Who should be tested for thrombophilia?

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INTRODUCTION

No general consensus exists in the medical profession as to which patients with venous thromboembolism (VTE) and which family members should be tested for thrombophilias. At least five guidelines or consensus statements exist, some of them outdated.[1–5] They vary markedly in their recommendations as to who should be tested and who should not, suggesting very limited testing,[5] widespread testing,[3] or some intermediate level.[1,2] The goal of the Evaluation of Genomic Applications in Practice and Prevention (EGAPP) Working Group to create a document providing evidence-based guidance whether one should test patients with unprovoked VTE and their family members for Factor V Leiden and the prothrombin 20210G>A mutation is, therefore, laudable.[6]

However, thrombophilia testing remains a complex issue, difficult to condense in a short clear guideline. There are two valid reasons for the clinician to consider undertaking a thrombophilia workup in a patient with unprovoked (also referred to as idiopathic or spontaneous) VTE. First, if identification of a thrombophilia would lead to the recommendation to continue anticoagulation, whereas absence of a thrombophilia would lead to the recommendation to discontinue anticoagulation after the initial 3–6 months of treatment. Second, if identification of a thrombophilia in the VTE patient would lead to testing for the same thrombophilia in first-degree relatives, and different treatment decisions in these relatives would result if they also had the thrombophilia.

PATIENTS WITH UNPROVOKED VTE

Overall, patients with unprovoked VTE have a high risk of recurrence once off anticoagulation—the cumulative risk for recurrent VTE is approximately 10% at 1 year, 30% at 5 years, and 50% at 10 years.[7,8] Because anticoagulation is very effective in preventing recurrences, long-term anticoagulation is recommended in these patients, if risk factors for bleeding are absent and good anticoagulation monitoring is achievable.[9] Finding a thrombophilia in this patient population does not change that recommendation, and absence or presence of inherited thrombophilia has, therefore, not been used in the 2008 American College of Chest Physician guidelines as a major factor to guide duration of anticoagulation.[9]

However, a number of patients have significant problems with warfarin anticoagulation: major or nonmajor bleeding, instability of the international normalized ratio, need for frequent clinic visits for international normalized ratio monitoring, or significant impact on their lifestyle from being on anticoagulation. This is the patient population where identification of predictors of a higher or lower risk of recurrence can have an influence on the decision to discontinue or continue anticoagulation. This is the patient group where finding a "strong" thrombophilia, i.e., one that predicts a higher risk of recurrence, may be of relevance, where continued anticoagulation becomes beneficial and acceptable, despite an increased risk of bleeding or inconvenience. These are the patients I consider for thrombophilia testing.

Are homozygous Factor V Leiden and the double heterozygous state for Factor V Leiden and prothrombin 20210G>A mutation "strong" thrombophilias? The EGAPP report in this issue of *Genetics in Medicine*[6] and the recent systematic review by Segal et al.[10] indicate that homozygosity for Factor V Leiden and maybe also the double heterozygous state are strong predictors of VTE recurrence, with an odds ratio (OR) of 2.65 (95% confidence interval [CI]: 1.18–5.97) and 4.81 (95% CI: 0.50–46.0), respectively. However, this conclusion has recently been questioned by the findings of a large case-control family study, which found that neither of these thrombophilias increase the risk of recurrence.[11] Our knowledge on these issues is in flux.

What has become clear, though, is that the heterozygous Factor V Leiden mutation by itself in patients with unprovoked VTE is only a mild risk factor for VTE recurrence (OR: 1.56; 95% CI: 1.14–2.12), and the heterozygous prothrombin 20210G>A mutation is not a risk factor for recurrence (OR: 1.45; 95% CI: 0.96–2.21).[6,10] Thus, finding one of these two mutations in the heterozygous state does not influence the length of anticoagulation decisions. Thus, the purpose of testing patients with unprovoked VTE for Factor V Leiden and prothrombin 20210G>A mutation is to detect the uncommon homozygous or double heterozygous state, not the simple heterozygous state. It should be formally evaluated, whether such strategy is cost effective and has an impact on outcomes. Thus, I agree with the EGAPP authors' conclusion number 1, expressed in their Summary of Recommendations, that they "recommend against routine testing for Factor V Leiden and/or the prothrombin 20210G>A mutation in adults with idiopathic VTE."[6] However, care needs to be taken to not miss the word "routine" in this sentence. Testing selected patients with unprovoked VTE may be beneficial; testing everybody with unprovoked VTE is, indeed, not useful.

