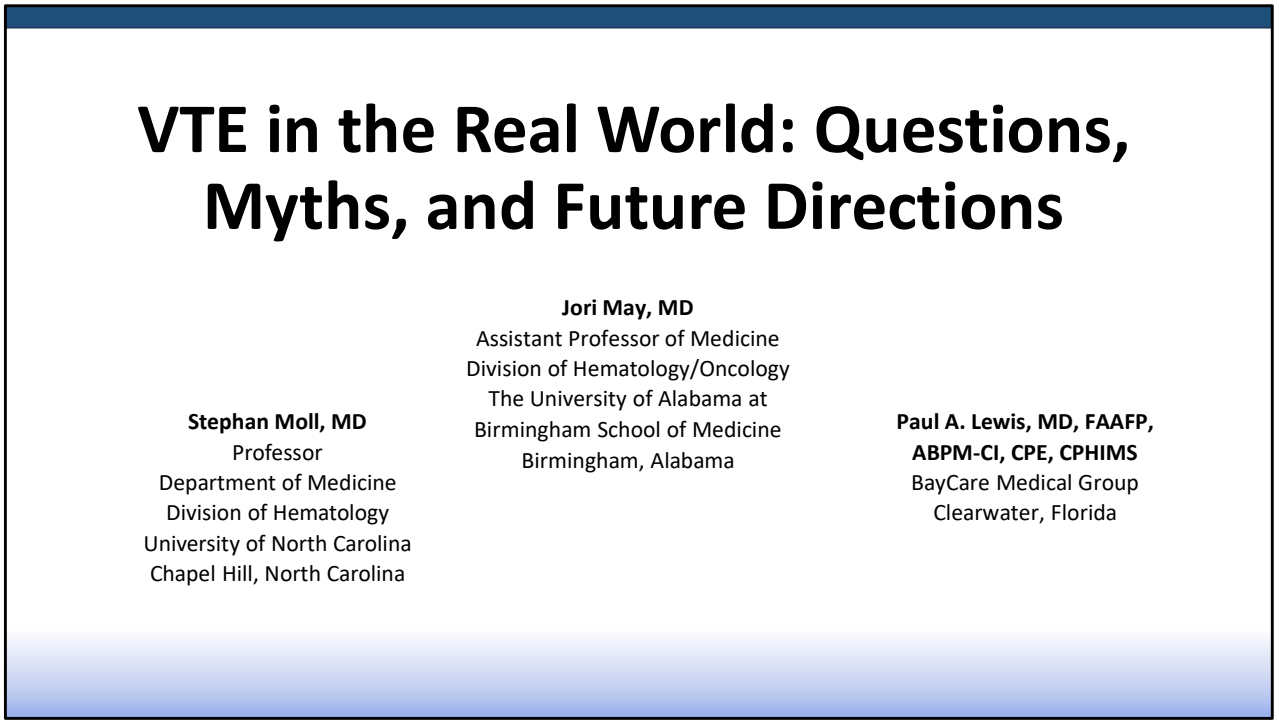


Jori May: Hello and thanks for joining us. We are here today in our fifth podcast in the series to discuss what we're calling questions, myths and future directions. So, my name is Jori May. I am a hematologist at the University of Alabama at Birmingham, and I am joined by two panelists today to help in our discussion. I'll clarify two things: first, that none of us have any conflicts of interest to disclose, and second, that we've opted to use our first names when referring to each other throughout the podcast. So, with that, I was hoping Paul, you could introduce yourself first.

Paul Lewis: Sure. Hi, Paul Lewis. I'm a family physician. I've been in practice for 25 years and I am academic faculty and community faculty at the FMSN residency program.

Jori May: Great, thanks Paul. And Stephan?

Stephan Moll: Thank you very much. Stephan Moll, I'm on faculty at the University of North Carolina in Chapel Hill. I'm a hematologist, specifically a coagulationist. I deal mostly with thrombosis anticoagulation, and I'm thrilled to be here. Thank you.

Learning Objectives

- Answer questions commonly asked by patients with a DVT or PE concerning imaging, travel and anticoagulation interruption
- Educate female patients with a DVT or PE concerning safe contraceptive strategies and management of perimenopausal symptoms
- Identify VTE patient types and scenarios in which a non-specialist should consider referral to a specialist
- Outline the role of family history in thrombophilia testing and identify when family members should be tested

Jori May: Well, let's dive right in. I'm going to outline some objectives for us. So we, in brainstorming this session, really came up with a mix of things. Like I said, questions, myths and future directions. Some of the things that we're planning to cover are questions about when do we need follow-up imaging for a patient that's had a VTE? Who needs it? When do they need it? What's the purpose of getting any sort of imaging? Then talking about questions that patients might have in their life after having a VTE: if they stop anticoagulation, what do they maybe need to do differently, or think about, in future high-risk scenarios? Thromophilia testing is an issue that comes out frequently for the hematologist and the primary care provider. So, we're going to talk specifically about some considerations of thrombophilia testing in the primary care setting. And then what to do in people who haven't had VTE, but may have a family history of VTE: do we need to think about thrombophilia testing in those patients? And then touching also on kind of future directions, clinical research in the VTE space that might be relevant to the primary care provider.

Patient Question/Myth 1: Imaging Studies

Don’t you need to take a look and see what my clot is doing?

- Patients who have had a blood clot
  - Either DVT or PTE
  - Currently on blood thinner
- They want to know: is repeat imaging required to identify whether clot is improving or moving

Jori May: So, with that, let's start with our first scenario. So, in a patient that's had a blood clot, either a DVT or a PE, a common question that I often get in my office is, “Hey doc, don't I need to take a look at it to see what it's doing?”

So, a patient who's been on a blood thinner and they want to know, do they need to get any sort of repeat imaging in order to see or know how that clot is improving or moving is a very common question that I encounter.

Jori May: So, Stephan, I wonder if you could take us through a little bit of a framework of how you think about what I'm going to call repeat imaging. So, a patient who's had a clot is on anticoagulation: if, and when we need to repeat any sort of imaging for those folks.

Stephan Moll: And I think that's pretty straightforward. There is no indication for follow-up imaging to see what the clot is doing, whether there's resolution, whether it's leftover clot. If the patient's doing well and improving, then there is no consequence of any imaging studies. So, we will reserve the imaging studies if the patient develops new symptoms that might be suggestive of a recurrent clot. That's the one thing.

