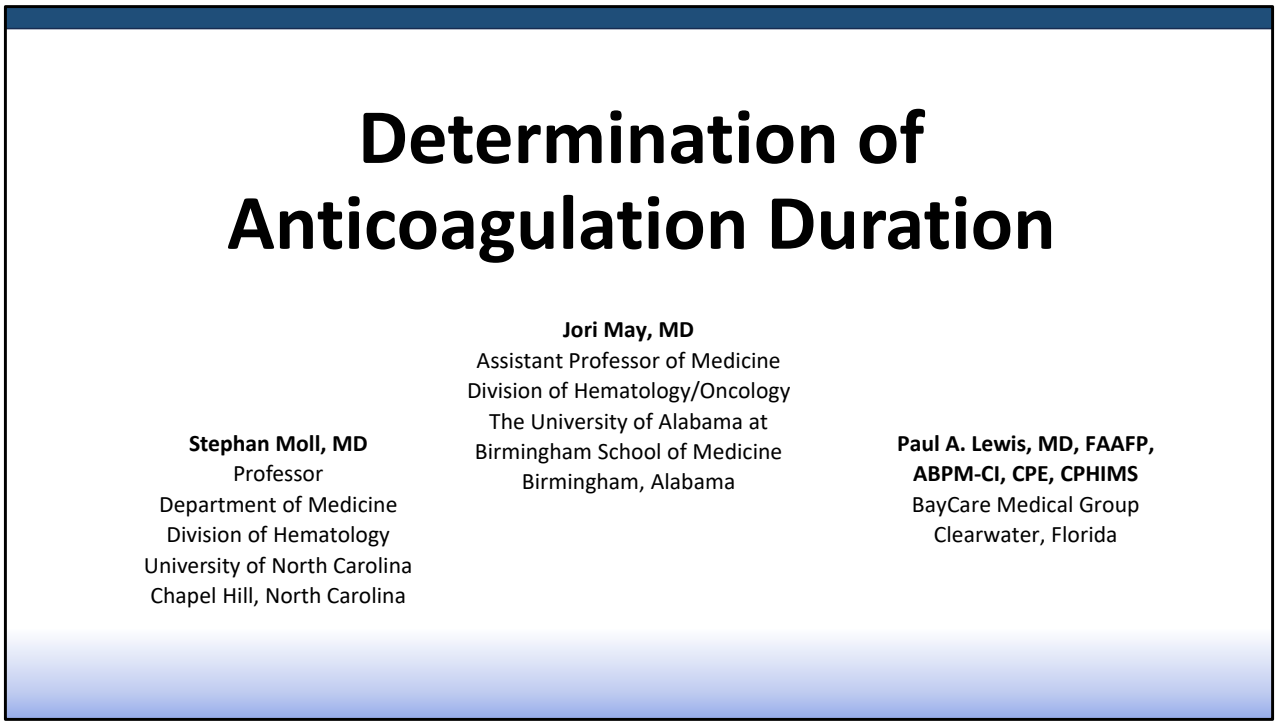


Jori May: So, welcome everyone, thank you for joining us today. We are in our second podcast in our six-podcast series on the diagnosis and management of venous thromboembolism. In our first podcast, we talked about acute diagnosis and management, how we find VTEs and how we start anticoagulation. Today, we're jumping into the question of how long do we anticoagulate a patient, the duration of anticoagulation, and I'm excited for our discussion today.

My name is Jori May. I am an Assistant Professor of Medicine here at the University of Alabama at Birmingham. I'm a hematologist that focuses on the care of patients with thrombosis and coagulation disorders. I have two esteemed panelists with me today and I will ask them to introduce themselves. I'll first say that we will be using first names throughout the podcast. We've agreed amongst the presenters that that's how we will address each other. So, Stephan, could you introduce yourself?

Stephan Moll: Thank you very much, Jori. I'm Stephan Moll. I'm a Professor of Medicine in Hematology at the University of North Carolina in Chapel Hill. I'm a coagulationist. I deal mostly with thrombosis and anticoagulation, but also bleeding disorders and other benign hematology, and I'm thrilled to be on this program. Thank you.

Jori May: Great to have you. And Paul.

Paul Lewis: Yes, hi, thank you, Jori. Paul Lewis, I'm a family physician. I've been in practice now for 20 years with BayCare Medical Group, and I'm also a Clinical Assistant Professor with the University of South Florida in the Department of Family Medicine. Also very excited to be here and have this discussion with you two about this great topic.

Learning Objectives

- Summarize factors to consider when determining duration of anticoagulation in patients with VTE
- Outline the roles of patient management tools such as the recurrence triangle and warfarin/DOAC “hate factor” in determining duration of anticoagulation testing
- Identify which patients require thrombophilia testing and correlate testing results with treatment decisions regarding duration of anticoagulation

Jori May: Alright, let's dive right in. So, our objectives today are going to be first to talk about the factors that you might consider when determining the duration of anticoagulation in a patient with a venous thromboembolism. We're going to hopefully provide you with some tools that are helpful in order to make those decisions and we'll go through details of how to use those specific tools. And then we are going to talk about thrombophilia testing, which is a huge area of question and often comes up in the management of these patients, of basically when to send testing and how that might influence the duration of anticoagulation.

Case 1

- 53-year-old female presented to the ED with 1 week of progressive shortness of breath
- Found to have bilateral main PA VTE
- Troponin elevation and evidence of hemodynamic instability
  - She was taken for thrombectomy in addition to anticoagulation
- She had a hip replacement 1 month prior, was placed on aspirin 81 mg BID for 4 weeks after surgery

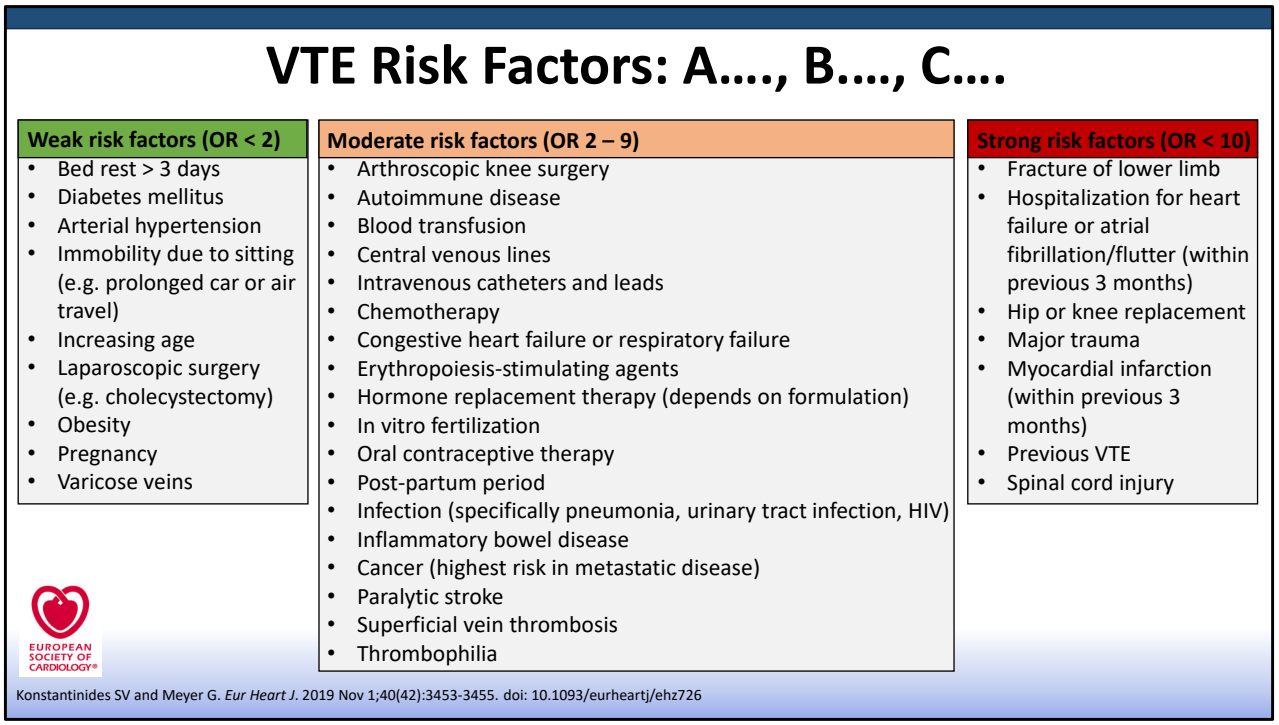
Jori May: So, we are going to try and make this as clinically useful for you as possible. We'll dive right into our first case. We've got a 53-year-old female who came to the emergency department with a week of progressive shortness of breath. She was ultimately found to have bilateral pulmonary embolism involving the main pulmonary arteries.

She was quite ill. She had a troponin elevation and some evidence of hemodynamic instability, and she required a thrombectomy in addition to starting anticoagulation. Her history was notable for a hip replacement one month prior. After hip replacement, she had been placed on aspirin 81 milligrams twice daily for four weeks after surgery for the prevention of venous thromboembolism. So, a lot to unpack in this case.

Faculty Discussion

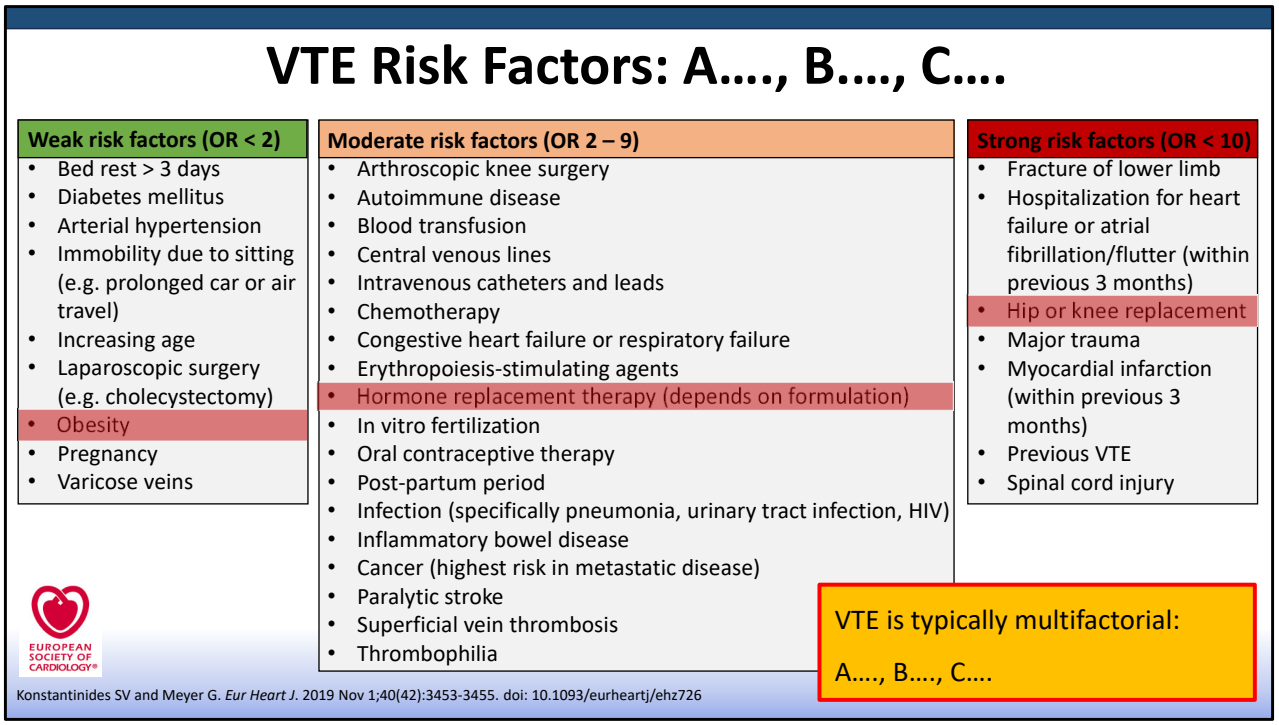
Jori May: Stephan, we're going to start with you and if you can maybe talk to us a little bit about kind of how we define risk factors in VTE. We used to have this framework of, we would say things were provoked and unprovoked and that still holds true to a certain extent, but I was wondering if you could tell us about some newer terminology that's used and how we can better refine when we're defining a patient's risk.

Stephan Moll: Yeah, thank you, Jori. And it's not that sophisticated when you say newer terminology. It's really a patient may have no identifiable risk factors. So, we call it an unprovoked VTE, or there are some identifiable provoking risk factors. And the key point is that provoking risk factors can be minor, such as obesity, a BMI above 30, or maybe an outpatient surgery, or travel of 8 or 12 hours, or they can be major, such as the hip replacement in this patient, or major trauma, hysterectomy, colon surgery. Often people have multiple risk factors.



Stephan Moll: VTEs are classically multifactorial. So, the challenge to us, challenge in a positive sense, what we need to do is when we see a patient identify all the contributing risk factors, the weak ones, the immobility, partial immobility, the obesity that I mentioned, birth control pills, family history.

Then there's some moderate ones, particularly in the cancer, chemotherapy, radiation therapy and then the strong ones that I mentioned.



Stephan Moll: And then list the risk factors in an A, B, C manner, realizing A, for example, the hip replacement surgery in our patient. B, her body mass index of 34 and C, well, her sister had a clot at age 55, D, she's a smoker, E, she also was on hormonal therapy.

Faculty Discussion

Stephan Moll: So, it's really the multifactorial nature. And why is that important? Because then we can see which ones of these risk factors were transient, are gone now, and which ones are permanent, which ones of these are major ones and which ones are minor ones. And that allows us to then think about, what is this patient's risk of recurrence.

Jori May: So, that's very helpful. I think in my mind, it's helpful to think about that this dichotomy of provoked and unprovoked is so much more nuanced than that. And that it's the strength of the risk factor, it's whether it's transient or non-transient, and really taking the time to sort through those risk factors and defining them for what they are is really helpful.

Specific Risk Factors to Evaluate in this Patient

- **Previous Thrombotic Challenges (pregnancy);**
- **Years on Birth Control**
- **Prior Surgeries**
- **Family History**

Negative History Is Critical: What Challenges Has She Had That Did Not Result in a Clot?

Jori May: And so, in this patient, you already touched on some of these risk factors that we're thinking about. But oftentimes, when I say have a trainee presenting to me and they give me this abbreviated history, what are the other details that I really want to ask about and make sure that I'm not missing in a patient with a new VTE? Are there specific risk factors that you think about and that you ask about?

Stephan Moll: Well, we've talked about the mild, moderate, and more strong severe risk factors. The other thing that's helpful in the history taking is what exposures did the patient have in the previous years in their life that did not lead to VTE? And I use the term whether a patient is a clotting nightmare or not. For example, the patient that you just described with a hip replacement associated VTE.

Well, she did fine, I think she said she's 57 or something, for 57 years of her life. So, then I would like to know, well, how many pregnancies has she had? How many years total has she been on birth control pills without a clot happening? Has she had prior surgeries without any clots happening? So, the negative history is really relevant to determine. Is there any suspicion for an inherited strong component? Because if she did find for 57 years in spite of multiple challenges, there's no – that indicates there's no strong inherited thrombophilia and there's no indication to test for inherited thrombophilias. However, what we have not excluded, and in this case with hip replacement, I wouldn't even think or test for it, but if somebody develops a clot at a more advanced stage, it could still be an acquired clotting disorder, such as the antiphospholipid antibody syndrome or the less common myeloproliferative neoplasms or paroxysmal nocturnal hemoglobinuria. These are unusual things. But the point really is, we don't really think

Specific Risk Factors to Evaluate in this Patient

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Negative History Is Critical: What Challenges Has She Had That Did Not Result in a Clot?

about a strong inherited thrombophilia and already rules out that you should be doing thrombophilia testing. The other thing that I really ask of, that I do and that I ask of the trainees is take a thorough family history. It's not like, did anybody have a clot in the family? I want to know, how many children do you have? How many siblings do you have? How many siblings did mom have and dad? So, I go chronologically from the lowest or youngest to highest that I know it's a wide family tree that's negative or it's a very narrow family tree. If that's negative, that's not very meaningful because they're barely any family members.

Jori May: That's all really helpful things to think about. Again, more details to fully understand a patient's risk, which really influences how you work them up and then ultimately how you manage them.

