EVIDENCE BASED STATEMENT

DOMAIN 06, Statement 04

TOPIC: "**Proper use of genetic testing for venous thrombo-embolism**"

SEARCH TERMS & SOURCES

("venous thrombosis" OR "venous thromboembolism" OR "VTE") AND ("genetic" OR "inherited thrombophilia") AND ("testing" OR "diagnosis" OR "risk") AND ("meta analysis" OR "Systematic Review")

INCLUSION CRITERIA

- Systematic review or meta-analysis focused on genetic testing for VTE
- From 2012 to 2022

SEARCH RESULT BEFORE - AFTER SELECTION

119 – 7

PERTINENT LITERATURE NOT IDENTIFIED BY THE LITERATURE SEARCH

1. Darlow J, Mould H. Thrombophilia testing in the era of direct oral anticoagulants. Clin Med (Lond). 2021 Sep;21(5):e487-e491.
2. Colucci G, Tsakiris DA. Thrombophilia screening: universal, selected, or neither?. Clinical and Applied Thrombosis/Hemostasis. 2017 Nov;23(8):893-9.
3. Stevens SM, Woller SC, Bauer KA, et al. Guidance for the evaluation and treatment of hereditary and acquired thrombophilia. Journal of thrombosis and thrombolysis. 2016 Jan;41(1):154-64.
4. Connors JM. Thrombophilia testing and venous thrombosis. New England Journal of Medicine. 2017 Sep 21;377(12):1177-87.
5. De Stefano V, Rossi E. Testing for inherited thrombophilia and consequences for antithrombotic prophylaxis in patients with venous thromboembolism and their relatives. Thrombosis and haemostasis. 2013;110(10):697-705.

EVIDENCE BASED STATEMENT

Domain 6; Statement 4

IDENTIFIED REFERENCES

1. Zhang Y, Zhang Z, Shu S, Niu W, Xie W, Wan J, Zhai Z, Wang C. The genetics of venous thromboembolism: a systematic review of thrombophilia families. J Thromb Thrombolysis. 2021 Feb;51(2):359-369. doi: 10.1007/s11239-020-02203-7. PMID: 32623564.
2. Lindström S, Brody JA, Turman C, et al. A large-scale exome array analysis of venous thromboembolism. Genet Epidemiol. 2019 Jun;43(4):449-457. doi: 10.1002/gepi.22187. Epub 2019 Jan 19. PMID: 30659681; PMCID: PMC6520188.
3. Lindström S, Wang L, Smith EN, et al. Genomic and transcriptomic association studies identify 16 novel susceptibility loci for venous thromboembolism. Blood. 2019 Nov 7;134(19):1645-1657. doi: 10.1182/blood.2019000435. PMID: 31420334; PMCID: PMC6871304.
4. Pomero F, Ageno W, Serraino C, Borretta V, Gianni M, Fenoglio L, Prisco D, Dentali F. The role of inherited thrombophilia in patients with isolated pulmonary embolism: a systematic review and a meta-analysis of the literature. Thromb Res. 2014 Jul;134(1):84-9. doi: 10.1016/j.thromres.2014.04.012. Epub 2014 Apr 29. PMID: 24837252.
5. Simone B, De Stefano V, Leoncini E, et al. Risk of venous thromboembolism associated with single and combined effects of Factor V Leiden, Prothrombin 20210A and Methylenetethraydrofolate reductase C677T: a meta-analysis involving over 11,000 cases and 21,000 controls. Eur J Epidemiol. 2013 Aug;28(8):621-47. doi: 10.1007/s10654-013-9825-8. Epub 2013 Jul 31. PMID: 23900608; PMCID: PMC3935237.
6. Dentali F, Ageno W, Bozzato S, Malato A, Gianni M, Squizzato A, Prisco D. Role of factor V Leiden or G20210A prothrombin mutation in patients with symptomatic pulmonary embolism and deep vein thrombosis: a meta-analysis of the literature. J Thromb Haemost. 2012 Apr;10(4):732-7. doi: 10.1111/j.1538-7836.2012.04656.x. PMID: 22329698.
7. Dentali F, Sironi AP, Ageno W, Turato S, Bonfanti C, Frattini F, Crestani S, Franchini M. Non-O blood type is the commonest genetic risk factor for VTE: results from a meta-analysis of the literature. Semin Thromb Hemost. 2012 Jul;38(5):535-48. doi: 10.1055/s-0032-1315758. Epub 2012 Jun 27. PMID: 22740183.

