Evolving paradigm in thrombophilia screening

Noman Ashraf^a, Nathan Visweshwar^c, Michael Jaglal^b, Lubomir Sokol^b and Damian Laber^b

The role of genetic thrombophilia screening for identifying a hypercoagulable state in the management of venous thromboembolism. We searched MEDLINE and EMBASE from 1995 to 2017, the websites of the professional bodies including American Society of Hematology, British Society of Hematology, International Society of Thrombosis and Hemostasis, College of American Pathologists, American College of Medical Genetics, and American Society of obstetrics and gynecology for their clinical practice guidelines. We used search strategy terms – venous thromboembolism, inherited, thrombophilia, and hypercoagulable state. Thrombophilia screening does not alter management in pregnancy, infertility, recurrent miscarriages, in primary occlusive arterial syndromes, and for primary prevention in relatives of venous thromboembolism patients considering hormonal manipulation including oral contraceptives. Routine thrombophilia screening for identifying a hypercoagulable state is not indicated in venous thromboembolism, as it is only useful in a select group of patients. There is no

difference in the treatment of venous thromboembolism in patients with or without an inherited hypercoagulable state. *Blood Coagul Fibrinolysis* 30:249–252 Copyright © 2019 The Author(s). Published by Wolters Kluwer Health, Inc.

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^aHematology/Oncology Section, Department of Hematology, James A. Haley Veterans' Hospital, ^bDepartments of Hematology/Medical Oncology, H. Lee Moffitt Cancer Center & Research Institute and ^cDepartment of Hematology, Morsani College of Medicine, University of South Florida, Tampa, Florida, USA

Correspondence to Nathan Visweshwar, MD, FRCPC, Department of Hematology, Morsani College of Medicine, University of South Florida, Tampa, FL 33612, USA
E-mail: nathan.visweshwar@va.gov

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Introduction

Venous thromboembolism (VTE) most commonly presents as deep venous thrombosis (DVT), pulmonary embolism, or both. Presentation of VTE can range from clinically asymptomatic incidental discovery by imaging, to highly symptomatic DVT or even fatal pulmonary embolism. Although most patients have an obvious provoking risk factor (e.g. surgery, prolonged immobilization, hospitalization, etc.) some features are suggestive of an inherited thrombophilia including an early age of onset (less than 50 years), a family history of VTE in first degree relatives, recurrent unprovoked VTEs, skin necrosis with warfarin or thrombosis in unusual sites including the portal, splanchnic and cerebral venous systems. Even in patients with an inherited thrombophilia, presentation can vary from an episodic disorder with prolonged asymptomatic phases to frequent recurrent VTEs. The exact prevalence of inherited thrombophilia is not known and varies between different racial groups. To complicate matters, there are yet many unidentified genetic abnormalities accounting for the high number of unexplained VTEs clustering in families with no identifiable genetic defects.

Epidemiology

Pulmonary embolism has an estimated annual incidence of two to three cases per 1000 in the general United States population, with a high fatality rate, if left untreated [1]. This is likely an underestimate, as the prevalence of

pulmonary embolism has been reported to be 7–30% in autopsy series [2,3]. The inherited defects of thrombophilia account for less than 10% of patients with VTE [4]. In the community, the Leiden Thrombophilia Study (LETS) demonstrated that an increased risk for VTE is mostly associated with a variety of acquired causes [5]. About 25–50% of patients presenting with a first episode of VTE have no clear provoking risk factors – inherited or acquired [6]. Recurrence rate of 5–10% for the initial 2 years and 1–3% per year thereafter are reported if patients with unprovoked venous thromboembolism do not receive anticoagulant therapy on a long-term basis [7].

Studies of VTE epidemiology are available mostly in populations of Caucasian origin, with sparse data available for others [8]. The overall incidence of VTE may be higher in African-Americans than in Asians [8]. Hence, prevalence and type of inherited hypercoagulable state is altered by racial differences [9].

Acquired factors in combination with inherited factors contribute to the development of VTE and have implications for both susceptibility and treatment of VTE [10]. The hypercoagulable workup for VTE, should progress from a detailed history focusing on identifying any provoking risk factors, prior history of VTEs and a detailed family history along with physical examination, followed by testing for inherited and acquired disorders based on the likelihood that it will change medical management for the patient or their family members.