Faculty Discussion

Jori May: And so, Paul, I wonder if you could speak a little bit about from your perspective, when do you as a primary care provider feel comfortable managing a VTE, determining the duration of anticoagulation versus when do you feel like you need to work with a hematologist in order to make that decision together?

Paul Lewis: Yeah, absolutely. Again, great question, Jori. And not to go backwards, but as I think of this patient's case, if I was the one that did the pre-op clearance, I'd often say, hopefully I listen to this podcast and I can anticipate what this individual's risk factors are and maybe tell the surgeon she should be on something more aggressive for primary prophylaxis besides aspirin. I know that's sort of a different discussion, but again, I think that's important when you're doing these pre-operative clearances for patients if they have a lot of thrombosis risk, to let the surgeon know that this is somebody that has perhaps some atypical risk factors or higher risk. So, just an aside, obviously we can prevent it, it's always great.

Jori May: Well, I think that I thank you for highlighting that. I think that's a really important piece to discover here. There's a lot of debate on kind of appropriate prophylaxis after hip surgery, but really talking through and evaluating those risks prior to surgery, working closely with a surgeon is so important because if this is someone that's higher risk, would something like enoxaparin, a low molecular weight heparin, or one of the direct oral anticoagulants be more appropriate in the post-operative setting? Thank you for highlighting that. I think that's really important.

Paul Lewis: Yeah, no, absolutely. Again, I think that's important as we do pre-operative clearance to not go into that automatic mode and just think of the immediate cardiovascular risk of that patient, but think of everything, all the other risk factors and things that can happen perioperatively, including venous thromboembolism with these sort of major surgeries. But again, having said that, and she has developed this significant venous thromboembolic event, and then following back up with me.

And I would do a very similar process that you all were mentioning of saying, well, okay, I know that she had a provoking event, right? So, she had an orthopedic surgery, perhaps she hasn't been as mobile as she had been. I'd also, of course, we're looking at her BMI as another risk factor, as you mentioned. So, in my mind, I'm trying to say, was there a reasonable cause for this to occur? Or is there something, as we alluded to, something secondary that could have contributed to this? And so, that's sort of what I'm weighing as I'm seeing the patient. And that's one of the bigger variables for me about sending to a hematologist, because again, if I do think that perhaps it was unprovoked or, well, you know, maybe there was some minor provoking risk factors, but nothing too significant, then it just makes me wonder why, like why it happened, right? And again, I guess in this case, after orthopedic hip surgery, I know that you're at risk for venous thrombo-embolism, and certainly I would ask her, has she been mobile? Has she been drinking, you know, perioperatively? I would also probably get into some of the things that Dr. Moll was, and you were talking about, about this person's history and family history also.

And then as I started thinking, and this goes back somewhat to our previous podcast of, huh, what is this patient's risk of being on an anticoagulant as they're presenting to me? And if they are at elevated risk, then I need to figure out, how do I approach that patient? And then ultimately, the question at hand is how long to keep this patient on anticoag-ulation. So again, those are all the thoughts that would be going through my mind: sort of at that point, that first visit, hospital follow-up kind of visit there. And then of course, other things, making sure the patient could get the medication that she's on as well as taking the medicine that she's on and there's no adherence issues. So, I sort of threw a lot back at you, Jori, but that's what's going through my mind as a primary care doc.

Jori May: Yeah, no, I think that's really important because there's so many things to consider. And so, I think it's a really hard question of when is this a time that a hematologist needs to be involved or not. I think what I'm hearing is that in someone where kind of the risk is clear, right? There is a major transient risk factor like this patient that had a major surgery. And we know that there's data to suggest that that patient should receive limited duration anticoagulation. Three months is appropriate if they have returned to mobility. That's something that a primary care doctor may feel comfortable making that decision versus some of the other cases that we're going to get to. I'll ask

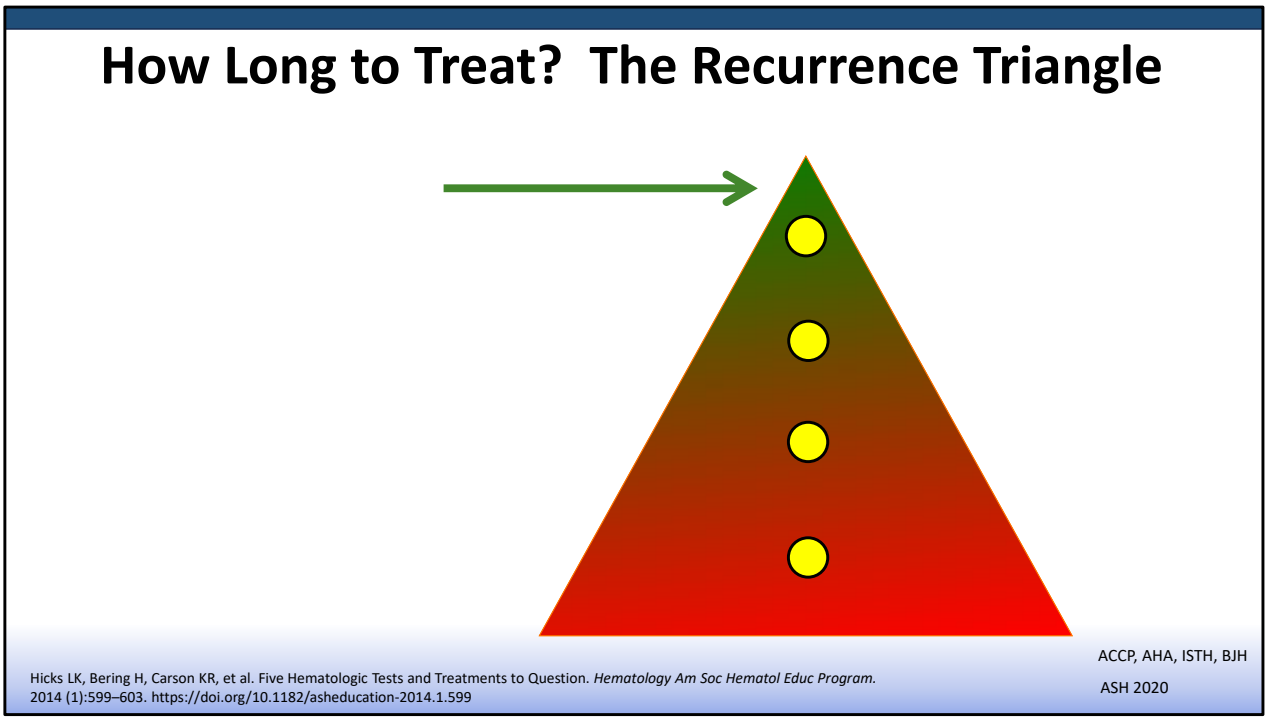
this question again, where there might be more nuance to minor risk factors, unclear risk factors, unclear family history that in an ideal situation involving a hematologist would be helpful.

I think that another thing that keeps coming up is, the system around you and how that influences care. Some of it is, there might be providers who don't have easy access to a hematologist. We know actually there's a national shortage of particularly hematologists focused on non-malignant issues. And so, some of it unfortunately is access. So, even if you would like to access a hematologist, you may not be able to do that. So, we're also going to try and cover some tools to help the primary care provider who may need to be making these decisions that are a little bit more challenging just because they may not have access to another provider to work with to make that distinction.

Stephan Moll: Jori, if I may, since you said access to hematologists, it's true, often hematologists are the ones who deal with venous thromboembolism, but there are also other subspecialties, general internal medicine people, cardiologists, some of them have focused on VTE. So, it's what whoever is more dedicated to thrombosis, that's what you're referring to.

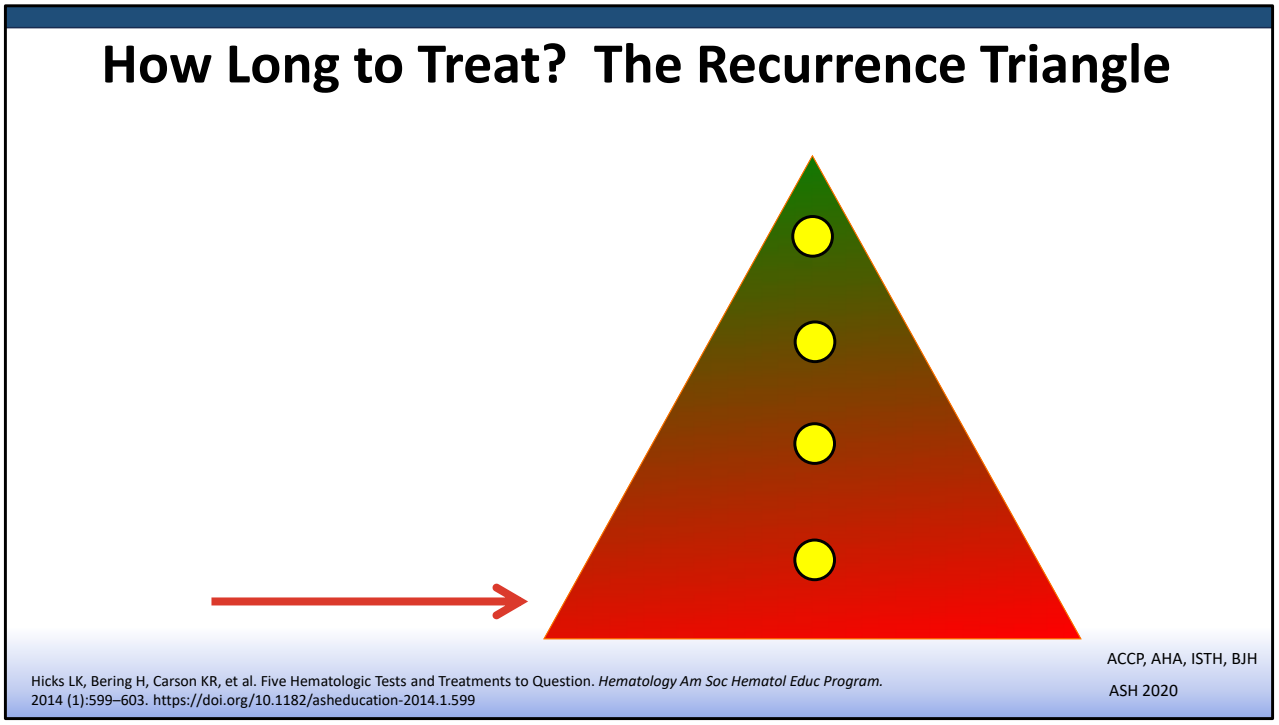
Jori May: Yes, thank you for clarifying that.

Stephan Moll: And I think the point that we are really making and that's for me, one of the major trends, take home point from this podcast today is, yes, unprovoked, that's pretty clear. It's out of the blue, unexpected, no transient risk factors. And then the provoked ones can be minor or majorly provoked, and that influences how long we treat.

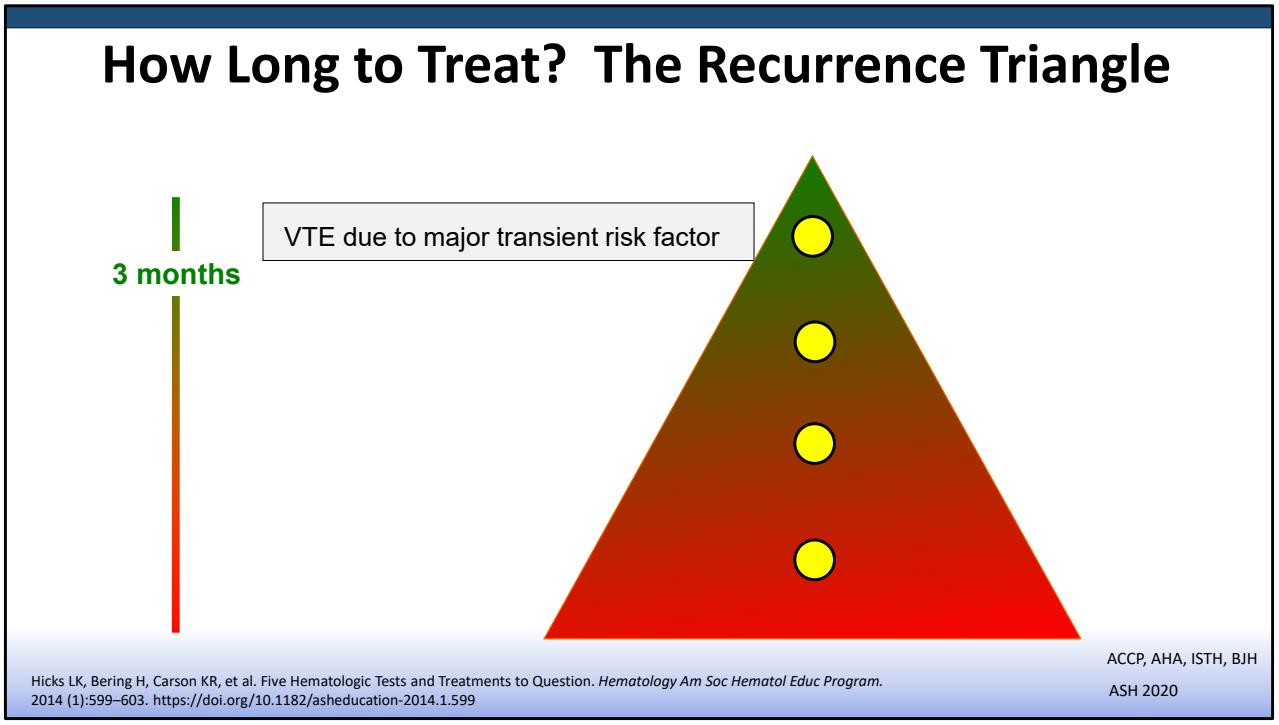


Stephan Moll: And I would like to introduce a concept that I've used for a number of years that I call the recurrence triangle. And it's a concept that helps me think about how long to treat. It helps me explain it to patients and it helps teach it to trainees. And anybody who had a DVT or PE who stops anticoagulation after three, six months, whenever, everybody has some risk for recurrence. And the risk of recurrence may be very low, such as a patient with a hip replacement associated VTE. Those people with major transient risk factor have a risk of recurrence in the order of less than 5% over the next five years. So, less than one in 20 over five years. That's low. And all treatment guidelines say, that patient only needs short-term anticoagulation.

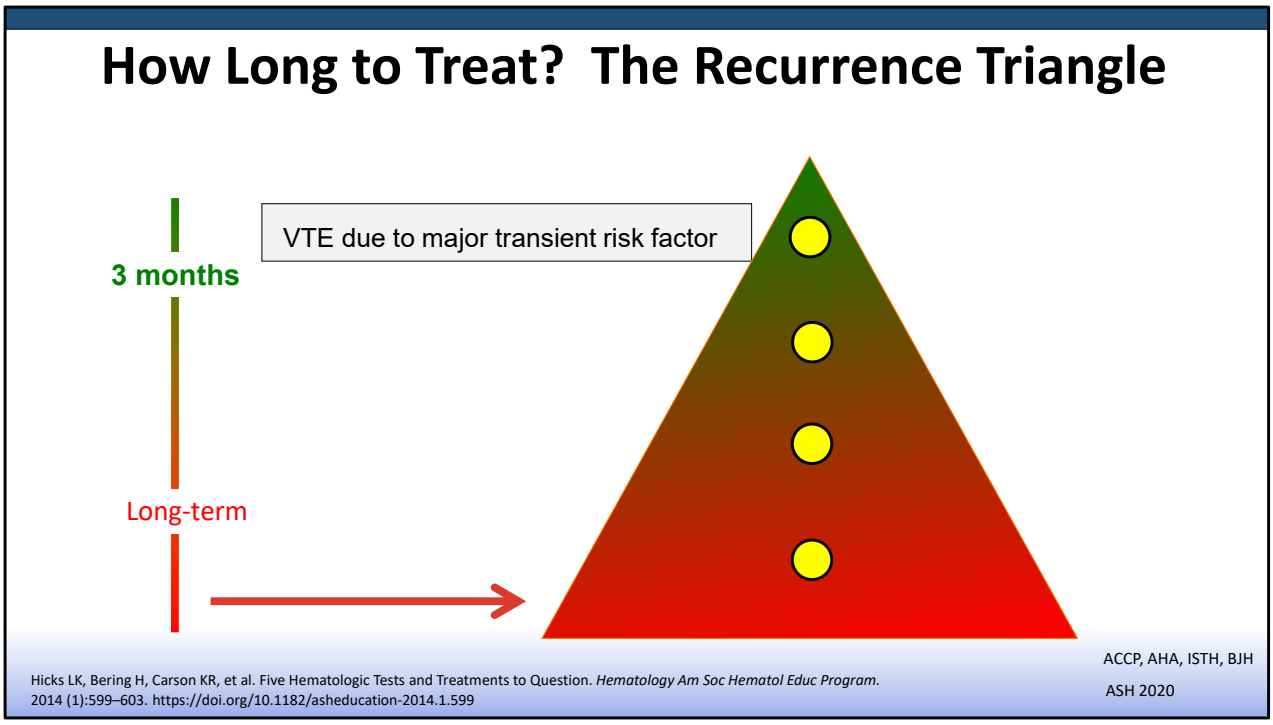
So, I put that person in a, if you imagine, a triangle. The tip means the low risk for recurrence, small area, and I typically make that green. Green is good.