Now, at three months or six months, many patients have leftover scar tissue, which is often referred to as chronic clot or leftover clot. I've never liked that term because patients think it's still clot that can break off, can cause a PE. It's not. It's scar tissue. So, I prefer to call it scar tissue. And probably 30 to 50% of people at three to six months still have scar tissue left. It does not influence our management. It does not influence how long we treat, whether we stop or continue for another three months and then repeat the imaging study. So, really, there's no consequence of finding scar tissue. However, and this is, I think important, when we take a patient off blood thinners, let's say they were treated with three to six months for major transient risk factors, so it's a clot, it's at that point that a baseline imaging study is appropriate. And it's not to decide should we continue blood thinners or not, but to have a baseline in case trouble comes up, new symptoms two years later and there's a question of when they see something, is it a recurrent clot or is it the scar tissue from previously? It's good to have a baseline when they came off blood thinners, so that we know, yes, this is new, since they came off or it's the same scar tissue that we saw before. Some of the guidelines, including the ones from the general Internal Medicine Society state if a patient had a clot with a major transient risk factor such as a hip replacement, they have a low risk for recurrence if you take them off at three or six months. They said maybe you don't need a baseline study because the chance of you having another clot in the future is quite low. But reserve it for the people where there is a somewhat higher risk for recurrence and there, they want a baseline. I think that's a little too much into detail and thinking.

My approach is whenever somebody comes off blood thinners, I get a baseline venous Doppler ultrasound.

Jori May: That's helpful to think about because I think, oftentimes, we get repeat imaging and then maybe even don't know what to do with it. So, I also set the expectation with the patient that if I am getting a baseline ultrasound that yes, we're going to get an ultrasound and we may see some abnormality there. It may be it's scar tissue. It's not necessarily something that we need to do differently, but it's just there for comparison in case of any problems in the future.

Stephan Moll: And, Jori, it may be worthwhile to mention there have been studies to see whether residual clot, what they called it, is a risk factor for recurrent VTE if patients come off blood thinners. And the data have been discrepant. Some Italian studies have shown if you have significant leftover scar tissue, which they have defined by Doppler ultrasound criteria, then you have a somewhat higher risk for recurrence. Whereas some other studies, US and Canadian, have not shown that it predicts recurrence.

So, they are discrepant data, and in that situation, I don't use it for decision making, because we don't have solid evidence that it really changes risk of recurrence and management.

Jori May: That's really helpful. And so often, we're talking about DVT, but what do we think about differently for PE? Anything differently that for a pulmonary embolism where you might think about imaging, a CT scan, a VQ scan, anything like that?

Stephan Moll: So, that's a little bit different. Again, it's mostly, if new symptoms come up, then repeat imaging is appropriate. And it can be difficult to assess, is something a new clot or is it the leftover previous clot or the scar tissue. So, it's often that we take a clinical history, yes, symptoms are worse. What is my pretest probability that the symptoms are due to a new clot? Secondly, a D-dimer can be helpful. A negative D-dimer argues somewhat against the recurrence. A positive D-dimer argues somewhat that this could be a new clot, and then an imaging in the case when we suspect a new PE, a CT scan would be appropriate . However, if the patient is doing well, has no new clinical symptoms, then I don't get a baseline study when we stop anticoagulation, just to avoid the radiation exposure. Plus, the lung has a pretty significant ability to dissolve clots from internal tissue, plasminogen activator that we have.

However, if the patient has not completely recovered, has some shortness of breath, dyspnea on exertion, just says, I haven't gotten back to baseline, I'm fatigued, and there's some suspicion for the post-PE syndrome specifically, or more relevant, the increased intra-pulmonary pressure, pulmonary hypertension, then the appropriate test to do would be a VQ scan, because that is the most sensitive to pick up chronic perfusion defects . You will, or some people hear and read in the literature that the very experienced radiologists or pulmonologists, they can also see chronic scar tissue that leads to pulmonary hypertension on a CT scan with web formation in the vessels. But the usual radiology team, the CT scan is not sensitive enough to pick up chronic changes that lead to pulmonary hypertension.

Paul Lewis: And Jori and Stephan, you know, you bring up a great point. It's hard when the patient is still symptomatic or has new symptoms because, right, that's when they probably ask the most questions. And again, you hit the nail right in the head, as Stephan, especially

Paul Lewis: when I work with residents and others to say, is this a new presentation because of the bias? They say, well, you just had a PE, but it may be something else too. So, we always have to use our differential diagnosis and clinical diagnosis, and think critically in those cases. But yeah, it certainly seems like occasionally, patients will say, I'm still symptomatic, I'm still short of breath, or I still have edema.

Stephan Moll: And we addressed that in one of the earlier podcasts on the Doppler ultrasound side in the legs. We look at the criteria of the Doppler ultrasound and maybe just for people who haven't watched the previous podcast, the three criteria of an acute or new clot are that the vein looks dilated, the clot looks spongy, and the clot looks hypoechoic blackish, whereas, a chronic one, this vein is scarred, retracted. The clot looks white, hyperechoic, and the clot is firm on compression . So, the thought, what is a, if somebody has new leg symptoms, what is a new clot and an old clot is really the pre-test probability, as I mentioned, the D-dimer, comparison to the old scan, and then the question, how does the clot look on the Doppler ultrasound? And it may look, what they call acute for a few weeks, before it has more the chronic scar tissue appearance. On the CT side, it's again the same, the pretest probability and D-dimer, but it's much more difficult on a CT scan to say, a clot looks old or it looks new. I would always take that with a grain of salt if the radiologist says this looks like an acute clot, unless it's really talking about very central PEs where the veins are big, then they can sometimes, they may be able to say this looks acute. If the filling defect is more central in the blood vessel, that looks more chronic, if the contrast filling defect is more wall-adherent and eccentric.

Patient Question/Myth 1: Imaging Studies

Don’t you need to take a look and see what my clot is doing?

- Routine follow-up imaging is not indicated
- Imaging is indicated if there is:
  - A change in symptoms in PE
  - Persistent symptoms
  - When anticoagulation is stopped for DVT

Jori May: I think that's helpful. And I guess to summarize, kind of the take home point, is just routine follow-up imaging is not indicated. You know, we're really talking about if there's a change in symptoms in pulmonary embolism, if there's persistent symptoms, and then if we're stopping anticoagulation for DVT, thinking about getting that repeat ultrasound in the leg.

Stephan Moll: Paul, can I ask you, in your experience, do you think this gets frequently done, that the baseline study is done when people stop anticoagulation and what do you think about that approach?

Paul Lewis: Yeah, yeah. I would say oftentimes, it's probably not done, right? And then you do have a conundrum if the patient presents later on. But I did like the way you broke it up is, to simplify it, is, if the patient is a higher risk for a thrombus in the future, you definitely want to get that repeat ultrasound at the end of therapy. So, I think that was a nice way to summarize it.