FAMILY MEMBERS OF PATIENTS WITH UNPROVOKED VTE

Barely ever is there an indication for treating an individual who has never had a VTE with long-term anticoagulation, whether a strong thrombophilia is present or not, as the risk for VTE in the majority of such family members is low, and the risk of major bleeding and inconvenience from long-term anticoagulation outweighs the potential benefit of such primary VTE prevention. Thus, I am in agreement with the EGAPP authors' conclusion number 2 in their Summary of Recommendations, in which they "recommend against routine testing for Factor V Leiden and/or the prothrombin 20210G>A mutation in asymptomatic family members of patients with VTE with Factor V Leiden or prothrombin 20210G>A mutation for the purpose for

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considering primary prophylactic anticoagulation," as long as it is clear that this statement is referring to primary long-term anticoagulation prophylaxis.[6]

However, the key question is, whether finding of a strong thrombophilia in a family member should lead to different short-term primary VTE prevention management: (a) an anticoagulant before long-distance travel; at times of nonmajor surgeries, such as arthroscopic knee surgery, or leg immobilization because of casts; in the ante- and/or postpartum period; and (b) longer-term anticoagulant VTE prevention for a few weeks after surgical procedures or hospital admissions where usually only short-term prophylaxis is given. The EGAPP authors appropriately acknowledge the lack of medical scientific knowledge on these issues. This is where the clinician will have to make nonevidence-based patient management decisions in discussion with the patient and family member seeking advice. This is where thrombophilia testing might be appropriate in selected individuals, particularly if a "strong" thrombophilia has already been identified in the index family member who had a VTE.

Finally, and not unimportantly, women may make contraceptive choices based on what they find an acceptable absolute VTE risk. The level of acceptance varies from individual to individual. Knowledge about her personal absolute VTE risk, based on all her VTE risk factors, may help a woman make a more informed decision on a contraceptive method that is acceptable and optimal for her. Knowledge of her thrombophilia status may help with the decision making and may be a reason to offer an asymptomatic family member of a patient with unprovoked VTE thrombophilia testing.

CONCLUSION

What should be self-understood, but seems necessary to mention in our fast-moving and test-focused clinical practice world: when considering thrombophilia testing, the health care professional needs to take the time and have the knowledge to review with the patient and/or family member how the test result will impact the person's management. Advice for or against testing should be given in the context of a discussion of the person's individual VTE risk factors that are obvious without genetic or biochemical/coagulation testing (obesity, smoking, immobility, contraceptive use, etc.), ways to modify them, education about environmental situations that further increase the VTE risk (hospitalization, surgery, travel, etc.), and the symptoms of deep vein thrombosis and pulmonary embolism so that the patient can recognize them and seek early medical care when they occur. The best advice to health care professionals to avoid inappropriate thrombophilia testing is probably: If you don't know what to do with the test result, don't test.

Increasingly, models are being developed and tested to determine which subgroups in the large group of patients with unprovoked VTE are (a) at higher and lower risk for recurrence and (b) at higher or lower risk for major bleeding, so that a more differentiated treatment approach than "everybody with unprovoked VTE who is at low risk for bleeding should get long-term anticoagulation" is possible.[12–15] Eventually, we will know enough about the interactions between the different risk factors for VTE recurrence and for bleeding and will have sufficiently validated data to be able to give more individualized treatment recommendations.

I think the topic of thrombophilia testing—who should be tested, who not; what does the finding of a thrombophilia mean to the patient and/or the patient's family member?—will become increasingly less of a subject of interest and relevance, as we discover that looking at individual thrombophilias does not give us a comprehensive or differentiated enough picture of a person's clotting risk. An assessment of a person's overall clotting tendency—by d-dimer, thrombin generation potential, or other future tests—will eventually make testing for individual thrombophilias look like dinosaur practice. Until then, there are selected patients with unprovoked venous thromboembolism and certain family members in whom I consider testing for a strong thrombophilia, which includes, at this point, Factor V Leiden and prothrombin 20210G>A mutation testing to discover homozygous Factor V Leiden and the double heterozygous Factor V Leiden plus prothrombin 20210G>A state.

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