Genetic screening for thrombophilia

Genetic studies suggest that common hereditary factors for thromboembolism vary widely according to the racial diversity in the population. Factor V Leiden mutation, prothrombin G20210A mutation and hyperhomocysteinemia occur mainly in the Caucasian population [11]. Africans have significantly lower protein S ($P < 0.001$) and protein C ($P = 0.049$) and a trend toward lower antithrombin ($P = 0.056$) levels, compared with white controls [12]. Recently developed techniques in genetic screening, particularly, next generation sequencing (NGS) is possibly a better choice to detect genetic risk variants for thrombosis in ethnic groups [13]. The data from NGS confirm that in non-Europeans, the prevalence of factor V Leiden mutation is at least seven times lower than in Europeans [14]. However, PCR performed for wild-type allele and factor V Leiden mutation in a Newark, New Jersey population, including African-Americans, indicates an apparent prevalence of 5% in this population [15]. The prevalence of factor II G20210A heterozygotes among Caucasian populations is 1–6%, whereas in non-Caucasian populations it is very rare or absent [16]. The inheritance and racial differences in coagulation are still poorly understood. Acquiring more insight into genetic and environmental risk factors remains important. This should ultimately lead to better prediction of risk and evidence-based management decisions for such patients [17]. However, most patients with inherited thrombophilia do not develop a VTE in the absence of a confounding acquired defect [18].

Evidence-based tenets of thrombophilia screening

Here, we will discuss the existing paradigm for thrombophilia screening, reviewing the current available evidence.

First, who needs thrombophilia screening?

Rationale: Patients presenting with VTE at a young age (under the age of 50 years), with a history of recurrent thromboembolism, thrombosis occurring in unusual sites including cerebral, portal, mesenteric and hepatic veins, history of thrombosis within first degree relatives, warfarin-induced skin necrosis and thrombosis following use of estrogen-containing contraception or hormone replacement therapy (HRT) are likely to benefit from screening for inherited or acquired thrombophilia [19]. Finding a strong hypercoagulable state has clinical implications for recommendations regarding preventive strategies, long-term anticoagulation for secondary VTE prophylaxis, and discussion with the patient and family members against hormonal contraception.

Second, thrombophilia screening is not necessary for patients with VTE following a major provocation.

Rationale: Extended duration of anticoagulation is not indicated for patients with VTE provoked by a major transient risk factor including surgery, immobility and

trauma (adopting ‘Choosing Wisely’ guidelines published by the American Society of Hematology (ASH), which recommend against testing) [17]. According to ASH, thrombophilia testing in patients with transient risk factors has the potential to cause harm if the duration of anticoagulation is inappropriately prolonged. One caveat to the above recommendation involves patients who experience VTE in the setting of a major transient risk factor but who have additional risk factors such as a strong family history or concurrent exposure to hormonal therapy. As indicated earlier, even patients with an inherited thrombophilia usually do not develop thrombosis in the absence of an acquired risk factor. Testing for thrombophilia should be individualized and clinical judgement used in such cases.

Third, inherited thrombophilia workup is not needed for patients with unprovoked VTE.

Rationale: Patients in this group need long-term anticoagulation therapy, regardless of screening results, provided there is no significant bleeding risk (in line with clinical practice guidelines of the American College of Chest Physicians). A negative thrombophilia screening is not sufficient to stop anticoagulation after a limited time interval following an episode of unprovoked VTE, in a patient with low-bleeding risk and willingness to continue therapy [20]. But one may consider testing for lupus anticoagulant because of the choice of anticoagulant therapy and addition of antiplatelet agents.

Fourth, work up for inherited thrombophilia is not indicated to prevent recurrence of VTE.

Rationale: Thrombophilia testing in patients with first VTE does not reduce the incidence of recurrence in clinical practice [21]. Recurrence risk is the same in patients with and without inherited thrombophilia [22]. Recurrence is mostly prevented by adopting a more vigorous prophylactic regimen in high-risk situations, such as surgery, immobilization, pregnancy, postpartum period and avoiding the use of oral contraceptive pills or hormone replacement therapy. Thrombosis of the same site is often secondary to local causes including chronic fibrosis and scarring of the deep venous system, indwelling central venous catheters, anatomic defects including May–Thurner syndrome (right iliac artery compressing the left iliac vein) and thoracic outlet syndromes.

Fifth, thrombophilia screening is not indicated for primary prevention in relatives of VTE patients considering hormonal manipulation including oral contraceptives.

Rationale: Normal thrombophilia testing does not exclude the risk of future thrombotic events [21]. First degree relatives have a predictable increased risk of thrombosis with estrogen use, even when thrombophilia testing is negative. This is likely a result of complex interactions between an unidentified inherited hypercoagulable state, and acquired factors including vascular

endothelium, tissue factor-bearing microparticles, circulating leukocytes, altered coagulation proteins and fibrinolytic system.

Sixth, thrombophilia testing is not recommended for VTE occurring during pregnancy.

Rationale: Pregnancy and the postpartum period are acquired hypercoagulable states, as the balance between intrinsic coagulation and anticoagulant factors is tilted in favor of the former. Coagulation factors including fibrinogen increase, and anticoagulants, such as protein S decrease during pregnancy and the postpartum period [23]. Avoidance of future use of combination oral contraceptives and antenatal/postpartum VTE prophylaxis during subsequent pregnancies are recommended, irrespective of thrombophilia status

Seventh, thrombophilia screening is not indicated for recurrent arterial thromboembolic episodes without VTE.

