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New American Society of Hematology Thrombophilia Guidelines Could Provoke Surge in Laboratory Testing

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Guest: Dr. Anna Merrill is a Clinical Associate Professor of Pathology at the University of Iowa Hospitals and Clinics in Iowa City, Iowa.

Bob Barrett: This is a podcast from *Clinical Chemistry*, a production of the Association for Diagnostics & Laboratory Medicine. I'm Bob Barrett.

Venous thromboembolism [VTE], or the formation of a blood clot in a vein, is a potentially life-threatening event. Patients recovering from major surgery are at the highest risk, but individuals with certain predisposing factors may also experience VTE in the absence of a surgical trigger.

Recently, the American Society of Hematology, or ASH, released a new clinical guideline that represents a significant departure from previous recommendations. For the first time, it is recommended that patients who experience VTE without a surgical trigger undergo thrombophilia testing to determine whether they would benefit from long-term anticoagulation. This recommendation has the potential to impact clinical laboratories as roughly 15% percent of VTE cases occur in the absence of a surgical precipitating cause. Are laboratories ready for this increased volume and are thrombophilia test methods sufficiently well-developed to guide patient care decisions?

A new News & Views article, appearing in the February 2025 issue of *Clinical Chemistry,* highlights the 2023 ASH guidelines for thrombophilia testing, describes the reasons for the updated recommendations, and identifies challenges for the clinical laboratory to overcome to support guideline implementation.

In this podcast, we welcome the article's lead author. Dr. Anna Merrill is a Clinical Associate Professor of Pathology at the University of Iowa Hospitals and Clinics, where she oversees clinical chemistry and coagulation. Her research interests include data-driven quality improvement initiatives in all phases of the total testing process.

So, Dr. Merrill, let's get to the basics first. What is venous thromboembolism, or VTE, and what are some provoking triggers?

Anna Merrill: All right. So, venous thromboembolism, or VTE for short, refers to blood clots that form in the veins of the body and VTE includes two different types. Deep vein thrombosis, or DVT--so, this is when a blood clot develops in a deep vein, typically in the lower leg. The other type is a pulmonary embolism, or PE. This is a particularly life-threatening condition when part of a DVT clot breaks off and then travels to the lungs.

It is estimated that about one million cases of VTE occur in the United States annually, and we think about one in 12 individuals will experience VTE at some point in their lifetime. And then, unfortunately, there is significant mortality and morbidity associated with VTE. So, about 20% of individuals will die within a year of their VTE, and then for survivors, they commonly experienced complications.

Now, some triggers that can provoke a VTE include recent surgery, immobilization, trauma, hospitalization, and certain hormonal states like pregnancy or the use of oral contraceptives. So, if VTE has occurred in the absence of any of these provoking triggers, it is considered to be unprovoked. And why it's important to differentiate provoked versus unprovoked VTE is that this differentiation is an important factor that then will guide the duration of anticoagulation therapy following VTE in order to prevent recurrent VTE in the future.

Now to make things even more complicated, not all of these different provoking triggers are created equal in terms of how much they increase the risk for VTE. So, for example, surgery is a pretty strong provoking trigger relative to other transient provoking triggers such as hospitalization, pregnancy, or oral contraceptive use.

Bob Barrett: Next up Doctor, what is thrombophilia?

Anna Merrill: All right, so thrombophilia can be defined as an acquired or inherited predisposition to thrombosis. The most common inherited thrombophilia is heterozygous factor V Leiden mutation. So, in people of European ancestry, about 5% of those folks will have this mutation and it puts those individuals at about a three-to-five-fold increased risk of venous thrombosis.

Now, on the side of acquired thrombophilia, the most common acquired thrombophilia is antiphospholipid syndrome, which interestingly increases the risk for both venous thrombosis and also arterial thrombosis.

Now, where does the clinical laboratory come in? So, thrombophilia can be diagnosed with specific laboratory tests, and even though thrombophilia testing is not necessarily

standardized across all labs, it typically includes assays for both inherited conditions such as the factor V Leiden mutation I talked about earlier or another mutation called the prothrombin gene mutation. Other inherited conditions that are commonly tested for include deficiencies and natural anticoagulants like antithrombin, protein C, and protein S. Thrombophilia testing typically also includes testing for acquired conditions, such as antiphospholipid syndrome.

Bob Barrett: So, following VTE, who should be tested for thrombophilia?

Anna Merrill: This is a good question and somewhat controversial too. So, while thrombophilia certainly can contribute to VTE, by itself it usually isn't a common provoking trigger.

However, in November 2023, the American Society of Hematology, or ASH, released new clinical guidelines for thrombophilia testing and the management of venous thromboembolism. These new guidelines do not recommend thrombophilia testing after unprovoked VTE or VTE provoked by a strong trigger like surgery, since the detection of a thrombophilic condition in these individuals generally does not influence treatment. Individuals who have had an unprovoked VTE should really be treated with long-term anticoagulation, and those with VTE provoked by a strong trigger like surgery should be treated with short-term anticoagulation. This should occur regardless of whether there is an underlying thrombophilia in those two conditions.

Interestingly, for patients of VTE who are provoked by a transient non-surgical trigger, something like hospitalization or pregnancy, these new guidelines do recommend testing for thrombophilia to guide the duration of anticoagulation treatment.

So, in this population of individuals, patients with thrombophilia detected by laboratory tests are treated with long-term or indefinite anticoagulation just like those with unprovoked VTE. Whereas patients without thrombophilia are treated with short-term anticoagulation just like those with a VTE provoked by a strong trigger.