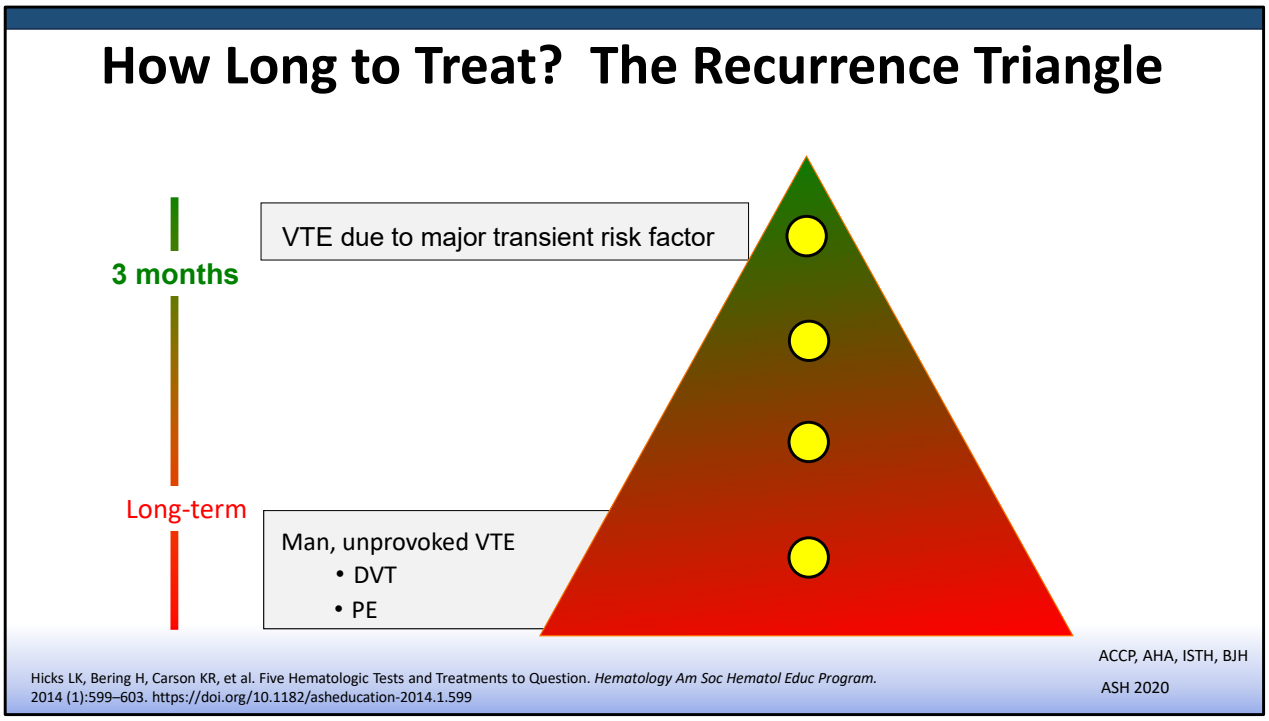
Stephan Moll: Broad base down in the triangle is broad high risk for recurrence. It's a red zone. Red is panic, really high, and you need long-term anticoagulation.



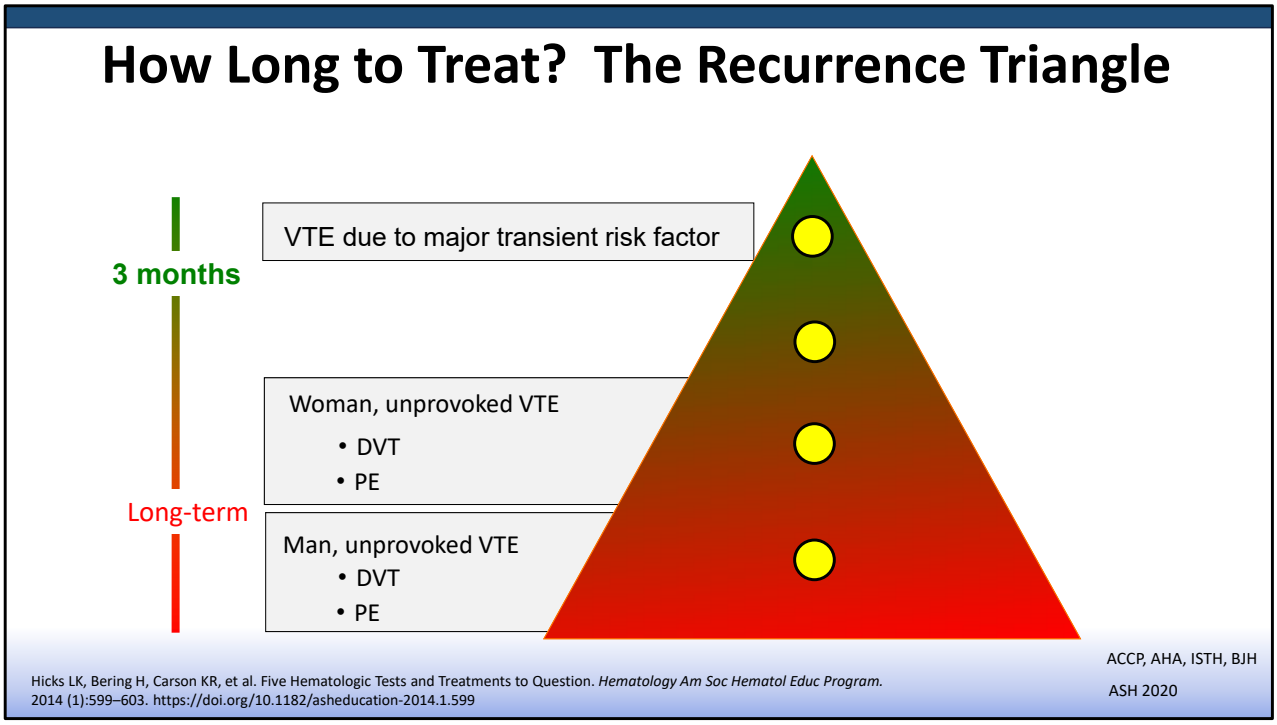
Stephan Moll: So, I put the patient with a hip replacement or knee replacement or hysterectomy, colon surgery, major trauma, up in the top of the triangle into the green zone, short-term anticoagulation. And while, Jori, you appropriately said often we treat for three months, there are some providers who go for three to six months, and we're really talking about short term. The patient that you presented who had thrombectomy, she was really sick, she was hemodynamically unstable. I would probably say well, three to six months and then see how you do. In any case, it is short term.



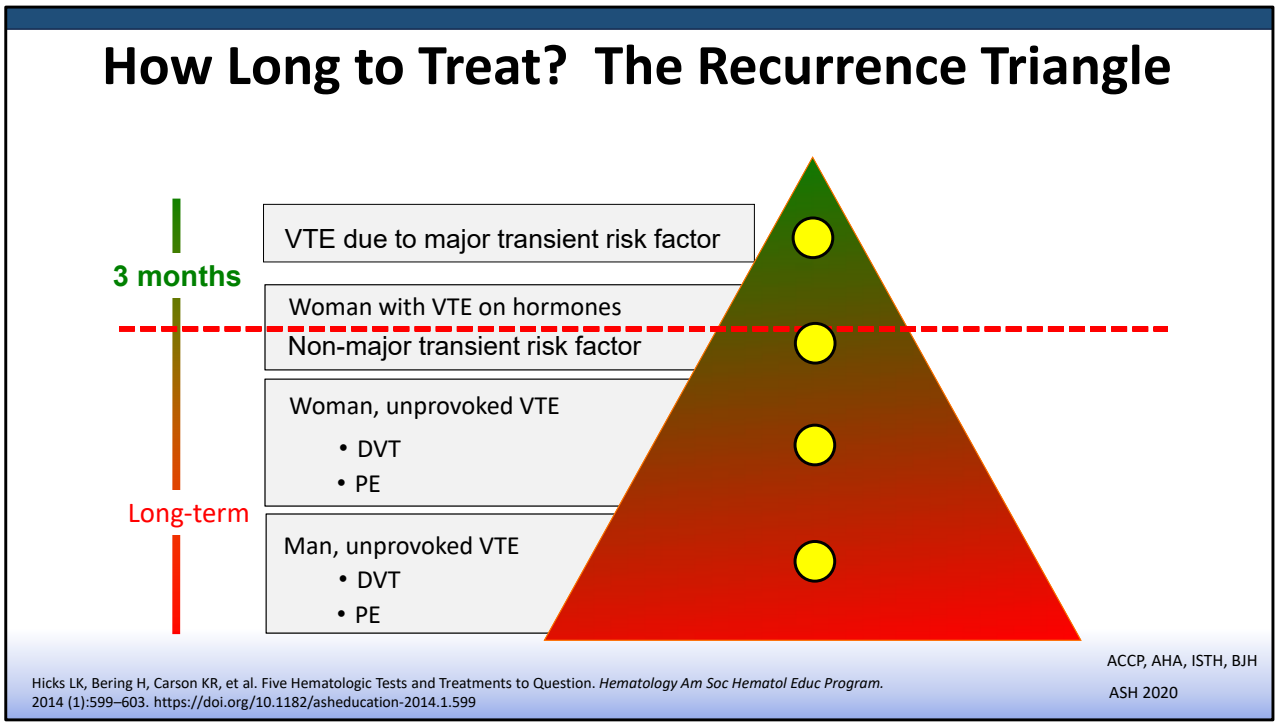
Stephan Moll: And then the person with an unprovoked VTE, I would put at the bottom of the triangle, broad base, high risk for recurrence, red zone, long term blood thinners, as long as it is tolerated and don't majorly mind being on it.



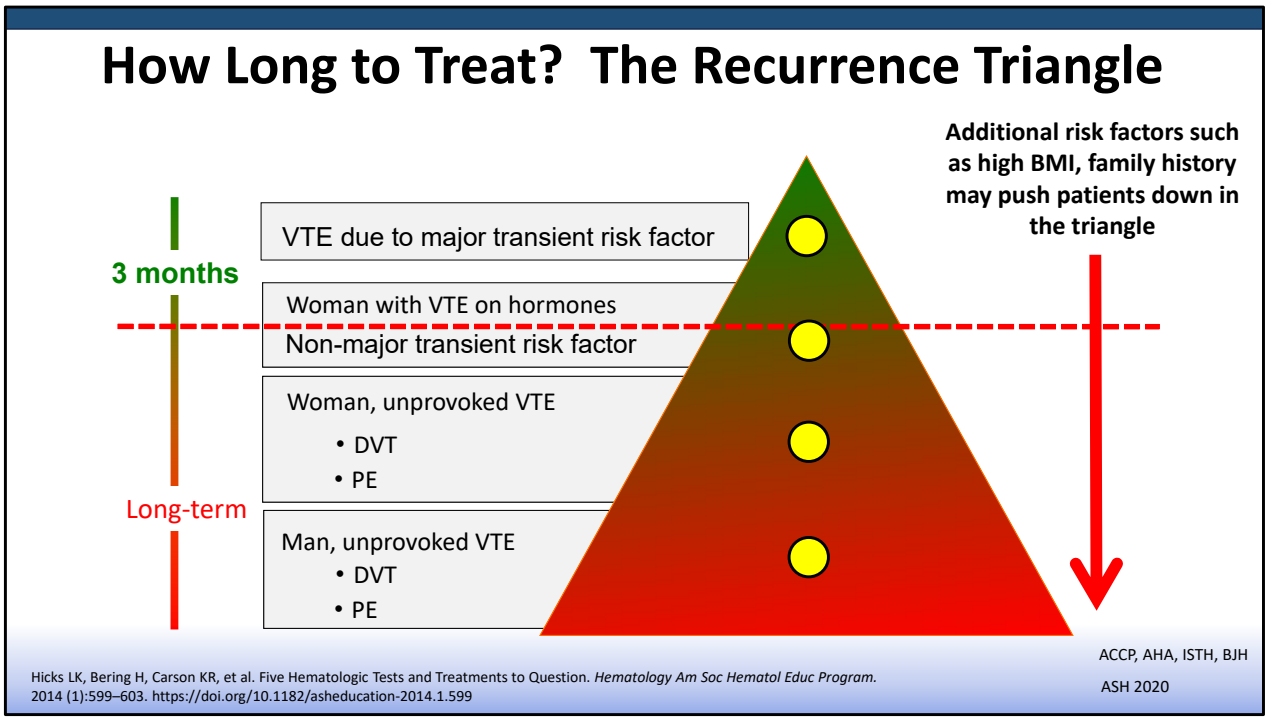
Stephan Moll: And the people with the highest risk for recurrence are men with an unprovoked proximal DVT or PE. They have a 30% risk of recurrence over five years, one in three. Everybody would agree that's a high risk. And all treatment guidelines from societies say that person should be on long-term blood thinners as long as they tolerate it well and don't mind majorly being on it with reevaluation every so often, once per year or so, what's the risk-benefit ratio?



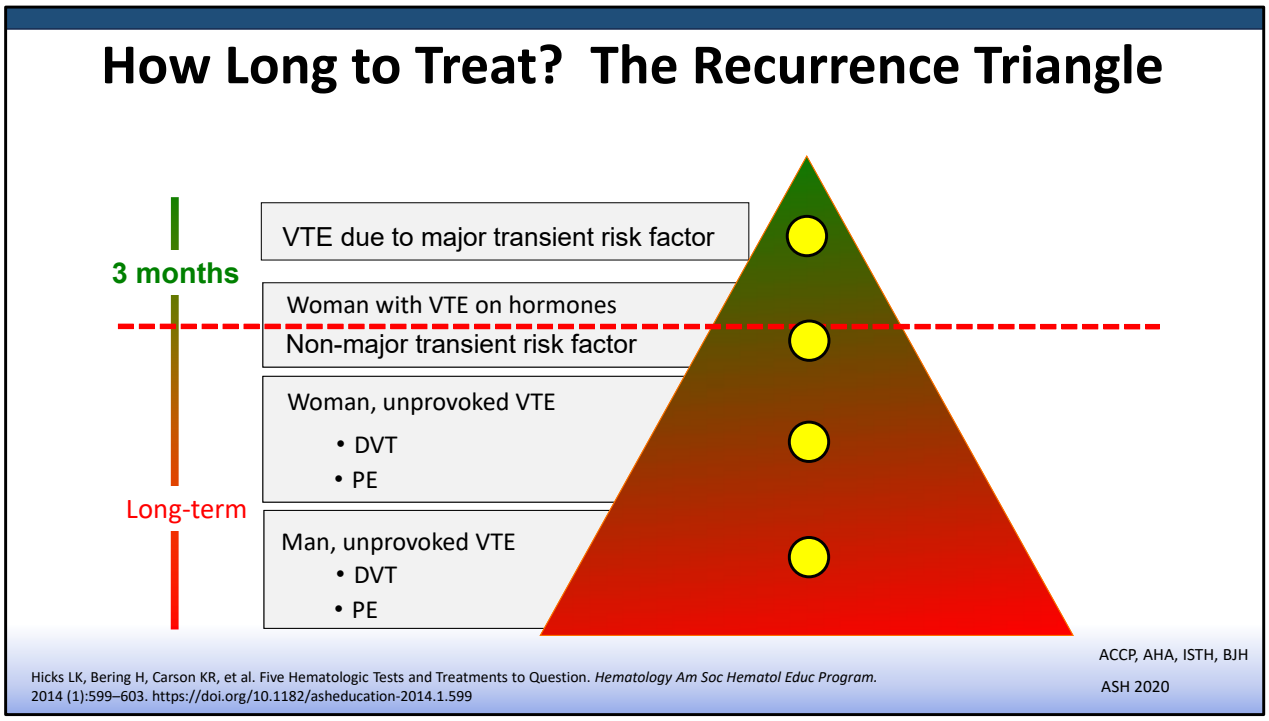
Stephan Moll: And then women with an unprovoked proximal DVT or PE, they're a little higher up in the triangle but still in the red zone, still in the area where we would say long-term anti-coagulation is appropriate. They have a 20% risk of recurrence over five years, one in five. That's high too. Most people would agree with that.