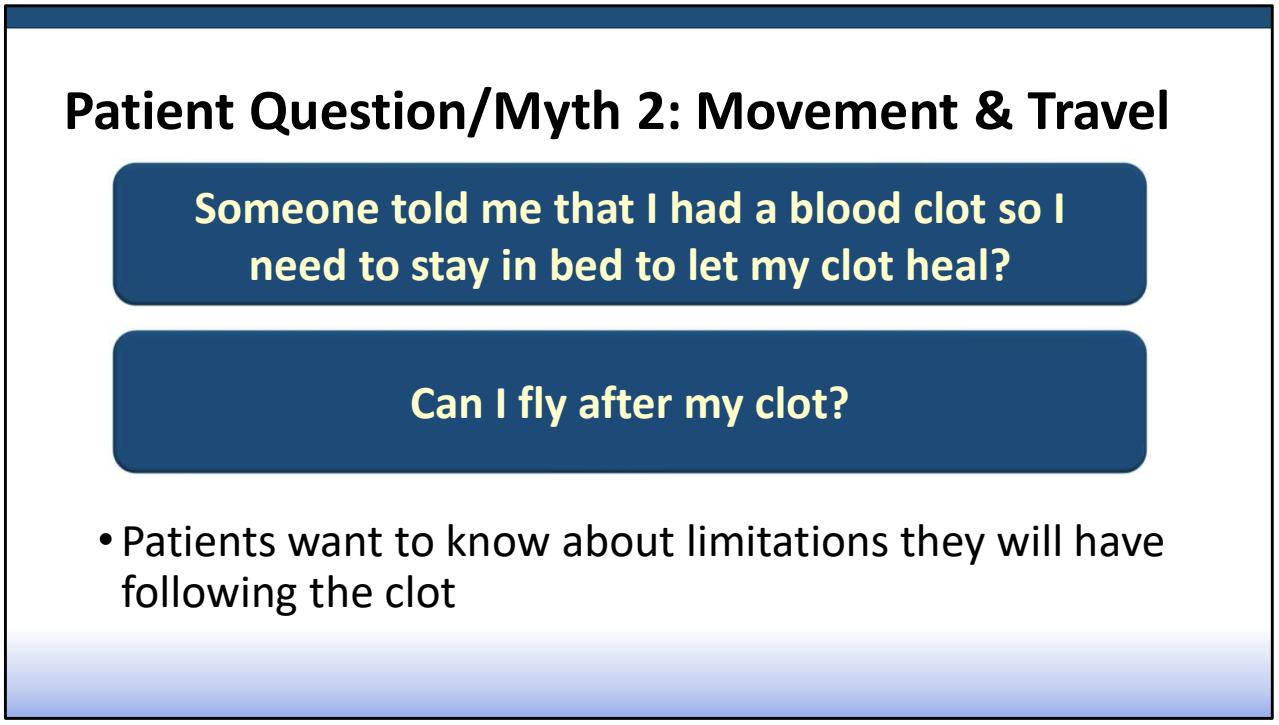
Jori May: I almost think of it as a favor to your future self because it'll be a lot easier to tell if there's a new clot there compared to previous.

Patient Question/Myth 2: Movement & Travel

Someone told me that I had a blood clot so I need to stay in bed to let my clot heal?

- Patients are concerned that the clot will break off and travel with movement

Jori May: All right, well let's jump to another kind of patient question that we might encounter. We say, comes to you and says, “Hey doc, someone told me that I had a blood clot, so I need to stay in bed to let my clot heal. Is that true?” I hear from patients often that they're worried that their clot will break off and travel if they move too much.



Jori May: And they'll ask questions about, can they fly? What sort of limitations do patients have after having a blood clot? So, Paul, maybe if you could start out, if there are kind of general counseling tips or guidance that you give patients based on how much physical activity they can do after either a DVT or a PE.

Paul Lewis: Yeah, absolutely. And, you know, again, thinking about earlier in our training, we used to have folks stay in bed, we realize that's wrong and not the right thing to do. Of course, we used to do that for MI too. But absolutely, again, they should move. A lot of it is, what is their baseline physical activity prior to the event? So, were they somebody that barely moved before the event? Or were they a marathon runner before the event? So, it's important to establish what that patient's pre-event activity level was, right? And then based on that, you can certainly counsel them to, after that DVT or PE, to slowly start to gradually increase their activity and to not, again, unless they have some other reason that they can't walk or they can't stand, to move, to again, improve their activity, decrease risk of future events, as well as just to improve their overall muscle strength.

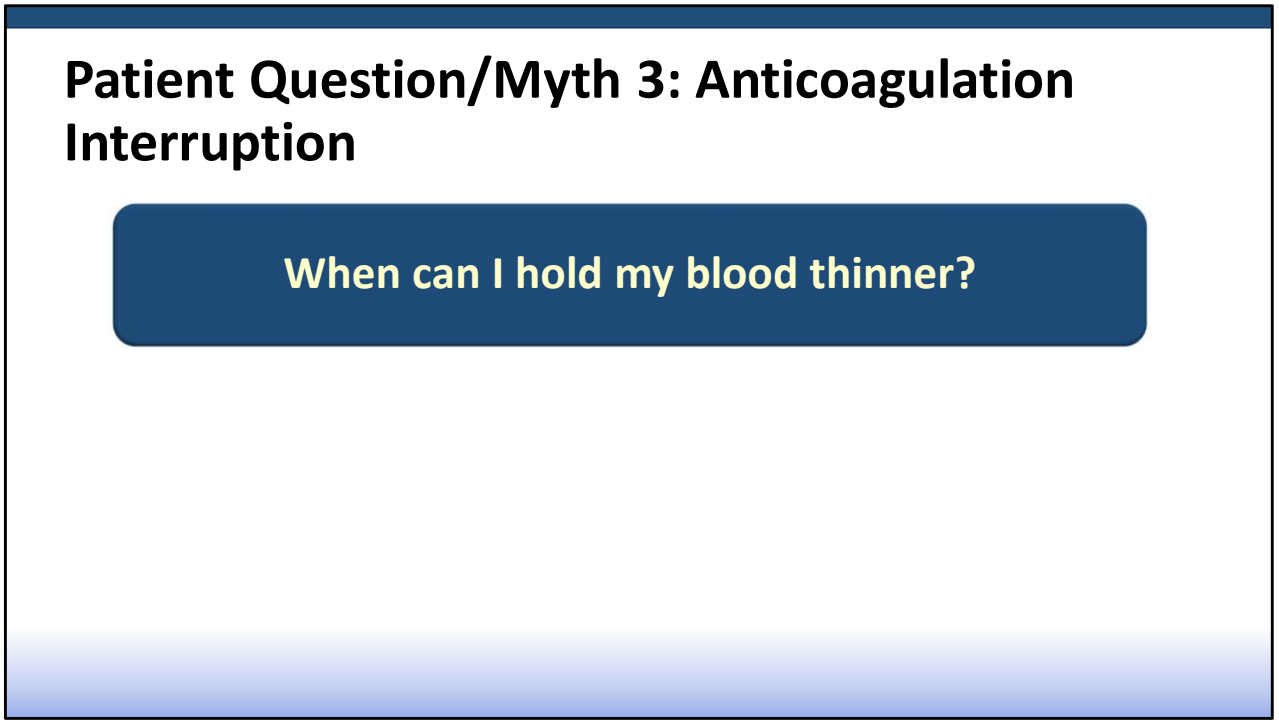
So, I will always tell them again, it's certainly scary to have an event such as this. And I can understand their initial inclination to not move or to limit their movement. But as we know, not something they should do and they need to walk, they need to move. I think it's harder when you have that higher level athlete. And I have a patient recently who is in his 80s and he's a marathon runner. And he says, and again, I'm going to refer this to one of you two, because he says to me, "I'm supposed to run in the Boston Marathon. And I think it was about eight months and I've always run. And so, can I run this year?" So, that's a tough question for that high level athlete. That's a little more challenging for me to answer. But for the average person, again, I'll encourage them to exercise, to move and to slowly, gradually increase their activity, especially once they're out a little further from the acute event.

