39.5%)	139 (13.9%)	<0.001
Male	35 (56.5%)	122 (48.2%)	504 (50.5%)	0.500
Venous Thromboembolism Type ^d				
Lower Extremity DVT	37 (59.7%)	119 (47.0%)	474 (47.5%)	0.165
Upper Extremity DVT	2 (3.2%) ^e	12 (4.7%)	93 (9.3%)	0.022
Pulmonary Embolism	30 (48.4%)	147 (58.1%)	527 (52.8%)	0.220
Other	4 (6.5%)	14 (5.5%)	42 (4.2%)	0.400
Thromboembolic Risk Factors				
Cancer	2 (3.2%) ^c	22 (8.7%)	260 (26.0%)	<0.001
Family History of VTE	13 (21.0%) ^c	34 (13.4%)	30 (3.0%)	<0.001
Heart Failure	1 (1.6%) ^e	3 (1.2%)	87 (8.7%)	<0.001
Hormone Therapy at index VTE	8 (12.9%) ^e	41 (16.2%)	70 (7.0%)	<0.001
Hospitalization in 30 days prior to index VTE	6 (9.7%) ^c	41 (16.2%)	304 (30.4%)	<0.001
Indwelling Catheter at index VTE	1 (1.6%) ^e	6 (2.4%)	79 (7.9%)	<0.001
Inflammatory Bowel Syndrome	0 (0.0%)	2 (0.8%)	8 (0.8%)	0.780
Lung Disease	4 (6.5%) ^e	11 (4.4%)	129 (12.9%)	<0.001
Non-Surgical Trauma in 7 days prior to index VTE	9 (14.5%) ^f	13 (5.1%)	55 (5.5%)	0.012
Pregnancy at index VTE	1 (1.6%) ^e	6 (2.4%)	2 (0.2%)	0.001
Prolonged Immobility in 7 days prior to index VTE	17 (27.4%) ^g	38 (15.0%)	154 (15.4%)	0.039
Recurrent VTE	9 (14.5%)	29 (11.5%)	125 (12.5%)	0.790
Sepsis	1 (1.6%)	3 (1.2%)	28 (2.8%)	0.322
Surgery in 30 days prior to index VTE	5 (8.1%)	39 (15.4%)	168 (16.8%)	0.181
Met Eligibility Criteria for Thrombophilia Testing ⁱ	27 (43.6%) ^h	115 (45.5%)	217 (21.7%)	<0.001
Met Eligibility Criteria for Thrombophilia Testing (alternate definition) ^j	14 (22.6%) ^h	65 (25.7%)	122 (12.2%)	<0.001

DVT - deep vein thrombosis; VTE - venous thromboembolism

^a - Across groups^b - As of date of index VTE^c - p<0.001 compared to Thrombophilia Negative and Not Tested Patients

^d – Patients could have had more than one type of VTE

^e – p<0.05 compared to Not Tested patients

^f – p<0.01 compared to Thrombophilia Negative and Not Tested Patients

^g – p<0.05 compared to Thrombophilia Negative and Not Tested Patients

^h – p<0.001 compared to Not Tested patients

ⁱ – No surgery in the 30 days prior to index VTE date AND a family history of VTE, VTE recurrence, or age <50 years at the time of index VTE

^j – No surgery, no prolonged immobility, no non-surgical trauma, no hospitalization, no hormone therapy, no cancer, and no pregnancy AND a family history of VTE, VTE recurrence, or age <50 years at the time of index VTE

Table IV

Association of Factors with Thrombophilia Testing

Factor	Adjusted Odds Ratio	95% Confidence Interval
Age < 50 years	2.73	1.98 - 3.75
Cancer	0.31	0.19 - 0.48
Family History of VTE	3.62	2.17 - 6.02
Heart Failure	0.20	0.07 - 0.57
Hormone Use	1.69	1.09 - 2.63
Indwelling Catheter	0.49	0.19 - 1.31
Lung Disease	0.54	0.30 - 0.95
Recent Hospitalization	0.52	0.36 - 0.75
Sepsis	0.91	0.35 - 1.58
Upper Extremity DVT	0.74	0.35 - 1.58

c-statistic=0.762

DVT - deep vein thrombosis; VTE - venous thromboembolism

Table VAssociation of Factors with a Positive Thrombophilia Test^I

Factor	Adjusted Odds Ratio	95% Confidence Interval
Age < 50 years	0.75	0.40 – 1.40
Cancer	0.34	0.07 – 1.56
Family History of VTE	1.85	0.88 – 3.89
Lower Extremity DVT	1.51	0.84 – 2.74
Non-Surgical Trauma	2.92	1.13 – 7.58
Prolonged Immobility	2.18	1.08 - 4.41
Recent Hospitalization	0.78	0.28 - 2.22
Recent Surgery	0.43	0.14 – 1.37
Upper Extremity DVT	0.82	0.16 – 4.05

c-statistic=0.684

DVT - deep vein thrombosis; VTE - venous thromboembolism

^I - Amongst patients who had at least one thrombophilia test (n=315)