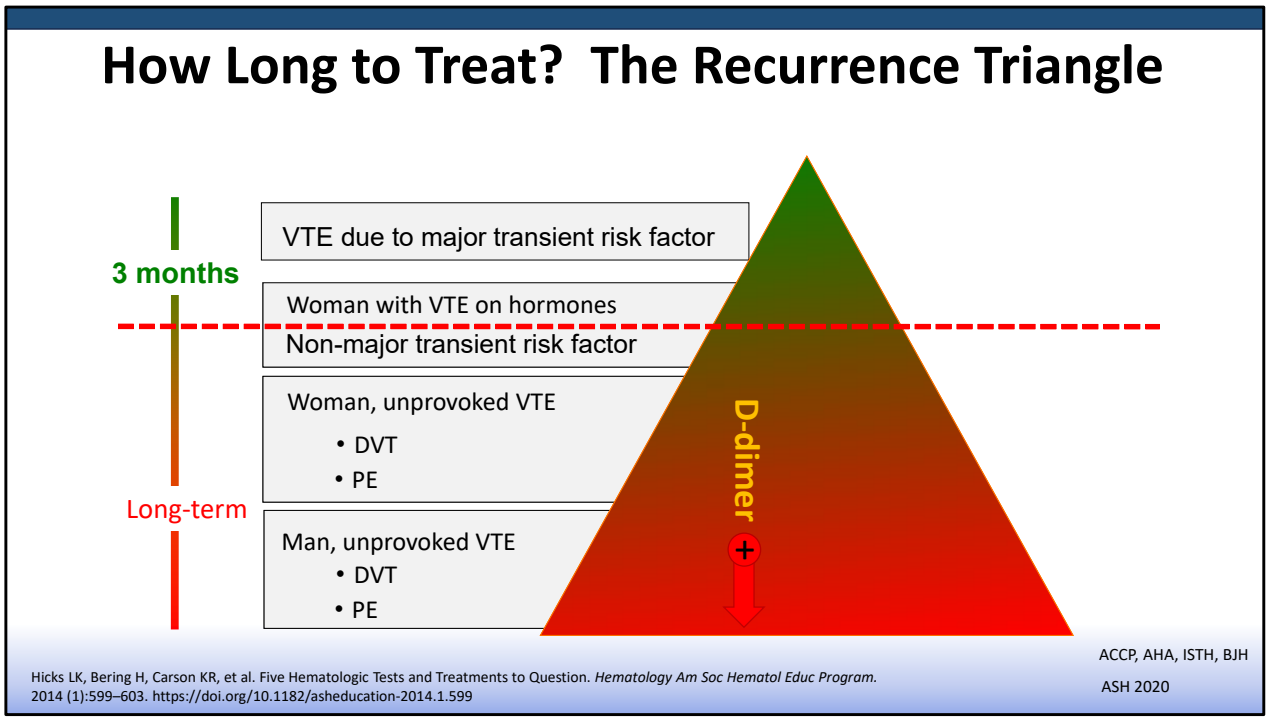
Stephan Moll: And then the people with these some risk factors like an outpatient liposuction surgery or an arthroscopic knee surgery or travel for 12 hours. Yeah, there's some risk, transient risk factor, but it's not a major one. They're in the intermediate area of the triangle where we don't quite know what to do. Is it low enough that we should stop? Is it high enough that we continue?



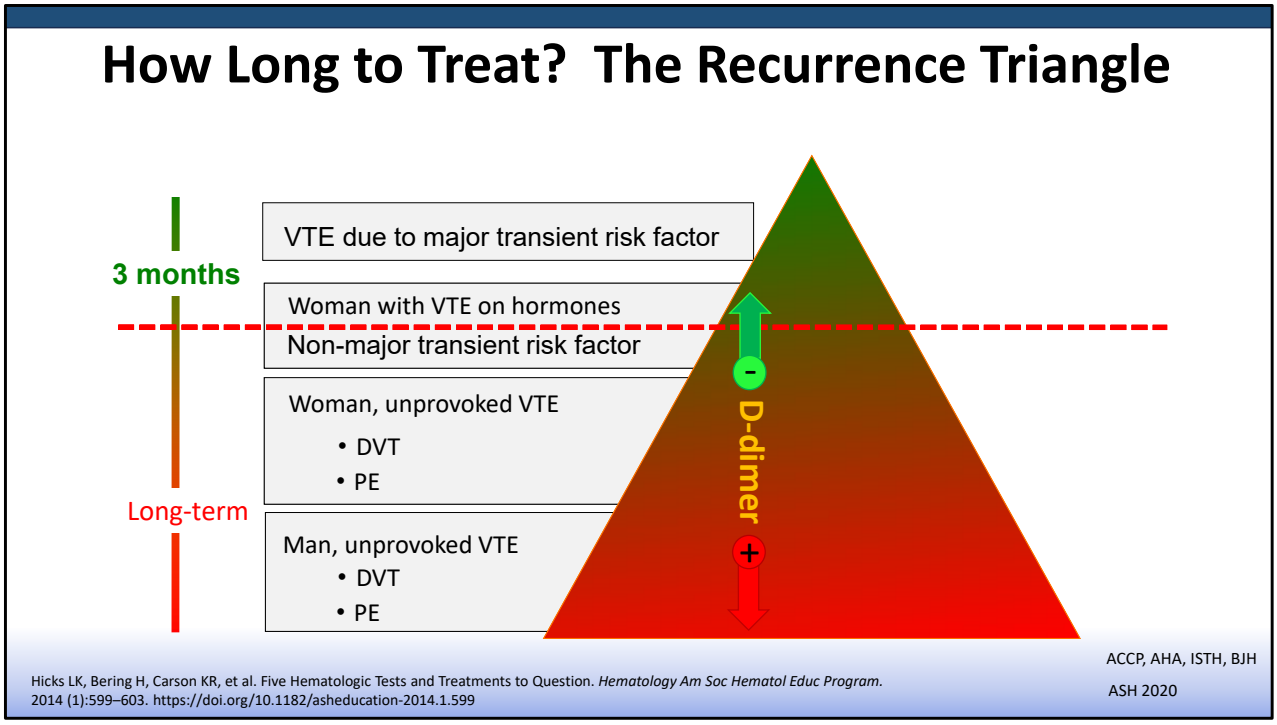
Stephan Moll: And that's where the additional risk factors come in. For example, a high BMI, typically pushes the patient down in the triangle. A family history may be indicative that there is something more prothrombotic inherited going on and may push them down in the triangle. And it's also those patients where we don't quite know what to do with it.



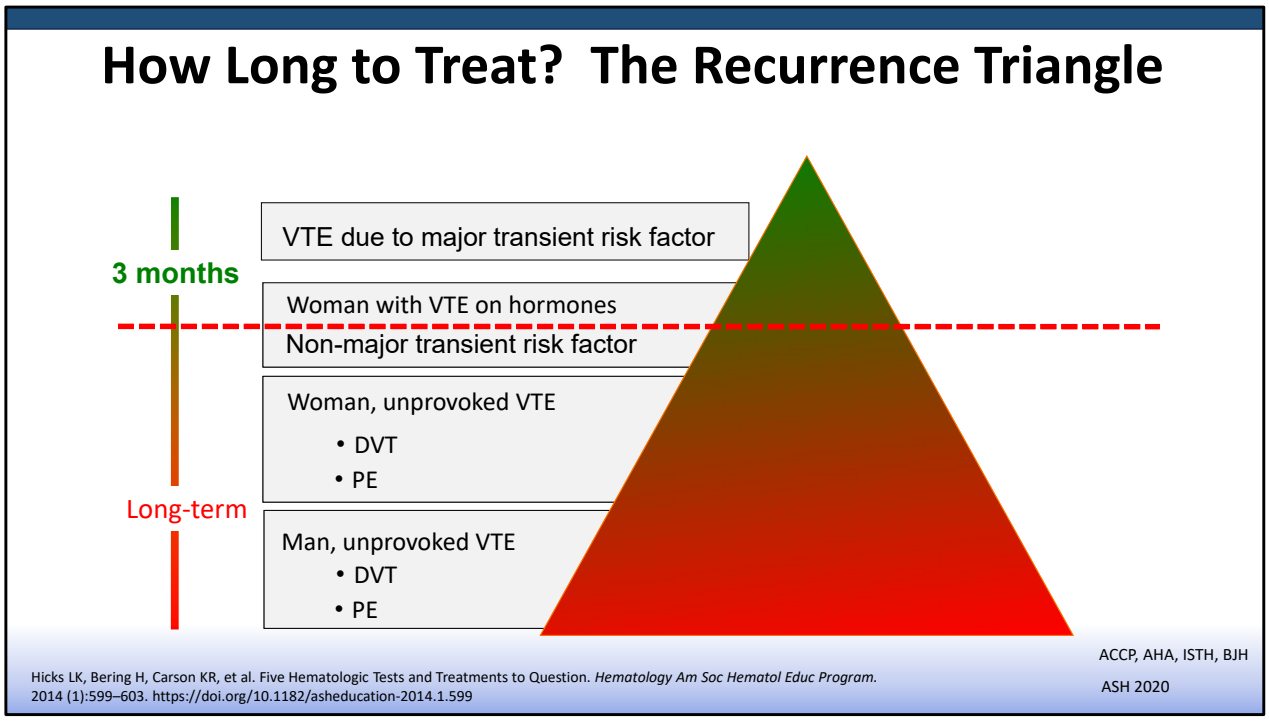
Stephan Moll: Thrombosis-focused physicians, at least a number of us, use the D-dimer for decision making.



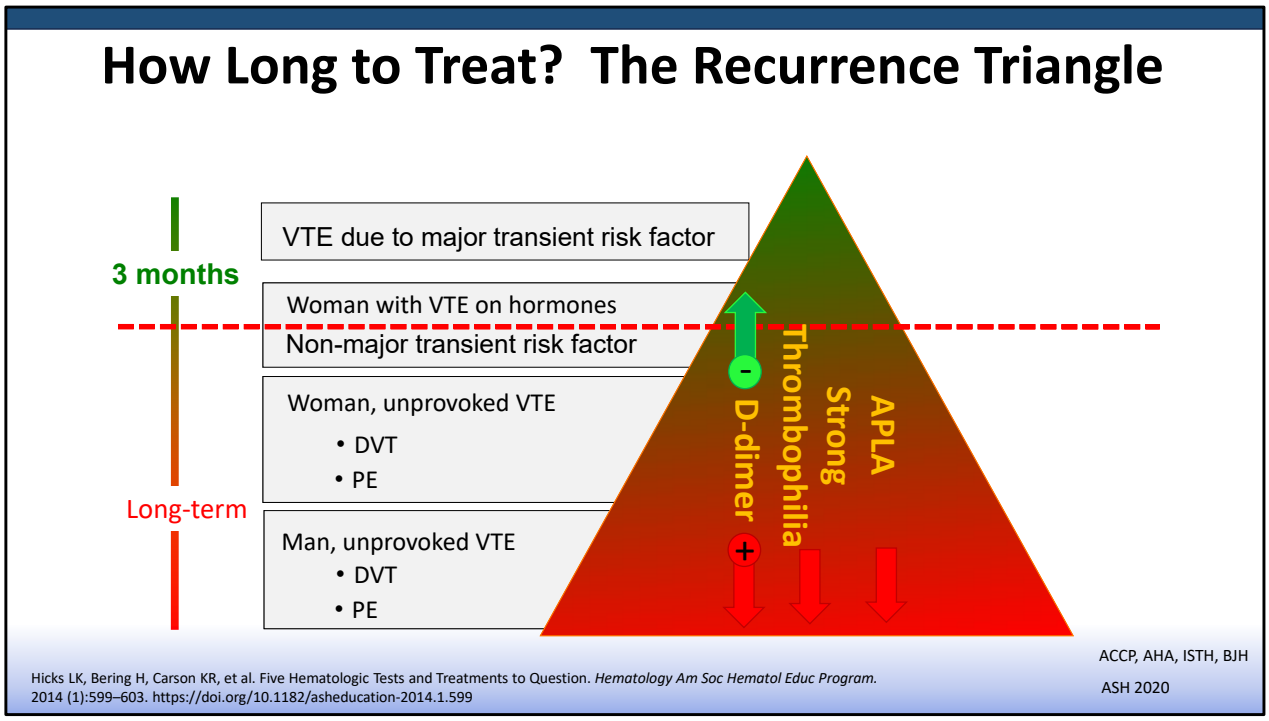
Stephan Moll: Positive D-dimer pushes people down in the triangle, higher risk for recurrence.



Stephan Moll: Negative D-dimer pushes them up. And that's initially on anticoagulation, and if the D-dimer is negative and the patient has been pushed into the tip of the triangle, then we stop anticoagulation four weeks later, repeat a D-dimer, still negative, still the tip of the triangle green zone, continue without. But if the D-dimer is positive or turns positive, patient pushes somewhat down in the triangle into the more red zone.



Stephan Moll: And it's also those people with this intermediate risk for recurrence, where we don't quite know what to do.



Stephan Moll
That's why I'm thinking about a thrombophilia workup, to find a strong thrombophilia, rare as they are as inherited ones, a strong one that would push them down into the red zone, higher risk for recurrence. And particularly the antiphospholipid antibodies, if repeatedly positive, push the patient down in the triangle.

Now, this is a lot of talk from me and I apologize to both of you that I'm taking over, but I'm...this triangle I've seen many people, or a number of people find helpful as a concept. And what I wanted to point out here too is, take the man with an unprovoked clot in the red zone broad base. It's an unprovoked clot and people may ask, well, why did the patient clot? It doesn't really matter. It's an unprovoked clot, higher risk for recurrence, long-term blood thinners. So, that person is not necessarily a person where I would think about a thrombophilia workup. The thrombophilia might only answer the question, why did I clot, but it does not change management. So, I would reserve typically the thrombophilia workup to the people in that intermediate risk for recurrence area of the triangle with a strong thrombophilia, pushes them down and helps me decide, it's one of the things that helps me decide what to do.

Faculty Discussion

Jori May: Thank you for going through that. I think it's extremely helpful and really provides a framework for just how to approach these types of cases. And so with that in mind, we're going to talk, see how we can apply this to some other situations and how it might be a helpful guide to folks.