Stephan Moll: And I think you say an important term there, Paul, to slowly get back to their previous activity level. And I don't have really scientific data, but my typical approach, and my thought is, within four weeks you can be back to your previous activity level. I mean, there is some concern that clots that just recently formed, they're in the big veins in the pelvis or the proximal leg, that with significant running and trauma, they could break off. Theoretically, that's reasonable. They have fragile clots to some degree. So, I don't want them to go back to complete full activity level within two days or so. I tell them within four weeks, get back to a previous level. The one thing, and you mentioned an 80-year-old athlete. I also deal with athletes, but more the younger ones. Nothing against an 80-year-old who's running the Boston Marathon. So, I deal with some professional athletes and college athletes, the high-level elite athletes. And the question comes up, if they have right heart strain from a significant PE, not just a smallish low-risk PE, but they had significant moderate right heart dysfunction from increased pulmonary pressure from a big PE, how quickly can they get back to full activity? How much does a right heart suffer from being too active?

And should one do a follow-up cardiac echo, which likely one should do before they get back to significant activity? I found myself interacting with pulmonary and maybe cardiology on that question. How do we follow this right heart dysfunction and make sure that we're not doing harm by letting the big-time athletes go back to full activity too quickly?

Paul Lewis: And then I guess, Jori, the second part of the question, and I would love to get Stephan's opinion and you, as well as yours, is the flying, right? So, flying after that acute event. And oftentimes I'll clarify with the patient, are we talking about a one-hour flight to Atlanta from Tampa, or are we talking Singapore, right? Or Asia? So, what's that duration of that flight? But, so those are certainly some questions. But, Stephan, in terms of the evidence regarding activity and as well as flying, I'd love for you to share your knowledge on that area.

Stephan Moll: Yeah, thanks for asking that. There is really limited data that I'm aware of. And up until probably four or five years ago, I used to tell the patient, for the first four weeks after an acute clot, I prefer that you not fly. And I was a little more firm on that. But these days I've gotten more, when there is limited data or no data, you can't really say too much. And I've had patients who had a family reunion two weeks or so, a flight of two, three hours or so. And I say, well, I don't have any good reason to advise you against it. You're on an anticoagulant, so it's probably fine. If it's avoidable, preferably not fly for the first four weeks, let the clot become wall-adherent. But I don't advise strongly against flying anymore. I tell them, scientifically, we don't know whether it's detrimental to fly in the first four weeks and take it from there. Now, if you're, say, flying to Singapore, there then becomes an issue also, not just the patient themselves, but also other customers who fly. If something were to happen during the flight, then it's not just for the patient, but also for the others. So, I would also be a little concerned about particularly if it was a big PE, there was maybe some right heart strain to fly 12 hours or so. But again, I wouldn't also be really solidly able to advise against it. I think in those situations, we just have to say what the limited data are. And then the patient needs to give input how important the flying is to them, and one makes a decision.

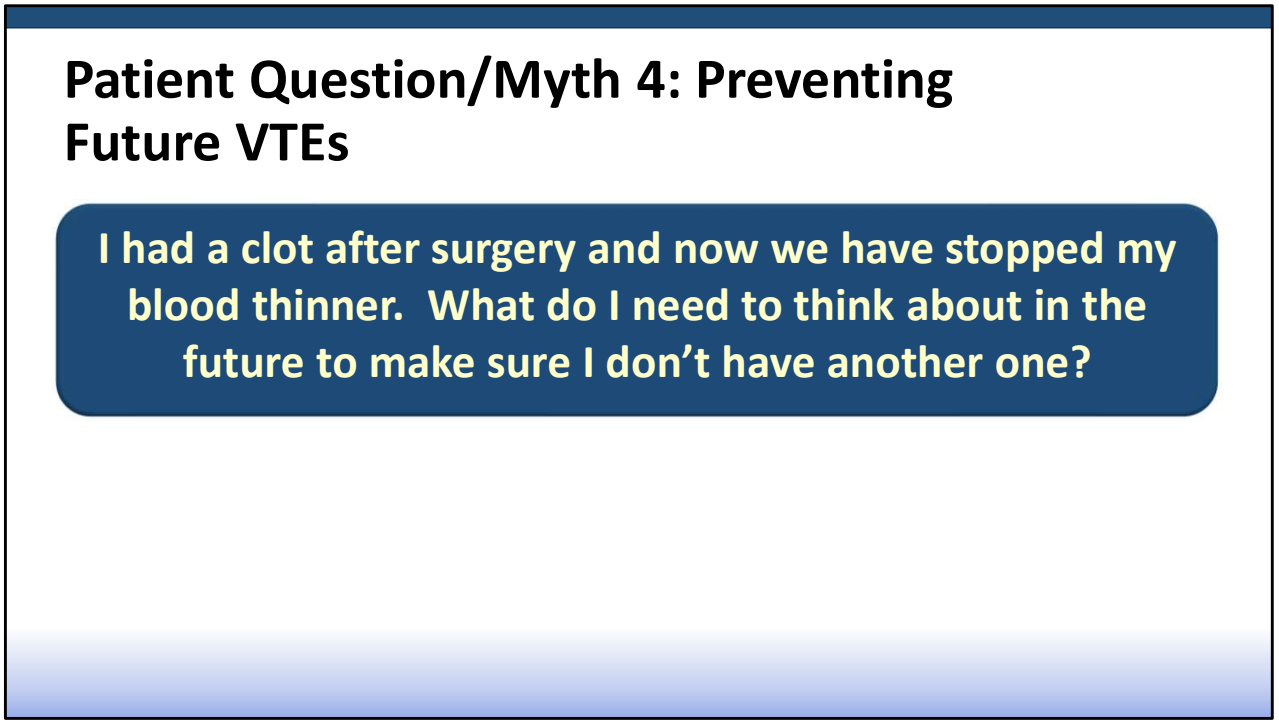


Jori May: That's all helpful. I think some other things that often come up that patients might ask about, one is, “when can I hold my blood thinner for any reason?” So, say they need a procedure, whether that's something elective or something that is relatively urgent, when can you come off of a blood thinner after you've been started on one for a VTE? Paul, maybe you can speak to that, what you do in your practice, or do you work with a hematologist to make those types of decisions?

