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ONE MINUTE CONSULT
BRIEF ANSWERS TO SPECIFIC CLINICAL QUESTIONS

Q: Should every patient with an unprovoked venous thromboembolism have a hypercoagulable workup?

A: The decision to order a hypercoagulable workup for a patient with an unprovoked venous thromboembolism (VTE) must be individualized based on the patient's clinical picture, medical history, and family history. This medical decision remains controversial, as no clear guidelines in the United States have been established on this topic. Testing patients with an unprovoked VTE may lead to excessive medical costs, but when done methodically, hypercoagulable studies may yield valuable results. Ultimately, the decision to test is made on a case-by-case basis.

See related editorial, page 535

UNPROVOKED VTE

VTE most commonly presents either as a deep vein thrombosis or pulmonary embolism. VTE is considered provoked if the patient has a temporary or a permanent risk factor. If there are no identifiable risk factors, then it is considered an unprovoked VTE.[1]

VTEs are diagnosed with a combination of clinical findings and imaging results. Treatment focuses on resolving active thromboses and preventing recurrence. This is achieved with oral factor Xa inhibitors taken for at least 3 months. Moreover, the American College of Chest Physicians recommends extended-duration anticoagulation for select patients with provoked VTEs and most, if not all, patients with unprovoked VTEs.[2] The American Society of Hematology even recommends indefinite anticoagulation for recurrent VTE as long as the patient can tolerate the anticoagulants.[3] Of note, oral vitamin K antagonists (ie, warfarin) are preferred anticoagulants for patients diagnosed with antiphospholipid syndrome.[2,3]

Treatment is started whether the VTE is provoked or unprovoked. First-time provoked VTEs do not require further workup. On the other hand, unprovoked VTEs may require a hypercoagulable workup.

THE HYPERCOAGULABLE WORKUP

Multiple studies in various hospital settings and locations have highlighted the number of inappropriate hypercoagulable tests ordered. One study showed that up to 55% of Medicare patients with provoked VTE received a hypercoagulable workup.[4] These studies pointed to various knowledge gaps and a lack of consistent guidelines as potential causes for inappropriate testing.[5–7] What to test, when to test, and who to test are important questions to consider.

The hypercoagulable workup most often includes 5 tests for inherited thrombophilia: factor V Leiden, prothrombin G20210A mutation, protein C deficiency, protein S deficiency, and antithrombin III deficiency.[8] Tests necessary to diagnose antiphospholipid syndrome might be ordered in certain clinical scenarios; these tests include the lupus anticoagulant functional assay (eg, dilute Russell's viper venom test, patient plasma correction tests), anti-beta-2-glycoprotein 1 antibody (immunoglobulin [Ig] M, IgG), and anticardiolipin antibody (IgM, IgG). One test that should be ordered

doi:10.3949/ccjm.91a.24016

sparingly is the methylene tetrahydrofolate reductase (*MTHFR*) gene test, as several studies have shown that *MTHFR* polymorphisms may not be risk factors for VTE.[9–11]

The ideal time to test patients depends on the nature of the test. For instance, factor V Leiden and prothrombin G20210A mutation are genetic tests, so these may be ordered any time. On the other hand, protein C deficiency, protein S deficiency, and antithrombin III deficiency lead to anticoagulant protein deficiencies during the acute phase of an illness, so testing at that time may lead to unreliable test results.[12] Another factor to consider is whether patients are currently taking anticoagulants. For example, oral factor Xa inhibitors may lead to false-positive lupus anticoagulant assays. Patients should be off oral factor Xa inhibitors for at least 2 to 3 days before testing, and those on a vitamin K antagonist should have therapy held for at least 2 weeks.[8] When testing to diagnose antiphospholipid syndrome, 2 sets of tests must be ordered 12 weeks apart.[8]

A patient with a personal history of recurrent VTE, a family history of VTE, or both may benefit from a hypercoagulable workup. On the other hand, patients with thromboses in the arterial circulation and unusual venous sites (ie, Budd-Chiari, cerebral venous thrombosis) may benefit from an antiphospholipid syndrome workup as this may affect the choice of oral anticoagulants. Patients younger than 45 who develop VTE may benefit from a hypercoagulable and antiphospholipid syndrome workups.[4,8]

POTENTIAL BENEFITS OF TESTING

Hereditary thrombophilias have not been shown to increase the risk of recurrent unprovoked VTEs.[13] Thus, the results of a hypercoagulable workup may only be relevant in select patients.[14] However, there may still be reasons why a patient with an unprovoked VTE should get a hypercoagulable workup.

First, testing allows clinicians to provide guideline-directed recommendations to patients. As noted above, if the hypercoagulable workup results are positive, the American Society of Hematology recommends indefinite use of oral factor Xa inhibitors while tolerated.

Second, some patients are simply curious as to what caused their unprovoked VTE.

Third, a patient may want to know about inherited conditions that could affect their offspring. People with thrombophilias are at an increased risk of developing VTE, which is compounded by taking combined oral contraceptives.[15] Patients found to have thrombophilia could be advised against using combined oral contraceptives.

Finally, doing a hypercoagulable workup may facilitate prevention of flight-related VTE through "flight prophylaxis."[16] A literature review from 2018 on this topic highlighted the Long Flights Thrombosis (LONFLIT)-3 study, which showed that taking low-molecular-weight heparin 2 to 4 hours before departure drastically reduced the risk of VTE.[16] At that time, there were no studies demonstrating the role of oral factor Xa inhibitors in preventing flight-related VTE.