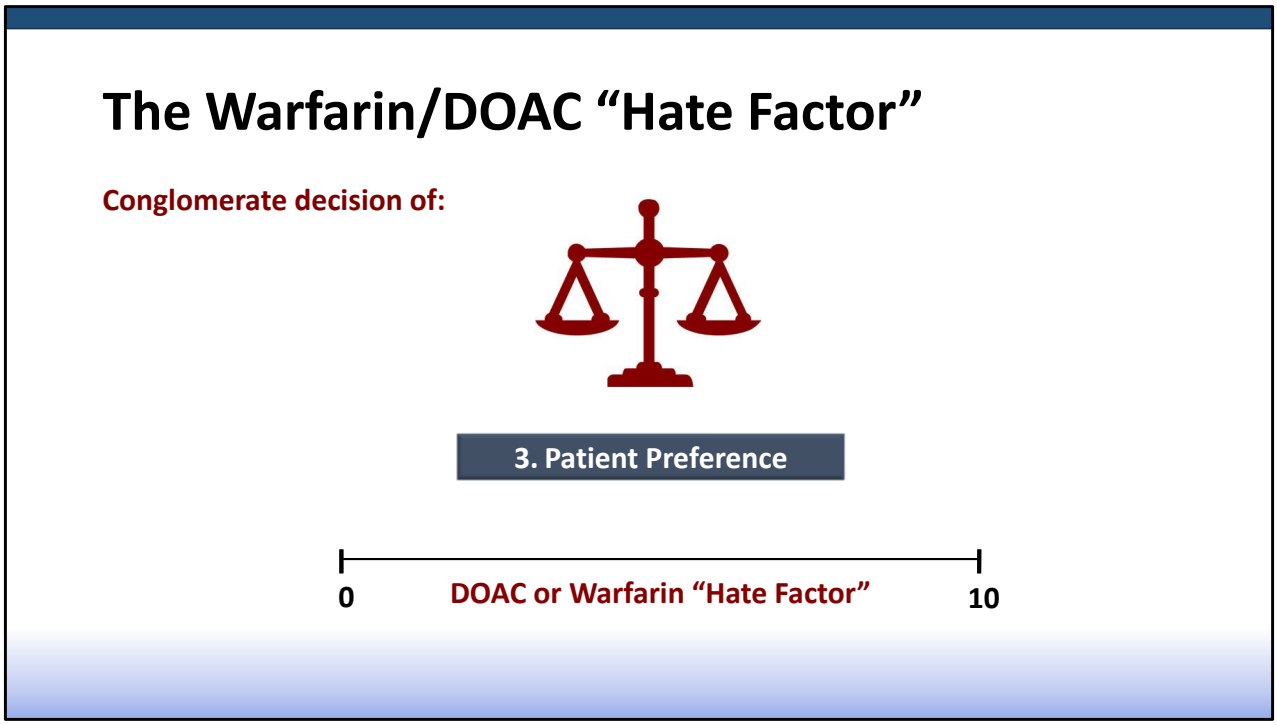
Stephan Moll: Paul, can I ask you as a primary care provider, general internist, does this concept make intuitive sense that the thrombophilia workup for clinical decision-making is really helpful in this intermediate range and not in the unprovoked where you have a clear indication of long-term anticoagulation anyway?

Paul Lewis: I agree, it is helpful. And the visual, again, love the visual because as we're seeing patients and we don't have the benefit of consistently seeing patients with venous thromboembolism, you're thinking about what tool do I have my tool belt to assess all these variables so the image is fantastic to have and sort of burned into your memory. And I understand what you're saying is, if you're going to put somebody on long-term anticoagulant prophylaxis, as you said, what does it matter if they perhaps have a minor thrombophilia? Because it's not going to change your patient management. And again, as I work with trainees, I sort of ask that same question, is how is this test, whatever it is you're going to do, ultimately change how you manage this patient? If the answer is nothing, then you're right. You sort of reevaluate, well, why are we getting the test then other than just because.

Jori May: That's fantastic. Well, let's kind of wrap up this case. And so maybe, Stephan, I would ask you in this patient that had a major transient risk factor for her thrombosis, can you kind of summarize your management plan, what it would look like for her currently and even thinking long-term and really the framework that you use in order to make those final decisions?

Stephan Moll: Yeah, so immediately when you presented the case, I heard hip replacement, major surgery, symptoms within a week, hadn't had a clot for 57 years. This is a woman in the top of the triangle, low risk for recurrence when the transient risk factor is gone. So, my mindset immediately is short term anticoagulation, which means three to six months for me. I am emotionally a little concerned about her. She almost died. I mean, she was hemodynamically unstable, and there's a 30% mortality in the acute setting in those patients. So, I'm not going to say after three months we can stop and we'll be good. I want to see her, but as a hematologist, I would want to see her at three months, see how she's doing, how she's recovered. And we'll talk in a future podcast about the development of chronic pulmonary hypertension and VQ scan echo and kind of follow up that we need to be done.

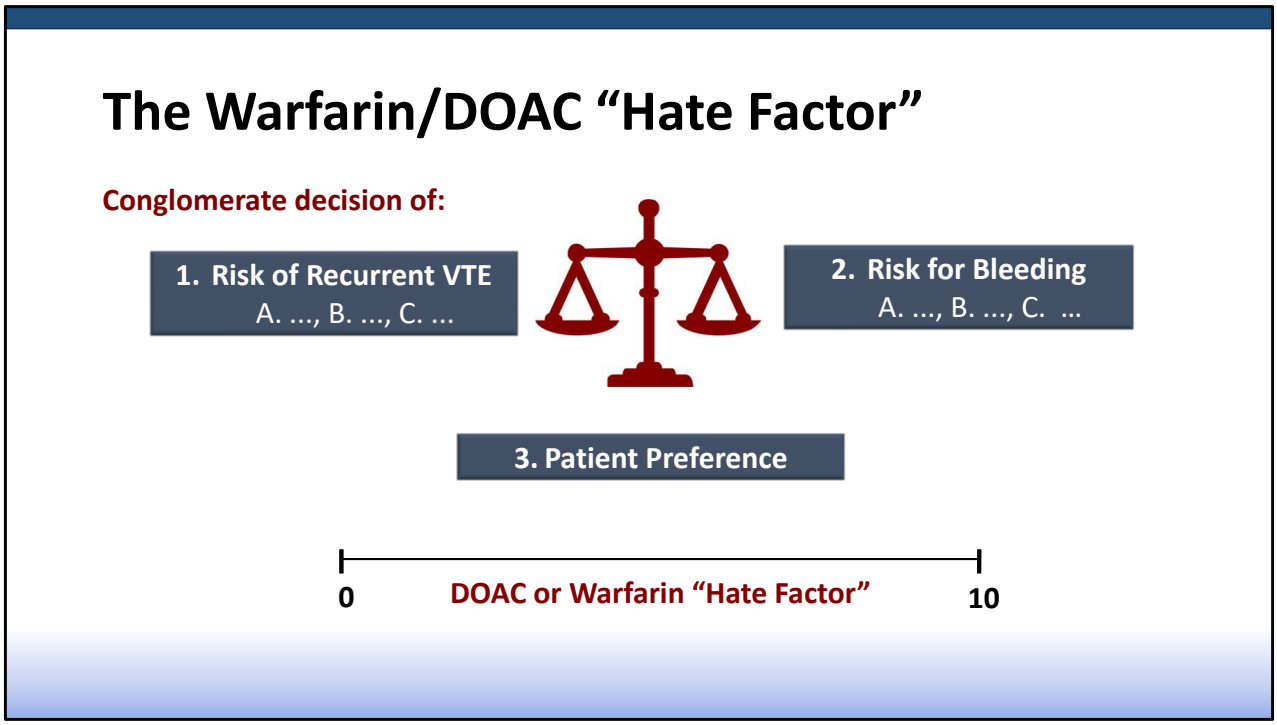
But my mindset in her is tip of the triangle, low risk for recurrence, as long as she tolerates anticoagulation well, and she doesn't mind being on it, I would treat with three to six months. If she's not fully mobile by then, I would go as long as she's not fully mobile, but she is not a candidate for long term anticoagulation. Unless, and that's a future topic, she has developed chronic pulmonary hypertension. That's a different story, but she had a thrombectomy. So hopefully, the clot is gone and there's no significant long-term damage to her lung.



Stephan Moll: We've talked about patient preference and I do want to introduce to the audience a second concept and for me the triangle is probably the main one. The second one is the assessment of patient preference. So, at three months or at six months when we see the patient we wonder, how did the patient tolerate anticoagulation? I use something that comes from the warfarin and coumadin time. I call it the warfarin hate factor. And let me talk about that first before I talk about the rivaroxaban and the apixaban and dabigatran hate factor. So, the warfarin hate factor, I ask the patient, how much do you hate to be on warfarin on a scale from 0 to 10? 0 means it's just a pill, no big deal. 10, I hate it incredibly. I really need to come off.

I tell them with warfarin, take together the need for monitoring, the diet interactions, having to go to your physician, the risk for bleeding and concern for bleeding. And then they tell you zero, my INR is stable, I don't mind it. That's good. Or they say 10, I hate it incredibly because of the diet interactions or dietary issues and the need for monitoring. Or then you can discuss the change to a direct oral anticoagulant, no monitoring, no diet.

In the case of being on rivaroxaban or apixaban or dabigatran, I also ask them on a scale from zero to 10, how much you hate that zero again is just a pill 10, I hate it incredibly. And I make sure that I ask how much does the drug cost you, take into consideration the cost, because that's typically the main reason why people give it a high hate factor. But it's a quick way to assess the patient preference. Some patients like to be on anticoagulation, they say it protects me. I feel much more comfortable. I'm not concerned about a little chest pain here, there are leg symptoms. Others say, I hate to be on a blood thinner. I hate to take any medication. I'm, I like to play soccer. I do mountain biking and I just don't want to be on a blood thinner.



Stephan Moll: So, the decision how long to treat is really A, what's your risk for recurrence in the triangle?

B, what is your risk for bleeding, which is multifactorial? The hemorrhoids, in the cancer patient, the fungating colonic mass, the thrombocytopenia in the liver cirrhosis patient, the coagulopathy in liver cirrhosis. So, risk for recurrence, risk for bleeding, and then the patient preference. That all coming together helps us make a decision.

Paul Lewis: I would imagine that you get a lot more zeros now with the direct acting anticoagulants than you did 10 or 20 years ago with warfarin.

Considerations in Choice of DOAC

- Co-pay: can the patient afford the medication?
- Dosing schedule
- Relative amount of associated bleeding risk

Stephan Moll: Absolutely true, except the cost is just a significant issue and takes up our time. And I have the really privilege that we have a pharmacist, most of the times in our clinic, who can then look at the insurance status. Key point is, and we've addressed this in the first podcast too, copay cards exist with all the direct oral anticoagulants, where people can often get it for $10 a month.

Important to keep in mind and they can get it for free for the first month often then ten dollars a month and key is also, this is often not just good for one year. It takes a little-a phone call to make sure they get it again. They re-enroll for a second year and third year, but that can be done. The problem is that the Medicare/Medicaid/Tricare patients and the uninsured don't have access to these copay cards. So, one needs to find some other way to solve that. My choice of which DOAC to use, direct oral anticoagulant, apixaban versus rivaroxaban, often deals with three issues. Number one, what's the copay? And I tend to then discuss the one that's least expensive to people. Number two, rivaroxaban is one state which some patients like. Apixaban is twice daily, which some people don't like. And then thirdly, and not necessarily in this order, maybe there's some evidence that apixaban has somewhat less of a bleeding risk than rivaroxaban, particularly vaginal bleeding with menstrual bleeds in women. But it's these three things that I discuss with the patient and we decide on which DOAC to use.

Case 2

- 22-year-old female with proximal leg DVT after 1 week of leg symptoms
- No recent surgery, travel, etc.
- Taking estrogen-containing oral contraceptive for management of heavy menstrual bleeding

Jori May: Great, I think those are all really helpful points. And so, with that in mind, I'd like to go ahead and jump to another case where maybe the duration of anticoagulation is not so straightforward. So, let's instead say we've got a 22-year-old female who is found to have a proximal lower extremity DVT after one week of symptoms. And if we do a very thorough review of her history, she tells us she has not been in the hospital, she has not had recent surgeries, she has not had prolonged travel anywhere, but what we find is that she has been taking an estrogen-containing oral contraceptive medication for the management of her heavy menstrual bleeding.

Jori May: And so, this patient is one, Paul, that I'm sure has come into your office, and Stephan, I'm sure has come into yours. And so, I wonder, Stephan, if you can talk about some of the things that you would want to know about this patient that has a new VTE in the setting of taking an estrogen-containing medication.

Stephan Moll: Yeah, so I do the same as I do in any other patient. I think multifactorial, what are the other risk factors for it? So, the concept immediately is, where in the triangle does she fit? Does she need short-term anticoagulation, or does she need long-term? Yes, she had a transient risk factor, but it's not a strong one. So, she really immediately is somewhere in that intermediate risk of recurrence, where should she be on long-term, or should she be on short-term?

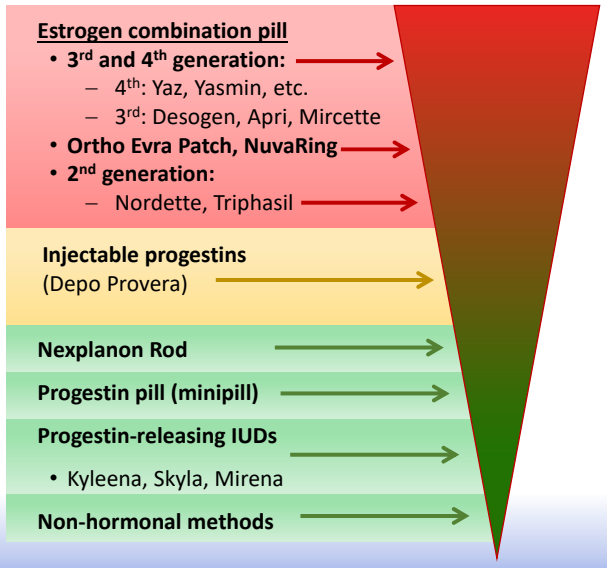
Oral Contraceptives and Risk of Recurrence

- Literature has historically grouped estrogen-containing birth control pills, pregnancy and hormone therapy
  - These are different groups of patients
- Estrogen-containing birth control pills: 5% - 6% risk of recurrence over 5 years

Stephan Moll: The literature has classically grouped hormonal-associated clots and what's the risk for recurrence. They have grouped together any kind of estrogen-containing birth control pills, often pregnancy and hormone therapy all together, but those are different groups of patients. We've learned in the last two years, and this is a meta-analysis and I was involved in that with my Dutch colleagues, our Dutch colleagues, birth control pills, estrogen containing birth control pills, roughly have a 5% to 6% risk of recurrence over five years. That's not high, 1 in 20, but it's also not low. So, I typically ask the patient, what do you think about that? Then we need to also be aware, but we don't know really how that factors into where in the triangle do they fit.

Oral Contraceptives and Risk of Recurrence

- Birth control pills have different pro-thrombotic potential
- Estrogen pills: generation depends on the progestin component
- While estrogen is a primary predictor of thrombosis, progestin component also adds to thrombotic risk



Stephan Moll: Birth control pills have different pro-thrombotic potential.

So, not estrogen pills, but the ones that are safe are the progestin contraceptives, IUDs with progestin, the rod, the progestin rods, then a little bit of a thrombotic risk the depo shots with progestin.

Then with the estrogen pills, they're the so-called second generation, third and fourth generation pills, and which generation they are depends on what progestin component they have.

And typically, it's been appropriately discussed, it's the estrogen that mostly predicts the thrombosis, but we've learned that it's the progestin component also that adds to the thrombotic risk.

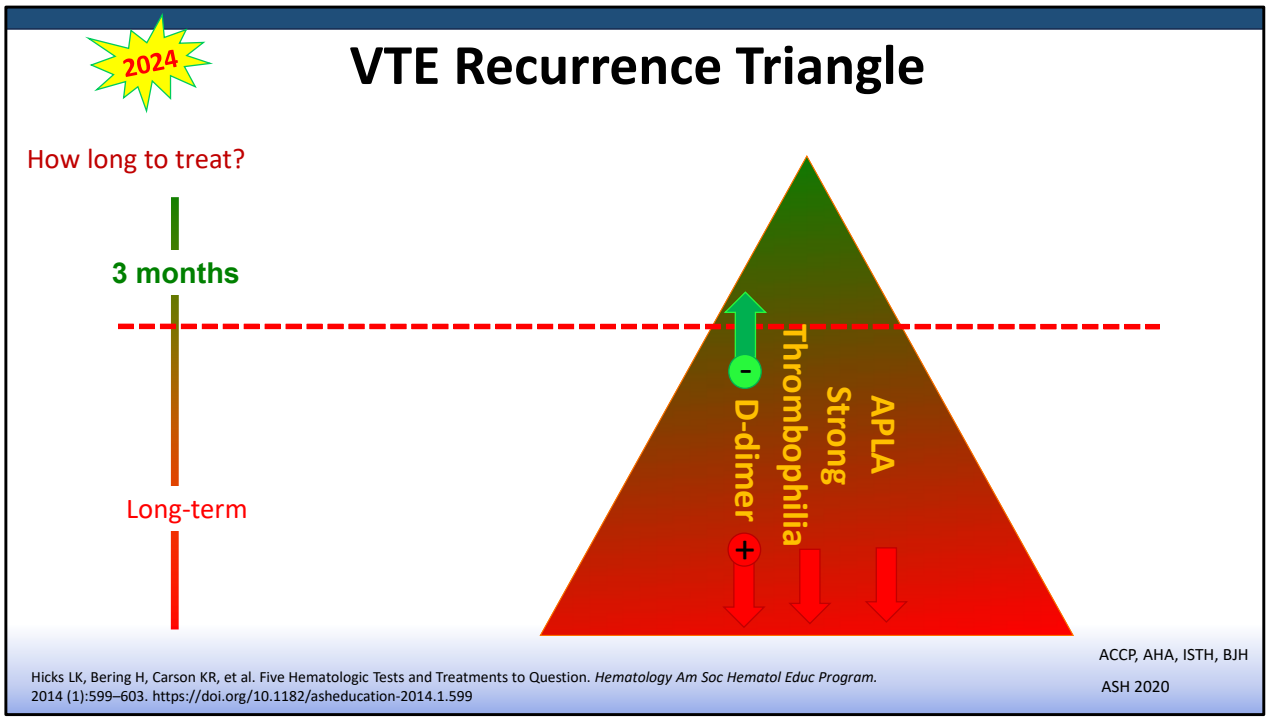
And the ones with the lowest risk are the second-generation birth control pills.