Paul Lewis: Yeah, and I will often consult hematology if it's an extremely difficult case. Again, a lot of variables in terms of stopping that anticoagulant. The question is, do they really need to stop it? Because you get a lot of requests in general to stop anticoagulants for all sorts of things. And that's why I always go back and ask the proceduralist, is it really... Well, first off, what's the evidence? We know there's, in the dental literature, there's lots of evidence to say, you can do a lot of things while on anticoagulant. But oftentimes you'll say, I'm going to pull one tooth and I'm recommending, we'd like you to stop the anticoagulant. So, the way I counsel again is, how long, if they are going to have to hold it, what is the indication? Is there truly an indication? And then how close are they to that acute event where that occurred? And if it's possible, is there a way to defer, at least until the, towards the end of that anticoagulation, assuming it's not something that, you know, acutely need to have?

Stephan Moll: And Jori, that matches my approach, but then I may even actually be more dogmatic. I almost say for the first three months, you should not interrupt your anticoagulation. Everything should be delayed until three months later. Now, it sometimes looks a little different, particularly in the cancer population where people need to do a biopsy, a bronchoscopy to clarify something. Then I say it would be really nice to wait at least four weeks because that's typically when we think the clot is wall-adherent and the risk for PE is less.

So, in the first four weeks, I'm uncomfortable. And then the question really comes up, should one place a transient IVC filter? Because they have an indication to be on anticoagulation. They are at high risk for recurrence in the first, at least, four weeks. You take them off for two or three days to do a higher risk bleeding procedure, like a bronchoscopy with a biopsy of a mass. Then a transient IVC filter would be appropriate, but make sure that it gets taken out again once the patient's back on anticoagulation.

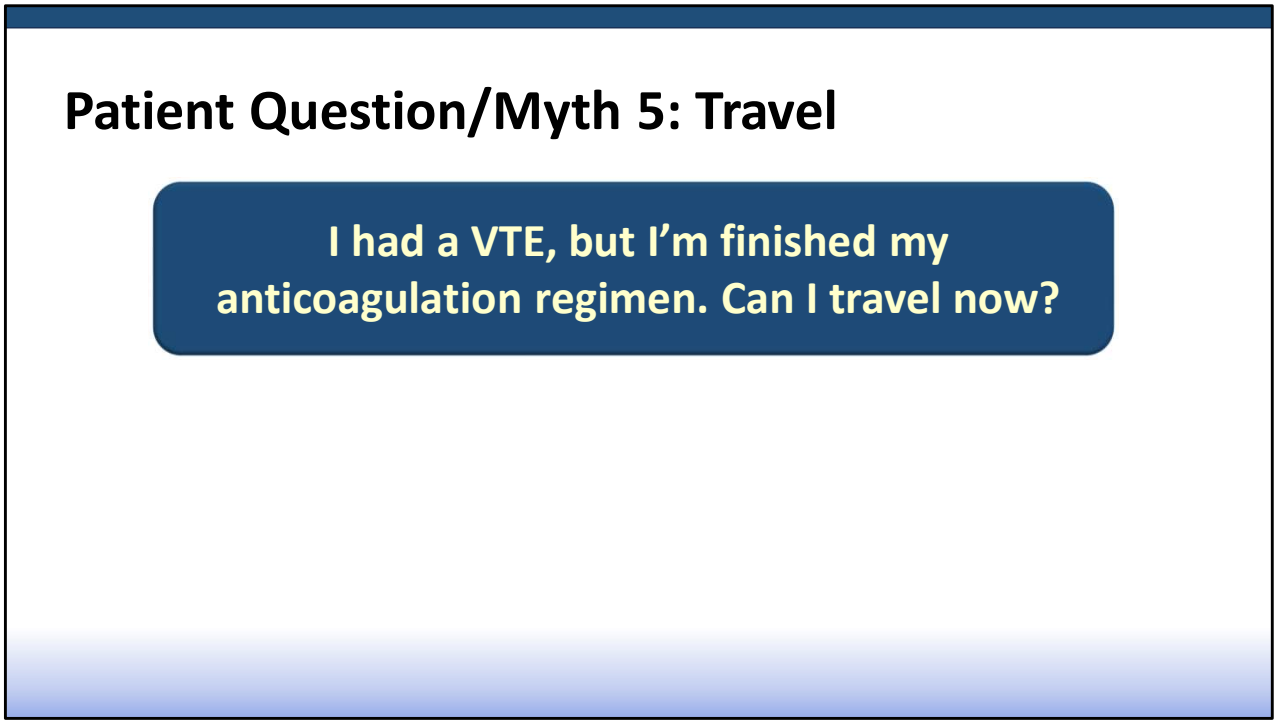


Jori May: So, let's move on to another question on the theme of stopping blood thinners. So, often a patient will come to me and they've stopped their blood thinners. So, say they had a blood clot related to a major transient risk factor. They had surgery, they developed a blood clot, they've recovered, and now it's time to stop their blood thinner. And so, they'll often ask what they might need to think about in the future to make sure that this doesn't happen again. I wonder, Paul, if you can talk to us a little bit about what do you think about or counsel a patient on when they've completed a course of anticoagulation and how that might affect their health in the future?

Paul Lewis: Absolutely. So, obviously for all of us, but in particular someone who has had a prior thrombus, the benefit of activity and of ambulation in particular, I often will preach to many of my older adults that ambulation in some capacity is good on so many levels, but in particular, obviously, if you've had a previous thrombotic event, even doubly more so important. So, ambulation, stretching, standing. I know, again, even just occasionally if they can't stand up, just pumping their legs and moving their legs and moving their feet could certainly be a benefit. And then the other question, of course, I always remind them is if you are going to have a procedure in the future, a major procedure to have that discussion of your risk and the fact that you had a thrombosis previously and to bring that up to their primary, their hematologist or their surgeon if they've had that. And then again, just being aware, listening to your body and if there's something new, as we mentioned, the shortness of breath, swelling in the legs, to be aware of that. I think sometimes I feel people are actually probably hyper-acute from once they've had a thrombosis and they tend to have a very low threshold to believe, appropriately so, that they may have had another recurrence. So, try to balance the two between being vigilant and not being overly vigilant.

Jori May: That's helpful. And Paul, you bring up a question that comes up a lot, of what if they have to have surgery again? So, they had a blood clot related to surgery. So, what do we do if they now require a new surgery? Do they require anticoagulation prophylaxis? Stephan, could you speak a little bit to how you make those decisions?