Rationale: Most arterial thromboses are secondary to underlying systemic disorders including dyslipidemia, hypertension, diabetes mellitus and atherosclerosis [24]. Arterial thrombosis results from platelet-rich thrombi with underlying atherosclerosis, whereas hypercoagulable states result in fibrin-rich thrombi producing mainly venous thromboembolism. An exception to this recommendation would be young patients or those lacking traditional risk factors for arterial thrombosis. Such patients should be evaluated for antiphospholipid antibody syndrome – an acquired hypercoagulable state associated with increased risk of arterial thrombosis.

Eighth, clinicians should adhere to the clinical practice guidelines available, while ordering a hypercoagulable work-up.

Rationale: The American College of Medical Genetics (ACMG) and College of American Pathologists recommend against testing for methyl tetrahydrofolate reductase (MTHFR) polymorphism as part of workup for thrombophilia, recurrent pregnancy loss or for at-risk family members [25]. The MTHFR deficiency leads to hyperhomocysteinemia, which was thought to lead to an increased risk for venous thromboembolism, coronary artery disease and recurrent pregnancy loss. However, recent data have disproven an association between hyperhomocysteinemia and the risk for coronary artery disease, and between the MTHFR polymorphism status and risk for venous thromboembolism [25,26].

Ninth, testing for lupus anticoagulant should not be performed while the patient is receiving rivaroxaban, dabigatran and enoxaparin.

Rationale: Presence of these agents in the blood results in false positive lupus anticoagulant testing, not only on screening, but also in confirmatory studies with rivaroxaban, dabigatran and enoxaparin [27]. Such erroneous results may lead to unnecessary prolongation of the

anticoagulant treatment regimen with its antecedent risks of excessive bleeding.

Tenth, routine thrombophilia testing in patients undergoing infertility evaluation should be avoided.

Rationale: Inherited thrombophilia testing in infertility is controversial. There is no evidence to support a strong association between thrombophilia and infertility. Thrombophilia testing in this setting may increase cost, with minimal potential benefit and lead to inappropriate use of anticoagulants with no proven benefit [28,29].

Eleventh, use of low molecular weight heparin in pregnant women with recurrent miscarriages (>3) does not prevent fetal loss, with or without inherited thrombophilia.

Rationale: The use of antepartum low-molecular-weight heparin (LMWH) prophylaxis to prevent recurrent placenta-mediated pregnancy complications has become common practice despite limited and conflicting evidence to support its use. Use of LMWH does not prevent recurrent placenta-mediated pregnancy complications in women with and without inherited thrombophilia [30]. In a meta-analysis of randomized controlled trials comparing LMWH vs. no LMWH in women with inherited thrombophilia and prior late (≥ 10 weeks) or recurrent early (< 10 weeks) pregnancy loss, there was no significant difference in live birth rates with the use of LMWH compared with no LMWH (relative risk, 0.81; 95% confidence interval, 0.55–1.19; $P = .28$) [31].

Finally, a negative thrombophilia screening for a patient should not be interpreted as absence of a hypercoagulable state, as presently available tests are inadequate to identify inherited risks of VTE.

Rationale: The inherited hypercoagulable state can be identified by personal and family history of patients with VTE. The thrombophilia screening also does not help in decision-making, future VTE prophylaxis, length of anticoagulation therapy, recurrence of VTE, help testing other family members or identify the cause of fatal VTE [22].

Conclusion

Hypercoagulable workup lacks clinical relevance unless the test results guide the management of VTE. Random genetic screening may not be relevant to a specific population. Thrombophilia workup must not be done for the sole purpose of identifying a genetic defect for future family screening. Thus far, hypercoagulable workup has not been shown to prevent recurrence of VTE, prevent postphlebotic syndrome, help guide the appropriate antithrombotic regimen or assess the duration of anticoagulant therapy. Therefore, testing for inherited and acquired hypercoagulable disorders should be pursued only in patients with VTE who are at increased risk, and who may benefit from testing for an underlying thrombophilia. Obesity, hormonal manipulation and a sedentary lifestyle

are significant but modifiable risk factors, even in patients with inherited hypercoagulable states. Therefore, in inherited thrombophilia, behavioral modification, including weight loss, aerobic exercise and avoiding hormonal manipulation are of paramount importance to prevent future thrombotic events.

Future direction

We need further research to better understand the molecular basis and pathophysiology of thrombosis, interaction of genetic mutation of coagulation factors in hemostasis, advance the knowledge of interaction between genetic and acquired risk factors, and improve diagnostic accuracy and therapeutic strategy of hypercoagulable states to ultimately decrease mortality from VTE.

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Conflicts of interest

There are no conflicts of interest.

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