And then the third and fourth-generation pills and the ring, they are roughly two times higher thrombotic risk than the second-generation birth control pill.

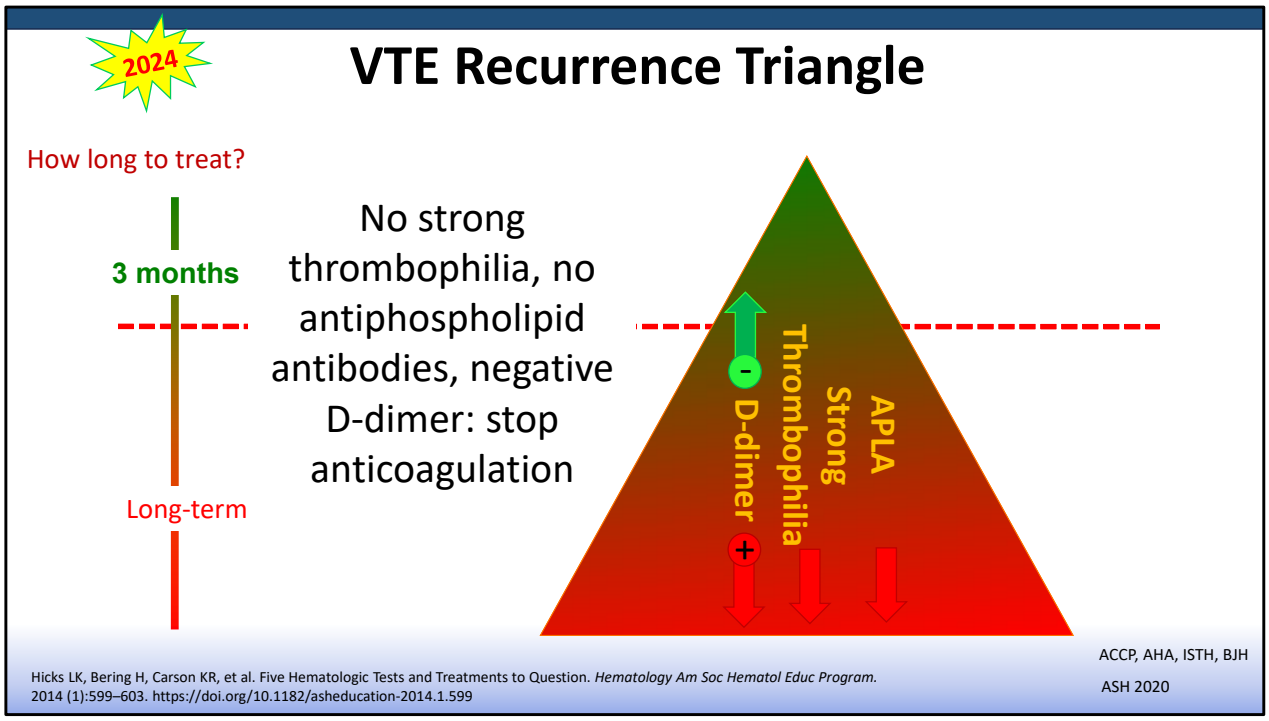
Questions to Ask a Patient

- Name of OCP / generation
- Duration of OCP
  - Long duration of OCP use with no clot: new clot probably **not** related to OCP
  - Short duration of OCP + immediate development of clot: OCP has a role in the clot
- BMI
- Smoking status
- Family history
- Other provoking factors (travel, etc.)
- Previous VTE risk exposures without developing a VTE

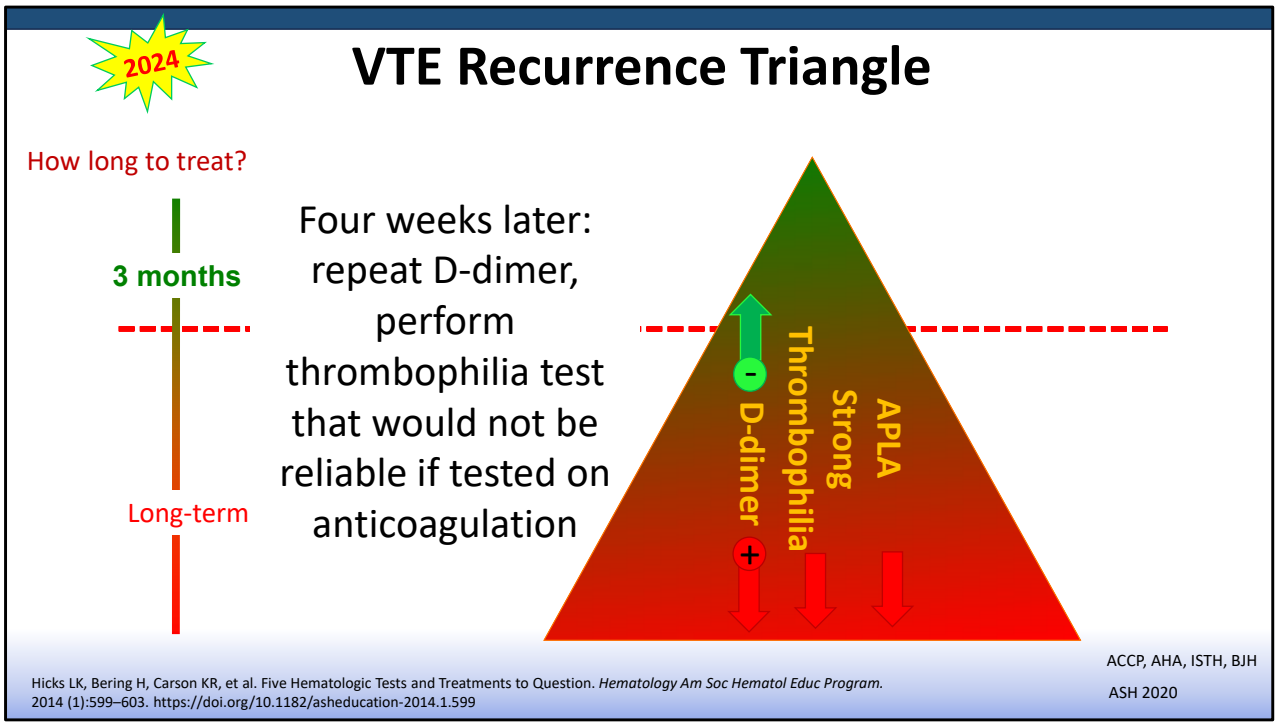
Stephan Moll: So, I really want to know from the patient that I'm seeing in front of me, which pill were you on? Is it a second, third, fourth generation? How long have you been on it? I'm pretty impressed if they were just started six or eight weeks ago and immediately clot, that they used think, whoa, that birth control pill contributed. Whereas if somebody had tolerated the birth control pill for the last 10 years and didn't develop a clot and now has a clot, it's probably more of an unprovoked clot and not the birth control pill probably didn't, in this patient, contribute all that much. That's somewhat of a subjective interpretation of how I do that. How long have you been on it? And then I want to know the other things in my ABC, the body mass index, the smoking status, the family history, and then again, in the past, did you have situations where you didn't develop a clot?



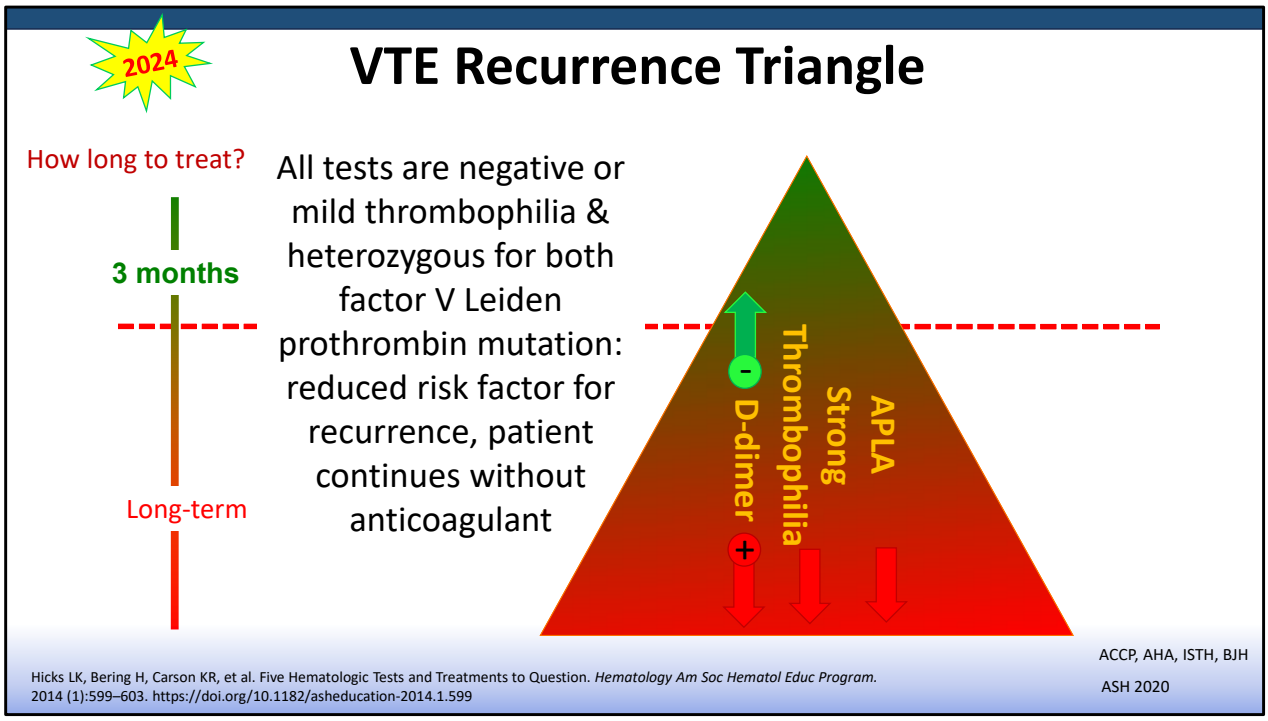
Stephan Moll: All that is to help me decide where in the triangle does the patient fit? Is it the risk for recurrence maybe in the tip of the triangle low enough that we can stop or is it high enough that we continue? But it comes down to in the birth control pill, for me and for a number of colleagues, and I've asked coagulation colleagues at an international meeting, there are many people use with birth control pills the D-dimer for decision making because the positive D-dimer pushes them down in the triangle and think about thrombophilia testing to look for any strong thrombophilia that pushes the patient down in the triangle and is a reason to continue anticoagulation including antiphospholipid antibodies not just inherited.



Stephan Moll: And if there's no strong thrombophilia, no antiphospholipid antibodies, the D-dimer is negative, the patient is more in the green zone and stop anticoagulation



Stephan Moll: and then four weeks later, I would repeat a D-dimer and do the thrombophilia test that would not be reliable if tested on anticoagulation.



Stephan Moll: And if everything is negative or there's just a mild thrombophilia, factor V Leiden heterozygous, the heterozygous prothrombin mutation, that's not much of a risk factor for recurrence. They stay in the green zone and continue without anticoagulants.

However, some thrombosis-focused providers say, whoop, birth control pill, transient risk factor, green zone, let's stop anticoagulation, there's no indication for thrombophilia workup. That's not what I do, what a number of colleagues do. And the recent ASH, American Society of Hematology guidance document on thrombophilia testing also suggests that in those people, thrombophilia workup might be appropriate. Well, that was a lot of information. You don't want me to dominate this discussion too much.

Faculty Discussion

Paul Lewis: One thing you mentioned, and we talked about earlier though, again, it's that shared decision making with the patient. Because again, in this case, well, certainly I would not feel comfortable restarting estrogen-containing contraceptives without, again, probably in this case, the guidance of a hematologist, you know, with, again, I know that estrogen is a risk factor. So if this person said, well, I'm willing to go on Depo-Provera or another progesterone-containing a contraceptive, I'd be more willing to do that, obviously. And so, and then the other thing, which we've also just been mentioning is shared decision-making, right? Because that, again, having that shared decision-making on all these topics, so important with the patient and presenting it to them in a way that they can understand the risks and benefits of all these various modalities.

Stephan Moll: Paul, let me just, so at this point, I'm only thinking about how long to treat, whether to restart the estrogen or keep the patient on it, for me is a different story. And I think we'll discuss that more because I have various issues. This patient was on the estrogen for heavy menstrual bleeding. So, if you take it off then, and now she's on anticoagulation, she'll bleed even more. We'll talk about those management issues in a future podcast.

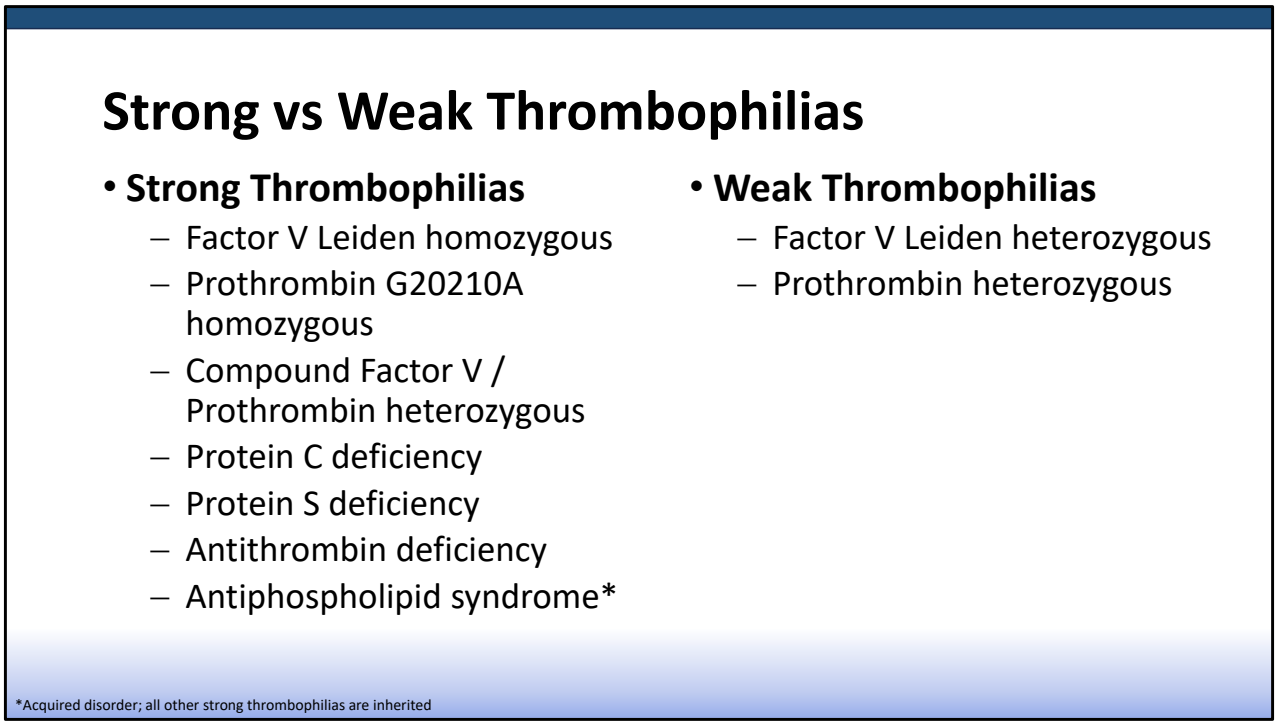
I would say in general if a patient on birth control pill develops a VTE, gets treated short term with anticoagulation, she should not be on estrogen therapy anymore. Can she be safely on estrogens while she is on anticoagulation is a different story and a number of people can be, but we'll discuss that more in detail.