Stephan Moll: Yeah, I tell the patient whenever you have surgery, tell the surgeons, I've had a blood clot, do I need DVT prophylaxis? And then I tell them, if there's any question with a degree of surgery, you can contact me and I'm happy to give advice. Sometimes one needs to make up particularly how long to treat after a certain surgery. For example, a patient who had a DVT or PE and came off blood thinners after three or six months now has an arthroscopic knee surgery. Typically, arthroscopic knee surgery patients don't get DVT prophylaxis, but this patient already had a clot in the past, so I would give DVT prophylaxis. How long? That is not scientific. It depends a little on how soon in the past, after that surgery, did they develop a clot, how big of a surgery was it in the past. And then I may say, let's treat you with two weeks and as long as you're not fully active. So, it may go up to four weeks if they still have a boot immobilizer. It becomes non-empiric at that time, but I think that's okay. But I also make sure that the patient really knows the symptoms of DVT and of PE. And here at UNC, we use a bookmark that we've created, which on one side has, you can't see that, but it has the four symptoms of DVT, the swelling, pain, redness, warmth and the four symptoms of PE, the shortness of breath, chest pain, unexplained cough, and a fast heart rate. And on the reverse side are the risk factors for DVT/PE. And I typically circle for the patient, which risk factors they have, the previous clot, the body mass index, the family history , just as a reminder for them, and then they have a bookmark. Hopefully they will put it somewhere where they will remember it. But tell the surgeon always, I have a history of blood clots, do I need DVT prophylaxis?



Jori May: That's helpful. What about in other situations, say a patient had a VTE associated with surgery, but now they're planning an overseas air travel trip? Or even a patient who's had a travel-associated VTE, has come off of anticoagulation and is now planning to travel again? I know we're getting into a lot of nuanced situations here, but I feel like, that these are the questions that, at least, I often get in my office. I'm sure both of you get, too.

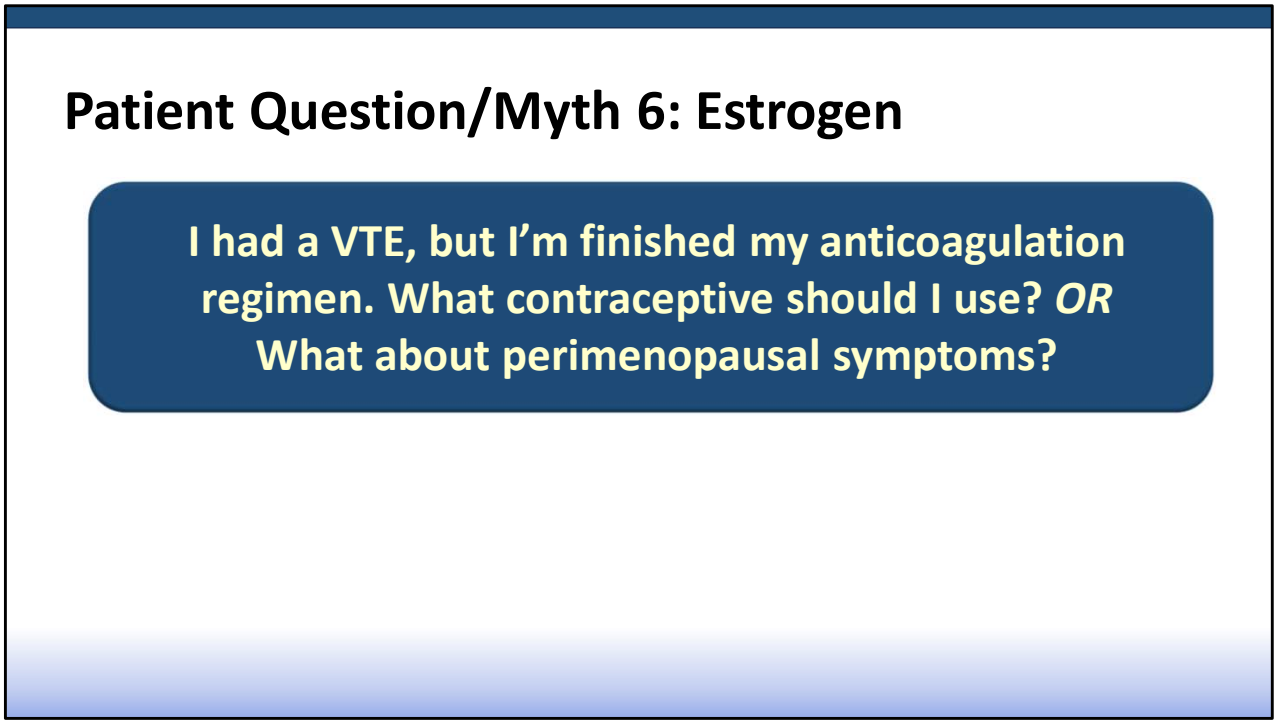
Stephan Moll: It can be a little difficult, and it depends on the previous clot, but in general, if somebody has had a blood clot before, they've shown that they clot more easily. And we know that airline travel, long distance airline travel is a risk factor for VTE. Now, typically people talk about long distance, 12 hours or more, but you start, we know that it's a gradual increase too, that eight hours and six hours, a slight risk factor as well. So, what I typically do is, if they came off blood thinners and now they have airline travel, I typically say anything more than six hours, take a blood thinner one to two hours before you fly. And that's specifically true here in the US if they go to a different continent, because from East Coast to West Coast is typically interruption or maybe five hours or so. So, it's intercontinental flights, flights more than six hours.

Since the DOACs, direct oral anticoagulants, reach their peak within three to four hours after intake, but they work fairly immediately, I tell them to take the pill one to two hours before flight. Then if it's a rivaroxaban, which lasts for 24 hours, they don't typically need to repeat it. But if it's an Eliquis prophylaxis, then after 12 hours, if they have not arrived, then take a second pill. Don't take it while you're where you are traveling to. But then when you fly back, do the same thing again.

Now, what about if they have a car ride or, rarely so in the US, train ride? I tend to say the same thing for anything more than six hours consider taking one pill before you leave, even though with car travel, people interrupt every so often to get gasoline or get some food. But in general, the six hours is what I do. Do I have much scientific data behind that? No. But it's something that makes common sense to me.