CONCLUSION

In patients with an initial provoked VTE, a hypercoagulable workup is not necessary. Patients who develop clots at unusual sites and are younger than 45 may benefit from an antiphospholipid syndrome workup. Left in the middle are patients with unprovoked VTEs. For these patients, clinicians must take an individualized approach that considers personal and family history to determine the appropriateness of a hypercoagulable workup. Knowing the nuances around testing may increase the value of this workup. A retrospective analysis showed that implementing local guidelines on thrombophilia testing reduced healthcare costs and improved patient care.[17] Establishing consensus guidelines in the United States may optimize the value of these tests further. Along these lines, the National Institute for Health and Care Excellence in England and Wales recommends thrombophilia testing for patients with an unprovoked VTE if it is recurrent or if there is a family history of VTE.[18] Other than these suggestions, a readily available medical calculator that incorporates multiple factors may be helpful in guiding a clinician on when to order a hypercoagulable workup for a patient with an unprovoked VTE.

DISCLOSURES

The authors report no relevant financial relationships which, in the context of their contributions, could be perceived as a potential conflict of interest.

REFERENCES

1. **Kearon C, Ageno W, Cannegieter SC, et al.** Categorization of patients as having provoked or unprovoked venous thromboembolism: guidance from the SSC of ISTH. J Thromb Haemost 2016; 14(7):1480–1483. doi:10.1111/jth.13336
2. **Stevens SM, Woller SC, Baumann Kreuziger L, et al.** Executive summary: antithrombotic therapy for VTE disease: second update of the CHEST Guideline and Expert Panel report. Chest 2021; 160(6): 2247–2259. doi:10.1016/j.chest.2021.07.056
3. **Ortel TL, Neumann I, Ageno W, et al.** American Society of Hematology 2020 guidelines for management of venous thromboembolism: treatment of deep vein thrombosis and pulmonary embolism. Blood Adv 2020; 4(19):4693–4738. doi:10.1182/bloodadvances.2020001830
4. **Gupta A, Sarode R, Nagalla S.** Thrombophilia testing in provoked venous thromboembolism: a teachable moment. JAMA Intern Med 2017; 177(8):1195–1196. doi:10.1001/jamainternmed.2017.1815
5. **Virparia R, Brunetti L, Vigdor S, Adams CD.** Appropriateness of thrombophilia testing in patients in the acute care setting and an evaluation of the associated costs. J Thromb Thrombolysis 2020; 49(1):108–112. doi:10.1007/s11239-019-01930-w
6. **Gupta A, Patel P, Anwar R, Villanueva D, Vasudevan V, Guevara E.** Hypercoagulable workup in a community hospital setting: to test or not to test; that is the question. J Community Hosp Intern Med Perspect 2019; 9(5):392–396. doi:10.1080/20009666.2019.1655627
7. **Alidoost M, Conte GA, Gupta V, et al.** Trends of ordering hypercoagulability workup at an academic medical center. J Blood Med 2021; 12:369–376. doi:10.2147/JBM.S271478
8. **Connors JM.** Thrombophilia testing and venous thrombosis. N Engl J Med 2017; 377(12):1177–1187. doi:10.1056/NEJMra1700365
9. **Bezemer ID, Doggen CJ, Vos HL, Rosendaal FR.** No association between the common MTHFR 677C->T polymorphism and venous thrombosis: results from the MEGA study. Arch Intern Med 2007; 167(5):497–501. doi:10.1001/archinte.167.5.497
10. **Hickey SE, Curry CJ, Toriello HV.** ACMG practice guideline: lack of evidence for MTHFR polymorphism testing [published correction appears in Genet Med 2020; 22(12):2125]. Genet Med 2013; 15(2):153–156. doi:10.1038/gim.2012.165
11. **Deloughery TG, Hunt BJ, Barnes GD, Connors JM; WTD Steering Committee.** A call to action: MTHFR polymorphisms should not be a part of inherited thrombophilia testing. Res Pract Thromb Haemost 2022; 6(4):e12739. doi:10.1002/rth2.12739
12. **Siu CT, Wolfe Z, DelaTorre M, et al.** Evaluation of thrombophilia testing in the inpatient setting: a single institution retrospective review. PLoS One 2021; 16(9):e0257687. doi:10.1371/journal.pone.0257687
13. **Christiansen SC, Cannegieter SC, Koster T, Vandenbroucke JP, Rosendaal FR.** Thrombophilia, clinical factors, and recurrent venous thrombotic events. JAMA 2005; 293(19):2352–2361. doi:10.1001/jama.293.19.2352
14. **Ashraf N, Visweshwar N, Jaglal M, Sokol L, Laber D.** Evolving paradigm in thrombophilia screening. Blood Coagul Fibrinolysis 2019; 30(5):249–252. doi:10.1097/MBC.0000000000000809
15. **van Vlijmen EF, Wiewel-Verschueren S, Monster TB, Meijer K.** Combined oral contraceptives, thrombophilia and the risk of venous thromboembolism: a systematic review and meta-analysis. J Thromb Haemost 2016; 14(7):1393–1403. doi:10.1111/jth.13349
16. **Marques MA, Panico MDB, Porto CLL, Milhomens ALM, Vieira JM.** Venous thromboembolism prophylaxis on flights. J Vasc Bras 2018; 17(3):215–219. doi:10.1590/1677-5449.010817
17. **Shen YM, Tsai J, Taiwo E, et al.** Analysis of thrombophilia test ordering practices at an academic center: a proposal for appropriate testing to reduce harm and cost. PLoS One 2016; 11(5):e0155326. doi:10.1371/journal.pone.0155326
18. **Jones NR, Round T.** Venous thromboembolism management and the new NICE guidance: what the busy GP needs to know [published correction appears in Br J Gen Pract 2022; 72(718):214]. Br J Gen Pract 2021; 71(709):379–380. doi:10.3399/bjgp21X716765

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