Jori May: Yeah, I think I appreciate you bringing that up. And I do want to highlight that, to bring attention to it, that in a person who is on estrogen and is anticoagulated for a new VTE, in general, the thought is that you don't necessarily need to stop the estrogen right at that moment. And particularly if you do, you're going to end up with new problems because her bleeding is going to be so severe. And so, it's really working to develop a plan for contraception and ultimately making sure that we have an option to switch to something that is lower risk, something progesterone only before stopping the estrogen. But there are nuances and systems-level concerns with that too. We need somebody who understands that they must keep taking their anticoagulation while they are taking any form of estrogen and knowing that they have follow up with us so we can monitor that and transition them appropriately. So, thank you for highlighting that.

Paul Lewis: And again, great point, depending on why they're on oral contraceptives. And if you were to stop it and now this individual becomes pregnant and they have a venous thromboembolism, then you have a whole other set of risk factors I would imagine. So yeah, got to have that discussion about stopping or not stopping and the other things that go along with that.

Stephan Moll: Jori, this is for me maybe also a good point to answer a question that came up 20 minutes ago or so. Which patient would be appropriate to send to a hematologist or thrombosis-focused physician? If I think about the recurrence triangle, for me it means really anyone in this, typically in this intermediate risk of recurrence, should be sent, as well as the unprovoked clot. The ones who I don't think necessarily need to be sent, and Paul highlighted that too, is the one where you have a clear major transit risk factor, the tip of the triangle. You treat short-term with anticoagulation. If they recovered well, you stop at three or maybe at six months. Those people don't need a thrombophilia workup. They don't need to see a thrombosis-focused physician. But intermediate risk, helping make the decision, and unprovoked as well. What do you expect in the future? I think that would be appropriate.

Jori May: Absolutely, thanks for highlighting that. And so I would, we've kind of touched on this topic, but I'd like to take a step back and really talk about thrombophilias in a little bit more detail, if that's okay with you. I think this is a challenge that comes up often. I think, I'm sure, Paul and Stephan, in your practice, there's patients who are reading about these things too. They sometimes ask about testing, want testing, but there's a lot of nuance to how to test, when to test, how to interpret the results. So I wonder if we could kind of take a step back and talk about what are the thrombophilias that we are talking about? When are we thinking about testing? And what are some of the laboratory tips or clues that we should know about? What are signs in the labs that indicate we might be concerned for thrombophilia? How do we order them and how do we interpret them? So, it's a lot of questions all at once.



Jori May: But maybe Stephan, I'll start with you, if you can kind of take us through, generally when you say thrombophilias, what are the ones that you're thinking about?

Stephan Moll: Yeah, and even though it's a big topic, I think I can make that pretty short and clinical. In general, there are seven strong thrombophilias, homozygous V-Leiden, not heterozygous, homozygous prothrombin mutation, maybe, limited data because it's so rare, the factor two mutation homozygous, protein C, protein S, and antithrombin deficiency, antiphospholipid antibody syndrome, the repeatedly clearly positive tests, and I should have listed this earlier, the double heterozygous. They have heterozygous V-Leiden plus heterozygous prothrombin mutation. So, it's not black and white. They're not all really strong thrombophilias. They're nuances, family, phenotypes, very particularly with protein C-pronase antithrombin efficiency, but in general, those are the seven strong ones.

Thrombophilia as a Risk Factor for Recurrence

- Some thrombophilias are associated with little or no risk of recurrence, do not influence anticoagulation duration decisions
  - Heterozygous Factor V-Leiden: minimal risk
  - Heterozygous prothrombin mutation: not a risk factor
- Stronger thrombophilias increase risk of recurrence
- Patients who should undergo thrombophilia testing: those in the intermediate zone of the recurrence triangle

Stephan Moll: So, mild thrombophilias affect the V-Leiden heterozygous and heterozygous prothrombin mutation, even though they are so common. V-Leiden, 5% of the population, prothrombin mutation, 2% of the US population. They're common, but they don't... And while they predict the first clot and contribute to the first clot, mild risk factors, they typically don't influence a recurrence rate. The factor V-Leiden is only a minimal risk factor for recurrence. Prothrombin mutation is not a risk factor of recurrence. What really predicts recurrence is much more the fact that the patient has had a clot before. So heterozygous V-Leiden or heterozygous prothrombin mutation do not typically influence our decisions how long to treat with anticoagulation. They do not move the patient down in the triangle. The patient stays right where they are. But the strong thrombophilias push the patient down in the triangle and would be one of the reasons a patient, we may decide to treat long-term with anticoagulation, one of the reasons, the D-dimer that I mentioned being another one. So, for me, as I said that earlier, the population where I really think about thrombophilia testing is the one where I don't know what to do and I want additional reasons, additional help.

Faculty Discussion

Stephan Moll: Yes, this patient is at high risk and maybe we should use long-term anticoagulation. That's where tests for thrombophilia and those are the people in that intermediate risk for recurrence. I do not test, as I mentioned, the unprovoked clot. They stay right where they are, thrombophilia or not. And even if they have a strong thrombophilia, they go even deeper down in the red zone. And there's no indication to test the people with a major transit risk factor, hip replacement, because they're already in the green tip zone and even if they have a strong thrombophilia, they only move down in this somewhat, but they're still in the green zone. So the Choosing Wisely campaign from the American Society of Hematology, a few years, probably eight, nine, 10 years ago now said, in the people in the tip of the triangle, major transit risk factor, don't do a thrombophilia testing, and I fully agree with that.

Jori May: And Paul, I wonder from your perspective, you know, when you are thinking about ordering these tests, you know, do you feel comfortable deciding, you know, when to order and how to order? You're a primary care doctor that thinks about VTE a lot. Or are there certain questions that you have that maybe we can, you know, help address and make sure that we're educating folks on kind of the challenges of ordering these tests and how to do it better?

Paul Lewis: Yep, absolutely. So again, sometimes working with trainees, which you sort of cringe is that they check every box on the EMR and they order every thrombotic test there is. And then you get these results back and you don't know what to do with them. So that's sort of the nightmare scenario. But even though you see that too, sometimes in patients after the hospitalization that somebody ordered these tests in the hospital and

no one's following up on them. And so again, the good question whether they should be ordered or not in the first place. But again, I guess the two things that come up for me a lot, one is, as we mentioned, the patient, if they have a thrombotic event, they're always worried about, well, if it is a hereditary thrombophilia, is a family member at risk? So if it's an older patient, they often want to know, is my daughter or granddaughter, et cetera, at risk. So that comes up a lot in discussion.

And then the other thing that just comes up a lot in my discussion within myself as well as with trainees is, is there some age that you would say, you know, this is probably not a hereditary thrombophilia I need to worry about. You know, again, maybe this, and I think we alluded this earlier, this person had pregnancies, this person had surgeries, they never had a clot. So probably not a hereditary thrombophilia in that case, but you often get the case of, well, what if they're 60 or 70 or 80 and they went through their whole life and they never had a clot and now they do. And does that patient need a thrombophilia workup or not?

Stephan Moll: I think it brings out a number of important points. I've created my own Choosing Wisely points for thrombophilia testing. And I cannot call them Choosing Wisely points, but that's what I think they are. There are four reasons in my mind not to test. And maybe that's easy to talk about.

Well, I've already talked to when to test the intermediate risk co-recurrence. We don't know what to do, but when not to test. A, in the acute setting, a patient gets admitted or who is seen with an acute clot, there's no reason to test for thrombophilia at that point. There's always some exceptions, but it doesn't change management. This patient needs anticoagulation for at least three months. And at three months, it's typically where we decide short-term versus long-term, depending on where they fit in the triangle.

So, don't test in the acute setting. And it doesn't change management, plus the acute setting changes the number of these thrombophilia tests. Protein C, protein S, antithrombin may be transiently low. Protein S is often low on birth control pills with pregnancy. The lupus anticoagulant can be falsely positive, can be falsely negative. On anticoagulation, the only reliable ones are the genetic tests, but they don't change management in the acute setting. So, don't test in the acute setting, that's number one. And I'm not telling you that, I'm just saying people shouldn't. Number two, the hospitalized patient. Any patient who's in the hospital, that's not the time to test for thrombophilia. That's the patient in the hospital because they have a pneumonia, congestive heart failure, the acute clot, all that, these acute illnesses change the thrombophilia activity assays, protein C, protein S, antithrombin, and the lupus anticoagulant as well.

And again, it doesn't change management. At that time patients need to be taken care of for their acute illness. And then the third one is don't test on an anticoagulant while the patient is anticoagulated. Again that's a general statement, but anticoagulants, warfarin we know lowers protein C and S. The direct oral anticoagulants increase protein C and S and antithrombin, falsely increase them and all anticoagulants may lead to a false positive lupus anticoagulant. Again, Factor V-Leiden and prothrombin mutation and then the ELISA-based antiphospholipid antibodies, anticardiolipin and anti-beta-2 glycoprotein 1, those can be reliable. But a good general statement is don't test while on an anticoagulant. And then the fourth one is, and that echoes with something that you said, somebody tested in the hospital.

The provider who doesn't know what to do with the results shouldn't be testing, not just checking a box because, oh, why did this patient clot? There should be a purpose behind it, and people should then also know how to interpret it. Those are my four choosing wisely points. There's some other reasons why thrombophilia testing is, one should be thoughtful about it. The genetic factor V-Leiden and pro-thrombin factor two mutation testing is often not reimbursed by the insurance companies. So, patients get a bill for it, which can be pretty significant depending on the healthcare system, $300, $400 or so for each test, $800 for two of them. And the antiphospholipid antibodies are pretty expensive as well. You can easily build up a bill for two, three, maybe even $4,000. And if you test, not you, if people test for irrelevant tests, for example, you still see the MTHFR polymorphism every so often in the homocysteine pathway. That's not a thrombophilia. It should, in my mind, never be tested for. All that builds up cost as well and concern with a patient. And if they're not fully knowledgeable, educated by the physician, and the physician doesn't quite know what to do with it, you just create a situation that's not very helpful and then it's a referral to hematology. It takes three months to be seen because it's so booked out and then in the meantime they think they have a strong thrombophilia etc, etc. Family-wide testing and I think maybe we have a future podcast on that because you could say a few words on that and I don't want to dominate this discussion too much.

Paul Lewis: That'd be great. Yep. That'd be great.

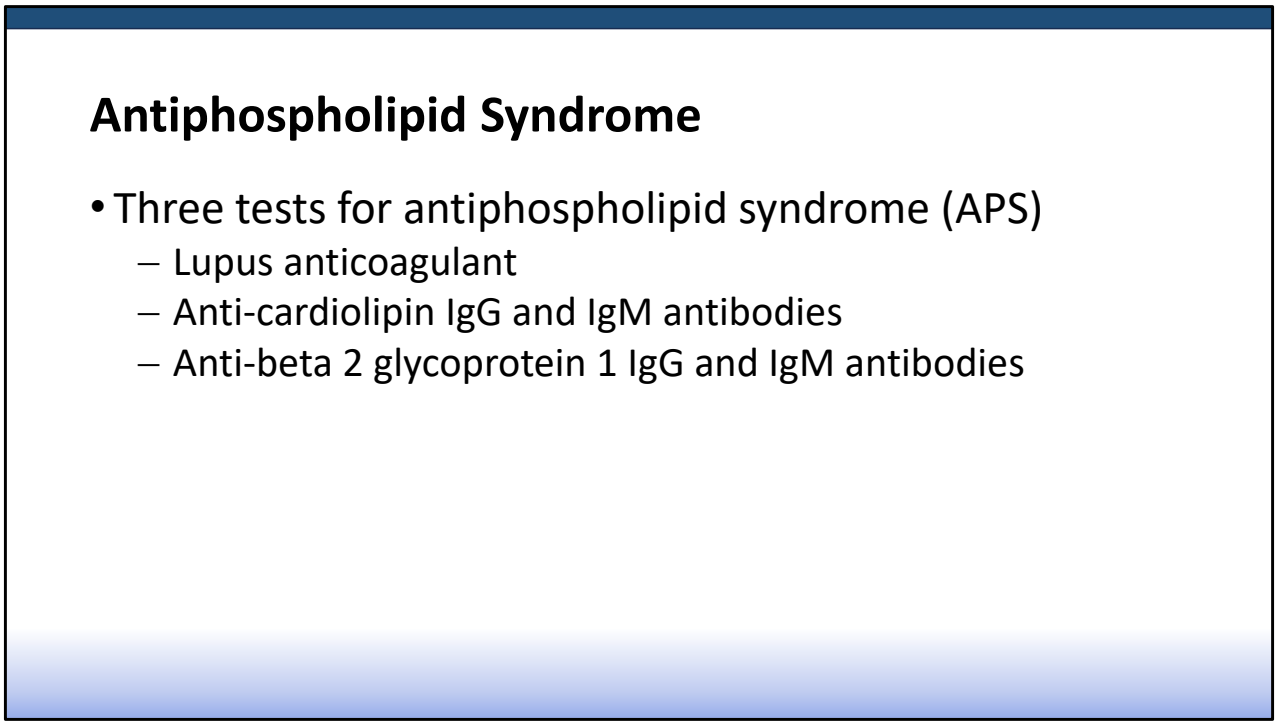
Jori May: Yeah, no, I think this is, I think the common questions that we have. So, if I might just summarize briefly, I think when we're thinking about thrombophilia tests, what we're usually talking about are the inherited thrombophilias, factor V, prothrombin, protein C, protein S, antithrombin, and then the testing for antiphospholipid syndrome, which I do want to highlight is an acquired condition. So, although we lump them together, it can happen that person doesn't have a family history. So, I do think they should be thought about somewhat distinctly and then to highlight the nuances of the

assays, like you said, the ones that are influenced by acute clot or being on a blood thinner are those functional assays. So, the lupus anticoagulant, usually protein C, protein S, and antithrombin are functional assays depending on what your lab does. Whereas those things that we refer, I tell trainees, genes and antibodies are ones that maybe are less influenced. So, the factor V Leiden and prothrombin mutations are mutation tests.

And then the antibodies for antiphospholipid syndrome, anticardiolipin, IgG and IgM, anti-beta-2 glycoprotein 1, anti IgG and IgM. I think, Stephan, what you also highlighted is what not to test for, because I think unfortunately there are panels out there that include an antiphospholipid antibodies that are IgA. It include other assays like the MTHFR mutations, PAI-1, other things that really don't influence our clinical decision making. So, really trying to be aware of what you have the capability to test for, what are the implications of what you are testing for, and making sure that you're only venturing into that at the appropriate time and kind of with the appropriate knowledge base, that it will influence your management.

Stephan Moll: And Jori, we haven't really talked about it, and maybe it's too self-understood. But obviously, we immediately also look at, when we see a patient with VTE, we look at the CBC to detect any possible anemia that could be a reason for an underlying malignancy or inflammatory bowel disease with anemia. Iron deficiency. Some data in the literature suggests that significant iron deficiency is also a prothrombotic state. We look at the CBC to detect elevated platelets and hemoglobin white cells for possible unusual myeloproliferative neoplasm, the polycythemia vera or essential thrombocytosis, and we look for the CBC to detect some low values that might be the rare paroxysmal nocturnal hemoglobinuria. Those are unusual thrombophilias and there's more to be said about them, particularly with the clots that we are not really fully addressing, unusual side clots, cerebral and sinus vein thrombosis, portal vein, hepatic vein. And I think, again, one of our future podcasts will deal with unusual clots. Those are interesting and challenging disorders because of the limited data, but I look forward to that podcast as well.

Jori May: Absolutely, and I want to highlight that point. I think oftentimes we're so focused on thrombophilia testing that we forget the more common thrombophilias, or things that increase blood clotting risk, particularly malignancy. So, I think highlighting that is important. And maybe highlighting that the data does not suggest that any patient with a VTE that's unexplained should have a scan head to toe, but that we make sure that patients have completed their age-appropriate cancer screening, or if they have symptoms of malignancy, that we certainly investigate those.