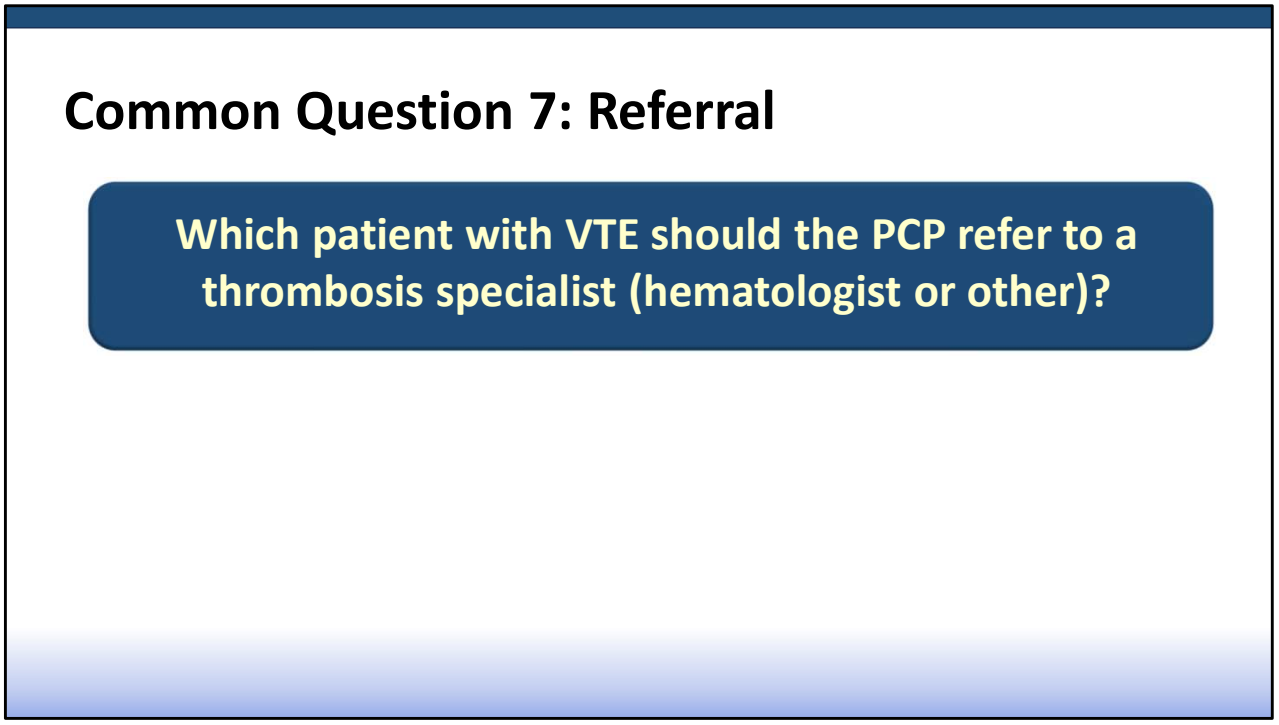
Jori May: Well, and I think the theme in all these situations is we don't necessarily have a lot of data to guide us. And that in addition to thinking about anticoagulation, there really is a key component of patient education on behavioral modification, monitoring for symptoms. And so, you know, keeping those things in mind when you are developing these plans, I think is helpful advice.

Stephan Moll: And the good thing is, in these patients that we're just discussing, they have been on an anticoagulant before for the DVT/PE. So, they've shown us that they tolerate it well, that bleeding is not a significant issue. So, to take one pill before they fly or travel by car is not in any way an extraordinary risk of bleeding, but it may be protective. So, I have a relatively low threshold to recommend that to people.



Jori May: I think one thing to touch on, we've spoken about issues specific to women's health in previous podcasts, but I think worth highlighting here in those patients that maybe have had an estrogen-associated VTE and ultimately stop anticoagulation, how we counsel them about future estrogen exposure, whether that's other contraceptives, whether that's pregnancy, or whether that's hormonal therapy. So, if we can maybe give a few pearls again on what to remember in those patients.

Stephan Moll: So, strong advice against estrogen or combined contraceptives, that's number one. Number two, a really good choice are the progestin IUDs. Superb, typically in my discussions, the preferred choice. Then also the injectable progestin contraceptives are good. The Nexplanon Rod. The progestin, the depo progestin preparations have a little bit of a risk. So, preferably stick with the progestin IUD and then the implantable, excuse me, the implantable of the rods would be a good choice. Now with hormonal therapy for perimenopausal symptoms, also the advice against estrogen hormones as a patch, pill, or a ring. But for vaginal dryness, for example, vaginal preparations at a low dose, try to see what is the lowest dose you tolerate seems very reasonable because there is quality of life issues. And much of that estrogen is local anyway to stabilize the mucosa and is not absorbed. There's some degree of absorption, but typically not much. So, then the vaginal estrogen preparations typically is, if needed, very reasonable to choose.



Jori May: Thanks for those tips. Let's move on to kind of a bigger global question, I guess. We've talked a lot about specific scenarios and kind of nuances of VTE care. And so, I wonder for our primary care audience, Paul, if you can take us through just your thought process again on if a patient is coming to you with clot-related questions. What are the ones that you feel comfortable in your office managing independently versus what are those that it's really helpful to work in conjunction with a hematologist or someone else who specializes in caring for blood clots?

Paul Lewis: Yeah, great question. So, you know, in general, as a primary care practitioner, it's important to know what you know and what you don't know. It's important to know what your limitations are. And there's some variation, right? Because some people do have a great understanding of thrombosis, thrombotic events, and others, maybe they have more training, maybe in their training they've worked more with hematologists and as a resident. So, I think there is some variation in general. But you know, clearly when there's been certainly a life-threatening event, someone has a significant risk of hemorrhage, there are obviously, we talked about when to stop, when not to stop. If there's some questions or concerns about, you know, should they stop? You know, those are, before I would stop if I'm not clear and haven't defined the risk factors, those are the cases I definitely want to get some help from my hematology colleagues. So that's again, it's a broad-brush definition. I'm not sure if there are specific hard and fast guidelines and I haven't seen in my literature, but perhaps there is in the hematology literature.

Jori May: Yeah, I'm not aware of that either. And I think it's a great point of just kind of knowing your limits of understanding and when it's better to collaborate. I think those cases that are straightforward, where there is a clear risk factor that's reversible, surgery, hospitalization, those things that we've talked about in previous podcasts, maybe that's something that you feel is within your scope of practice. But if there's nuanced decisions about duration of anticoagulation or any areas of uncertainty, it makes sense to seek a collaborator for sure.

Stephan Moll: And take that a step further, also, if there's significant long-term complications, i.e. the post-thrombotic syndrome or significant leg pain and swelling, then it's worthwhile to either send to the hematologist or maybe a vascular surgeon, vascular intervention radiology, maybe. The thought comes up, is there some iliac vein narrowing that's worthwhile to stent, to balloon, to decrease post-thrombotic syndrome?

And then on the pulmonary embolism side, if it was a significant PE with right heart strain, if it is a sub-massive or even a massive PE, I think a follow-up with either hematology or pulmonary is very appropriate to make sure this patient does not develop pulmonary hypertension that needs to be approached somehow differently.

Paul Lewis: I know sometimes a case that comes up occasionally is the patient that has either a relative thrombocytopenia and then you're sort of struggling of what you do. And again, this is interesting because in primary care, we think of thrombocytopenia often as less than 100,000 where my understanding a lot of times in hematology, it's really more or less than 50,000. So, those are some of the nuances where I will pause and maybe call one of my hematology colleagues and sort of curbside them on those type of questions. But again, that's always a dilemma from a primary care perspective.