EVIDENCE BASED STATEMENT

Domain 6; Statement 4

TEXT FOR INCLUSION IN THE DOCUMENT

DOMAIN 06, Statement 04, TOPIC: "**Proper use of genetic testing for venous thrombo-embolism**"

There are many inherited genetic risk factors for VTE, including non-O blood type (the most common inherited risk factor for VTE), protein C and S deficiency, factor V Leiden, antithrombin deficiency, prothrombin G20210A, and methylentetrahydrofolate reductase (MTHFR). These inherited risk factors increase VTE risk at any age, but commonly present with VTE in patients younger than 40 years old (**Colucci G, Tsakiris DA. Thrombophilia screening: universal, selected, or neither?. Clinical and Applied Thrombosis/Hemostasis. 2017 Nov;23(8):893-9**).
Screening for inherited thrombophilia is controversial, and may only be performed for specific at-risk groups when it is likely to change management. There is no replacement for a thorough personal and family history and physical exam to evaluate patient risk and determine the need for screening. Current expert recommendations include genetic testing after unprovoked VTE in patients younger than 50, VTE in pregnant patients/OCP/hormone therapy, and VTE in patients with a positive FH. In these patient groups, patients who test positive can be counseled about preventing VTE recurrence by avoiding further risk factors such as OCPs or smoking and using prophylaxis in high-risk events such as surgery (**Stevens SM, Woller SC, Bauer KA, et al. Guidance for the evaluation and treatment of hereditary and acquired thrombophilia. Journal of thrombosis and thrombolysis. 2016 Jan;41(1):154-64**; ***Darlow J, Mould H. Thrombophilia testing in the era of direct oral anticoagulants. Clin Med (Lond). 2021 Sep;21(5):e487-e491**).
Screening may also be performed in patients with a history of multiple pregnancy loss due to the strong association with inherited thrombophilias, and in patients with thrombosis in unusual locations (e.g. cerebral venous sinus thrombosis, porto-mesenteric venous thrombosis) (**Connors JM. Thrombophilia testing and venous thrombosis. New England Journal of Medicine. 2017 Sep 21;377(12):1177-87**). Genetic testing should be considered for young women with a positive family history of VTE prior to oral contraceptive use (**Colucci G, Tsakiris DA. Thrombophilia screening: universal, selected, or neither?. Clinical and Applied Thrombosis/Hemostasis. 2017 Nov;23(8):893-9**; **Stevens SM, Woller SC, Bauer KA, et al. Guidance for the evaluation and treatment of hereditary and acquired thrombophilia. Journal of thrombosis and thrombolysis. 2016 Jan;41(1):154-64**). Physicians should be aware that DOAC use can affect functional assays like deficiency of natural anticoagulants. DOACs typically need to be held for 4-5 half lives to prevent interference with thrombophilia assays. Although data are limited, DOACs appear to be safe and effective in treating VTE for patients with inherited thrombophilias (***Darlow J, Mould H. Thrombophilia testing in the era of direct oral anticoagulants. Clin Med (Lond). 2021 Sep;21(5):e487-e491).**

EVIDENCE BASED STATEMENT

Domain 6; Statement 4

STATEMENT FOR PUBLIC EVIDENCE-BASED AWARENESS

DOMAIN 06, Statement 04

"Genetic testing may be suggested in a first episode of unprovoked thrombosis for patients under 50 years old, thrombosis with the only risk factor of hormonal therapy or pregnancy, and recurrent VTE if it will affect the further clinical decision on treatment and prophylaxis"

4 SELECTED REFEREENCES

1. Colucci G, Tsakiris DA. Thrombophilia screening: universal, selected, or neither?. Clinical and Applied Thrombosis/Hemostasis. 2017 Nov;23(8):893-9.
2. Connors JM. Thrombophilia testing and venous thrombosis. New England Journal of Medicine. 2017 Sep 21;377(12):1177-87.
3. *Darlow J, Mould H. Thrombophilia testing in the era of direct oral anticoagulants. Clin Med (Lond). 2021 Sep;21(5):e487-e491.
4. Stevens SM, Woller SC, Bauer KA, Kasthuri R, Cushman M, Streiff M, Lim W, Douketis JD. Guidance for the evaluation and treatment of hereditary and acquired thrombophilia. Journal of thrombosis and thrombolysis. 2016 Jan;41(1):154-64.

identified LITERATURE BIAS

There is an inherent publication bias favoring studies that find a significant association between specific genes or variants and VTE. The use of meta-analyses to determine the most significant inherited risk factors mitigates, but does not eliminate, this bias.

SUGGESTED NEXT LINES OF RESEARCH

Inherited factors weakly associated with recurrent VTE. Because most guidelines recommend testing for inherited thrombophilia after unprovoked VTE, it would be important to know which thrombophilias are most associated with recurrence. There is a need for further evidence to support the use of DOACs in the management of thrombophilias.