Jori May: So, I do want to see if we can briefly address antiphospholipid syndrome, which is an extremely complex topic, but like I said, is somewhat distinct. Dr. Moll, Stephan, if you can speak a little bit about, there has been a new publication recently about guidelines for how we diagnose antiphospholipid syndrome, and maybe to give us some take-home points from that guideline.

Stephan Moll: It's as you say, it's a big topic and you've already made one important point that I would also make. If we test for antiphospholipid antibodies as an acquired disorder, there are three tests that should be done. Lupus anticoagulant, anti-cardiolipin IgG and IgM antibodies and the anti-beta 2 glycoprotein 1 IgG and IgM antibodies. Not testing for the IgA and not testing for the phosphatidylserine, phosphatidylethanolamine, phosphatidylserine, those are research tests that are clinically not established.

Antiphospholipid Syndrome

- Three tests for antiphospholipid syndrome (APS)
  - Lupus anticoagulant
  - Anti-cardiolipin IgG and IgM antibodies
  - Anti-beta 2 glycoprotein 1 IgG and IgM antibodies
- To be classified as having APS, a patient must have:
  - Repeatedly positive tests, three months apart
  - A thrombotic event

Stephan Moll: And the repeatedly clearly positive tests, repeatedly at least three months apart, plus a thrombotic event, they classify patients as having antiphospholipid syndrome as an immune disorder where the immune system is confused, makes the antiphospholipid antibodies. Those people, in general have a high risk for recurrence.

Antiphospholipid Syndrome

- Three tests for antiphospholipid syndrome (APS)
  - Lupus anticoagulant
  - Anti-cardiolipin IgG and IgM antibodies
  - Anti-beta 2 glycoprotein 1 IgG and IgM antibodies
- To be classified as having APS, a patient must have:
  - Repeatedly positive tests, three months apart
  - A thrombotic event
- Triple positivity: strongest predictor of recurrence

Stephan Moll: And the ones who have the highest risk for recurrence are the ones who are triple positive with all three and clearly positive. So, the strongest predictor of a recurrence is the triple positivity.

Antiphospholipid Syndrome

- Three tests for antiphospholipid syndrome (APS)
  - **Lupus anticoagulant**
  - Anti-cardiolipin IgG and IgM antibodies
  - Anti-beta 2 glycoprotein 1 IgG and IgM antibodies
- To be classified as having APS, a patient must have:
  - Repeatedly positive tests, three months apart
  - A thrombotic event
- Triple positivity: strongest predictor of recurrence

Stephan Moll: And then of the individual tests, it's the lupus anticoagulant, more so than the anti-cardiolipin and anti-beta-2s.

Antiphospholipid Syndrome

- Three tests for antiphospholipid syndrome (APS)
  - **Lupus anticoagulant**
  - Anti-cardiolipin **IgG** and IgM antibodies
  - Anti-beta 2 glycoprotein 1 **IgG** and IgM antibodies
- To be classified as having APS, a patient must have:
  - Repeatedly positive tests, three months apart
  - A thrombotic event
- Triple positivity: strongest predictor of recurrence

Stephan Moll: And of the subtypes of the antibodies, it's the IgG that's more important than the IgM.

2023 ACR/EULAR Antiphospholipid Syndrome Classification Criteria

Entry Criteria[a]
At least one documented[b] clinical criterion listed below (domains 1-6)
plus
A positive antiphospholipid antibody (aPL) test
(a lupus anticoagulant test, or moderate-to-high titers of anticardiolipin or anti-β_2-glycoprotein-I antibodies [IgG or IgM])
within three years[b] of the clinical criterion

If absent, do not attempt to classify as APS - If present, apply additive criteria

Additive clinical and laboratory criteria[a]
Do not count a clinical criterion if there is an equally or more likely explanation than APS.
Within each domain, only count the highest weighted criterion towards the total score.

Clinical domains and criteria	Weight	Clinical domains and criteria	Weight
D1. Macrovascular (Venous Thromboembolism [VTE])		**D2. Macrovascular (Arterial Thrombosis [AT])**	
VTE with a high-risk VTE profile[c]	1	AT with a high-risk CVD profile[c]	2
VTE without a high-risk VTE profile[c]	3	AT without a high-risk CVD profile[c]	4
D3. Microvascular		**D4. Obstetric**	
Suspected (one or more of the following) Livedo racemosa (exam) Livedoid vasculopathy lesions (exam) Acute/chronic aPL-nephropathy (exam or lab) Pulmonary hemorrhage (symptoms and imaging)	2	≥3 Consecutive pre-fetal (<10w) and/or early fetal (10w 0d -15w 6d) deaths	1
Established (one of more of the following) Livedoid vasculopathy (pathology[d]) Acute/chronic aPL-nephropathy (pathology[d]) Pulmonary hemorrhage (BAL or pathology[d]) Myocardial disease (imaging or pathology) Adrenal hemorrhage (imaging or pathology)	5	Fetal death (16w 0d – 33w 6d) in the absence of pre-eclampsia (PEC) with severe features or placental insufficiency (PI) with severe features	1
		PEC with severe features (<34w 0d) or PI with severe features (<34w 0d) with/without fetal death	3
		PEC with severe features (<34w 0d) and PI with severe features (<34w 0d) with/without fetal death	4
D5. Cardiac Valve		**D6. Hematology**	
Thickening	2	Thrombocytopenia (lowest 20-130x10^9/L)	2
Vegetation	4		
Laboratory (aPL) domains and criteria[e]	**Weight**		
D7. aPL test by coagulation-based functional assay (lupus anticoagulant test [LAC])		**D8. aPL test by solid phase assay (anti-cardiolipin antibody [aCL] ELISA and/or anti-β_2-glycoprotein-I antibody [aβ_2GPI] ELISA [persistent])**	
Positive LAC (single – one time)	1	Moderate or high positive (IgM) (aCL and/or aβ_2GPI)	1
Positive LAC (persistent)	5	Moderate positive (IgG) (aCL and/or aβ_2GPI)	4
		High positive (IgG) (aCL or aβ_2GPI)	5
		High positive (IgG) (aCL and aβ_2GPI)	7

TOTAL SCORE
Classify as Antiphospholipid Syndrome for research purposes if there are
at least 3 points from clinical domains AND at least 3 points from laboratory domains

Barbhaiya M, Zuily S, Naden R, et al. on Behalf of the ACR/EULAR APS Classification Criteria Collaborators. 2023 ACR/EULAR antiphospholipid syndrome classification criteria. *Annals of the Rheumatic Diseases*. 2023;82:1258-1270.

Stephan Moll: And then the titer matters, the higher the titer, the more the prothrombotic risk. So, all these, what is more relevant and such that didn't used to flow into the criteria, how would you find antiphospholipid syndrome. But last year, the American College of Rheumatology together with the European society, I don't know exactly what it's called, EULAR, European something for rheumatology, came out with criteria, how do you define this antiphospholipid syndrome? And for anybody who deals with these patients, that's a really worthwhile publication. Not the whole thing, the whole thing is incredibly long and complex and not really clinically very useful. But there's one table in there, the key one, how do you define the antiphospholipid syndrome, where now you get certain, or you give the patient certain points, the more prothrombotic the lab test, the more points you get.

If it's truly an unprovoked clot, you get more points because it really suggests this is an immune auto antiphospholipid antibody syndrome. Whereas if it's a hip replacement-associated clot, well, first of all, the patient should not have been tested. But if they were tested, then antiphospholipid antibody is probably just coincidental.

Stephan Moll: Anyway, so that is the new criteria that were developed as research criteria. But at least, clinically also relevant and interesting because it tells us which ones of these findings are more relevant and really are the significant risk factor for the clot. These are antibodies that can, is a syndrome and antibodies that can occur in any age group. It's more commonly in people with autoimmune disorders thus, it's more the female, younger to middle-aged group, but they can occur in elderly people, cancer-associated, or idiopathic without any unknown reason. And traditionally, historically, it was said, if you have the syndrome of clot plus repeal of your positive test, you need to be on long-term blood thinners, high risk for recurrence. But now with these more finities, where which antibodies are positive and which ones are only mildly and strongly positive, this thought, everybody needs to be on long-term blood thinners is probably not correct. And this has really become relevant in the last two years because, or three years, because there has been some degree of failure of the apixaban and rivaroxaban, the DOAC-treated patients with two antiphospholipid syndrome. There's some comment that people should be on warfarin rather than a DOAC. And that's likely true for the triple positive patients.

For the double and single positive patients, there's a lot of nuances to it. So that should not be said that everybody with antiphospholipid syndrome should be on warfarin rather than a DOAC. There are a number of people with double and single positive who in whom it's appropriate to treat with DOAC. Maybe that's what I can say about that. One could.

Jori May: That was extremely helpful. And again, you summarized a very complex document in a very brief time. So, thank you for doing that. And certainly for those who need more detail, we encourage you to check that out. So, we...

Stephan Moll: I hope nobody who was an author on that paper listens to this where I said there's a lot of information that's difficult to digest.

Jori May: Well, I think the nice thing is that they put a lot of thought, there's a lot of detail in there because this is so complex, but there are really helpful take home tables that, like you said, I think for the really clinically focused person are extremely helpful.

Case Summary

- Estrogen-associated VTE: placement in the recurrence triangle is flexible
- May consider D-dimer testing or thrombophilia testing to help guide decisions concerning duration of anticoagulation treatment
- Critical areas of shared decision-making
  - Menstrual bleeding
  - Contraception
  - Future pregnancies

Jori May: So, if I might kind of briefly summarize this case and then lead us to our conclusion, you know, we talked about the fact that this patient had an estrogen-associated VTE, and so her place in the recurrence triangle is a little bit flexible. So, somewhere where we might think about D-dimer testing, or we might think about testing for thrombophilias in order to make a decision about how long to anticoagulate this patient. Of course, taking into account her preferences, really guiding her in this decision-making process. And of course, keeping in mind in a patient like this that we're having conversations about menstrual bleeding, contraception, thinking about future pregnancy. And so those implications can be really significant for this patient. And whether that's something that a primary care provider may feel comfortable managing on their own, or if this is someone that in partnership with a hematologist or other thrombosis-focused clinician, might be better to manage as a team.

Conclusion

- Risk factor terminology: major, minor, transient, non-transient; unprovoked VTE; multifactorial
- Tools to support clinical decision-making
  - Recurrence triangle
  - The warfarin or “DOAC Hate Factor”
- Thrombophilia testing not often indicated: rarely changes management

Jori May: So, with that, we could talk about this for so much time, but unfortunately we're coming up on the end of the time that we have. But I wonder, Paul, if you could maybe wrap us up with some take home points, things that you've gathered from our conversation that you think would be helpful for our listeners to take away.

Paul Lewis: Yeah, absolutely. And again, this is certainly today is very interesting and questions we get and it's a complex topic. And just to have these references in your mind as a primary care clinician is helpful as you're trying to quickly make some of these decisions. And really, again, as you get into these more complex cases, it's exactly that is, should I send this patient to hematology if I can find one or is this something I'm comfortable managing and I feel like there are, you know, a low risk or I know what I'm doing. And hopefully after listening to this podcast, more and more folks will know what they're doing. So, a couple take home points, again, I agree. If you're seeing a patient thinking about those risk factors, those major and minor risk factors and the moderate risk factors, does it make sense that the patient had a clot because of whatever their event was or is it really more of an unprovoked event?

And of course, what are the factors that go into it? I really like the point you made too, Jori, as we see these patients, we say, well, it was a unprovoked event, and especially in a patient older of, I wonder if there is an underlying cancer, that malignancy, that maybe there was a reason it was provoked, but again, not having to scan them from head to toe. I think that's a great take-home point, make sure they're up to date in all their preventative care and age-based guidelines.

Conclusion

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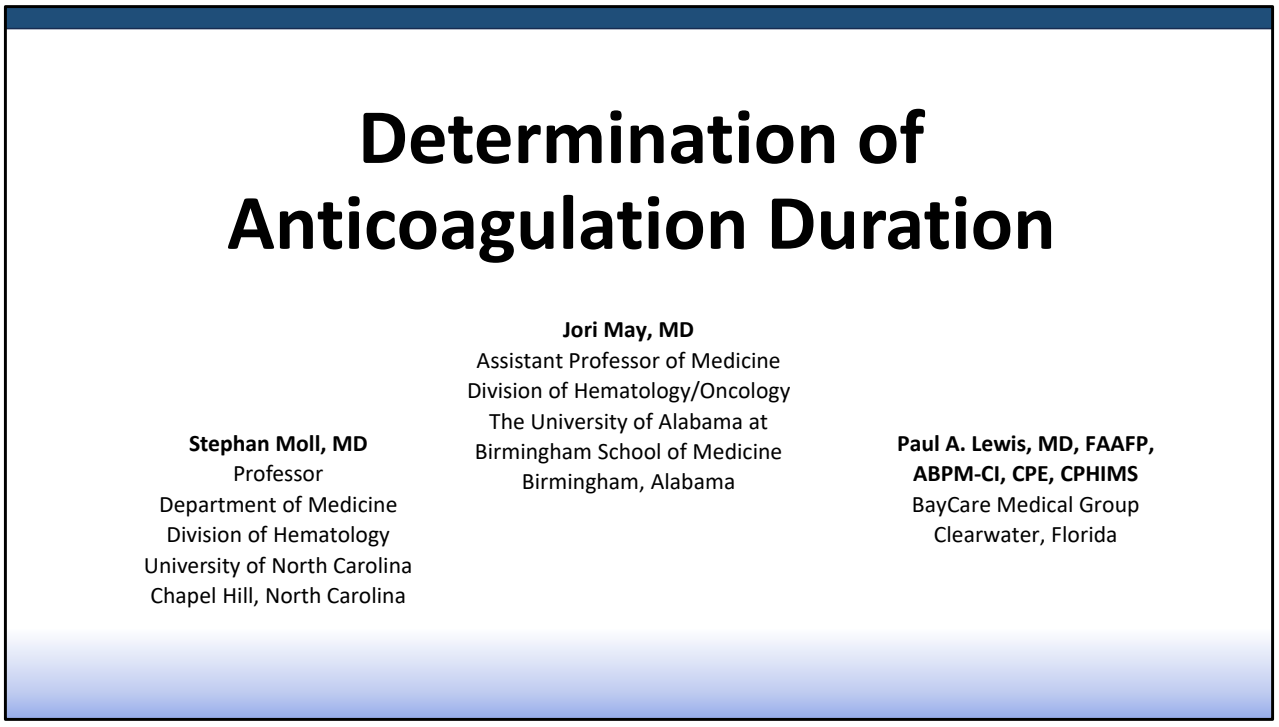
Again, the concept of the recurrence triangle is fantastic and thinking about where your patient falls in that recurrence triangle because again, that helps you decide are they in that intermediate risk, right? Because as I heard you say, Stephen is low risk, pretty straightforward, high risk, they may be in anticoagulation forever and I want to get hematology involved with those folks and intermediate risk, maybe I can use a D-dimer to predict recurrence as well as look for other reasons to consider.

Thrombophilia workups. Again, I love the concept of the hate factor of what is this patient's desire and shared decision making to stay on the anticoagulant, as well as of course their bleeding risk and of course always finances too. And then again, thrombophilia testing comes up a lot, especially with trainees it seems like, and maybe newer clinicians that they wanted to order everything and they order it while they're on the blood thinner and they order it when the acute event occurs. And what I heard you say is there's many things you can go wrong when you're looking at thrombophilia testing and there's really only a few things that are going to change how you're going to treat the patient and that duration to try to focus on that. And again, if you don't know what you're doing, perhaps the best thing is if you think there's a secondary thrombophilia and you're not comfortable with it, is to have a consultation with an expert because otherwise again, you get these false positives, false negatives and you go down some tracks that you don't want to go down, and then ultimately we could cause harm, which we want to avoid. So, I think I love the concept of getting somebody involved as it gets more and more complicated.



Jori May: Wonderful. Well, this is going to conclude our discussion of the diagnosis and management of acute VTE. Thank you, Stephan. Thank you, Paul, for talking with me today. Our next podcast, we're going to be talking about long-term complications that may be associated with chronic VTE management. So, I hope our listeners will tune in. Please do not forget to complete your CE evaluation and claim your credit. And thank you again for your attention.