Bob Barrett: How do these new ASH thrombophilia guidelines compare with other thrombophilia guidelines?

Anna Merrill: These new ASH guidelines do deviate from recent guidelines from other organizations. So, one example is the guidelines from the National Institute for Health and Care Excellence. So, these guidelines were originally published in 2020, but they were updated in August of 2023. They do not recommend thrombophilia testing in people who have had VTE provoked for any reason, whether it be a surgical or non-

surgical factor. These new guidelines also deviate from ASH's own prior guidance on the topic.

So, back in 2013, as part of the Choosing Wisely campaign, ASH advised against thrombophilia testing in adults with VTE provoked by major transient risk factors like trauma and immobility, and these types of factors would now fall into the bucket of non-surgical triggers, where thrombophilia testing is newly recommended.

Bob Barrett: Well, please tell us about that change. Why is the change in recommendations to now test for thrombophilia following VTE provoked by non-surgical triggers?

Anna Merrill: This really is a complex question and I think there are multiple contributing factors that led ASH to expand its recommendation for who should be getting thrombophilia testing following VTE. As far as evidence supporting this change, ASH cites that estimates from some observational studies demonstrate that about 40% of patients with VTE provoked by these non-surgical factors will be found to have an underlying thrombophilia by laboratory testing. If we are to continue anticoagulation therapy indefinitely in these patients, it will cut their risk for recurrent VTE in half from about 5% to about 3% in the first year following that initial VTE, while only causing a small increase in bleeding risk.

So, it is worth noting that the risk of VTE recurrence and bleeding was not really extrapolated beyond the first year following VTE. Typically, the bleeding risk does increase over time and may eventually equal or exceed the risk of VTE. So, most of the evidence going into this new recommendation was really focusing on that first year and not necessarily the impacts on lifelong anticoagulation.

Certainly, one factor contributing to the new recommendation to test for thrombophilia and to do indefinite anticoagulation if a thrombophilic condition is detected, is that we do now have access to newer oral anticoagulants like the direct oral anticoagulants, or DOACs. Some examples of these are apixaban or betrixaban, dabigatran, and these do have a lower risk of bleeding compared to their predecessor, which was warfarin, a vitamin K antagonist.

So, therefore, the DOACs do confer a better benefit-risk ratio for long-term anticoagulation. It is safer than it maybe would have been with Warfarin. But this might be true regardless of whether a patient has a thrombophilic condition or not. So, maybe we should be treating all VTE provoked by non-surgical triggers with lifelong anticoagulation and not necessarily making that management decision based on the results of thrombophilia testing.

It's also important to note that ASH clearly acknowledges that this new recommendation for thrombophilia testing following VTE provoked by a non-surgical trigger is a conditional recommendation based on very low certainty and evidence about the effects. And so, more studies and high-quality evidence are definitely still needed in this area.

Bob Barrett: Well, finally Dr. Merrill, what are the implications of the new ASH thrombophilia guidelines for the clinical laboratory?

Anna Merrill: So, given that these guidelines are still relatively new, we aren't really sure yet what the clinical uptake of them will be.

Time will tell on that, but considering that about 15% of the estimated 1 million cases of VTE that happen in the U.S. annually are thought to be provoked by these non-surgical triggers, it means that there is the potential for a significant increase in thrombophilia testing.

So, whether your lab performs the thrombophilia testing in-house, or whether you are sending it out to a reference laboratory, you should be prepared for a potential increase in the volume of this testing. Beyond the logistical challenges that an increase in testing could bring, another complication is that the patients who are most likely to be tested for thrombophilia with these new guidelines may be at increased risk for diagnostic error related to this testing due to a variety of different endogenous and exogenous factors.

So, for example, thrombophilia testing may often be requested soon after a VTE so that a provider knows if this is a patient who will need to have lifelong anticoagulation or just short-term anticoagulation. But this time immediately after VTE is a time where decreased natural anticoagulant activities are actually expected because they can be consumed during the thrombosis process. So, it's not an ideal time to be testing for inherited deficiencies of these natural anticoagulants.

Now another significant issue is the impact of anticoagulants, and specifically, the increasing use of DOACs, on thrombophilia assays. I wouldn't be surprised if the majority of patients for whom thrombophilia testing is now newly recommended are taking a DOAC at the time at which their thrombophilia testing is performed.

So, whether or not a thrombophilia test will be affected or interfered with by an anticoagulant depends on the assay methodology and the anticoagulant's mechanism of action. So, it really can become quite complicated as there can be multiple different methodologies available for a single analyte.

Now, I should mention at this point that there is an ADLM Academy guidance document on this exact topic titled, "Coagulation testing and patients using direct oral anticoagulants." This guidance document is currently open for comments from ADLM members and its goal is to provide practical recommendations for how laboratorians can deal with samples sent for testing from patients who are prescribed DOACs.

So, overall, in the wake of the new ASH thermophilia guidelines, it will be really important for clinical laboratory professionals to be aware of the challenges associated with expanded thrombophilia testing and also, to reach out to your clinicians to make sure that the risk of diagnostic error is mitigated as much as possible.

Bob Barrett: That was Dr. Anna Merrill from the University of Iowa in Iowa City. She served as the lead author of a News & Views article in the February 2025 issue of *Clinical Chemistry,* highlighting the potential impact of the American Society for Hematology guidelines on laboratory test volume and she has been our guest in this podcast on that topic. I'm Bob Barrett. Thanks for listening.