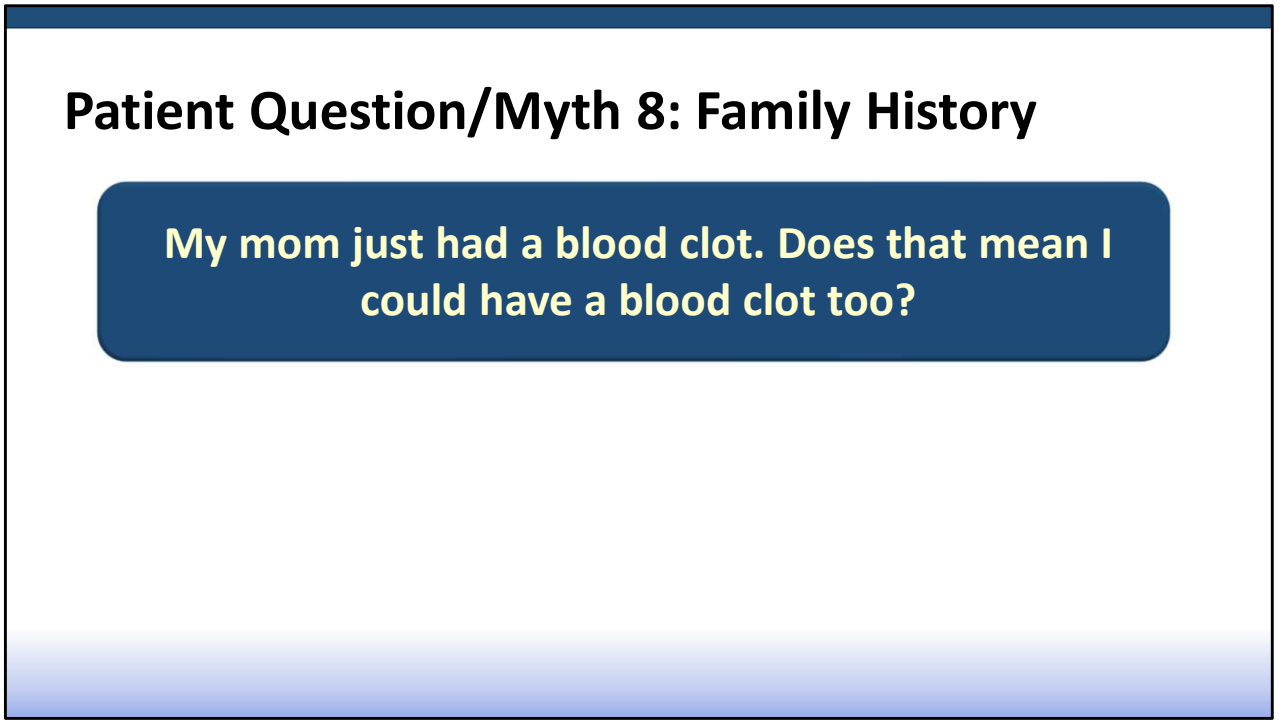
Stephan Moll: Yeah, and it's a dilemma for the hematologist too, the patient who clots and bleeds, and then take the liver cirrhosis patient, right? They have a coagulaopathy plus they bleed, they have low platelets because of big spleen. Those are very individual cases. Yeah, I think they are very appropriate to refer.

Paul Lewis: Good to hear.

Stephan Moll: But the problem often is, and Paul, you probably can comment on that, how available are thrombosis specialists and why we often hear on this call, talk about a hematologist. We have to mention that some general internists are thrombosis specialists, some cardiologists, some pulmonologists, whoever takes special career interests in that might be suitable, but they are probably not widely available. At least I see that in my practice in North Carolina, there are not many folks available and the waiting period to be seen can be quite long. I used to have a discussion with one of my slightly more junior colleagues when we developed the thrombosis program and said, well, which patient should we really accept and promote that they'll be seen with us? You could make a comment, anybody with thrombosis is suitable because, look, you can discuss how long to treat. We can enroll you into clinical trials because you have clinical trials open. You can discuss the complications, probably better than somebody who just sees this every so often. But then the volume is so big, that's not doable either. It depends on your local resources.

Paul Lewis: Yeah, great point. And again, I think that's part of the reason we're doing this series, is to empower the primary care practitioner. So, because oftentimes you're right, folks such as you and Jori are in short supply or there's a long wait, or you may not have a relationship to call them or touch base with them. So great, great comments. And I guess if you're lucky to be by a university referral center, but many parts of the country are not. Good point.

Stephan Moll: But if I may put this into maybe a summarizing statement, the patient who had a major transient risk factor associated, DVT or PE, who's mostly just recovered, can be treated with three to six months of blood thinners and then stop, and I don't think in general needs to be referred to a specialist. But anybody with an unprovoked, unexplained clot might be reasonable to refer, and definitely the one who has comorbidities with bleeding risk and renal failure and those kind of things.



Jori May: So, let's go a different direction and talk about folks who themselves have never had a blood clot. But I think a common question, probably for primary care doctors is, “well, my mom just had a blood clot. So, what does that mean for me? Does that mean that I'm going to have a blood clot too?” And so Paul, I'm assuming you've heard this question before and would love to hear kind of how you've responded or how you've approached this.

Paul Lewis: Yeah, I get that question a lot, but anything hereditary, family history, obviously, you know, again, important to have more details. Certainly, one can imagine the degree of anxiety if they have a family member who's had a significant event or even a mortality related to a thrombotic event, how concerned they would be. But oftentimes, again, it's the devil's in serving the details of this, because how old was their mother when they had the event, what else was going on? Do they even know or is this sort of a third-hand history from cousin Joe, right? So, how much detail do you have? What were the circumstances and what was the age of the individual when that event occurred? So that's at least where I start. Stephan, thoughts that you have?

Stephan Moll: Yes, a few observations. Number one, patients often don't know the difference between arterial clots and venous clots. They just say, had a clot in the leg, which, and then you hear, oh, they had an amputation. So, then you think, oh, it was probably an arterial clot, not a venous clot. So, that may be completely irrelevant for this individual that you are now trying to see. So, arteries and vein difference.

Secondly, I see there's a lot of confusion with patients, they think an aneurysm is a blood clot. And I clarify that, that an aneurysm is an outpouching of the blood vessel that can bleed, but it's not a thrombotic problem. And that's often reassuring for patients.

Then thirdly, patients may say, oh, yeah, mom or whoever has a, or I pass a lot of clots with my menstrual bleeds. Well, that's not a clotting disorder, that's typically a bleeding disorder or fibroids or what have you. And I explain that is not a clot, so that doesn't mean that person's at higher risk for thrombosis.

And then every so often I have a patient, just had this last week, who had significant bruising in her abdomen after enoxaparin shots that she was taking for history of VTE, they feel knots in the abdomen and they think that's a blood clot. Well, it's a hematoma that eventually becomes firm. So, that patient thought the enoxaparin had failed her because she developed clots in her abdominal wall in spite of being on enoxaparin. So, the terminology needs to be clarified first. And then one can discuss as you did, what were that person's individual risk factors and what are your asymptomatic individual risk factors? And then you can say, well, that's a completely different story in your family member.

The fifth point that I should mention, confusion that I see every so often, is that the sister died from a blood clot. And then you ask, well, was an autopsy done? No, but they thought it was a blood clot. So, then you wonder, well, it could have been a burst aneurysm or it could be the cardiac arrhythmia? Could be so many other things.

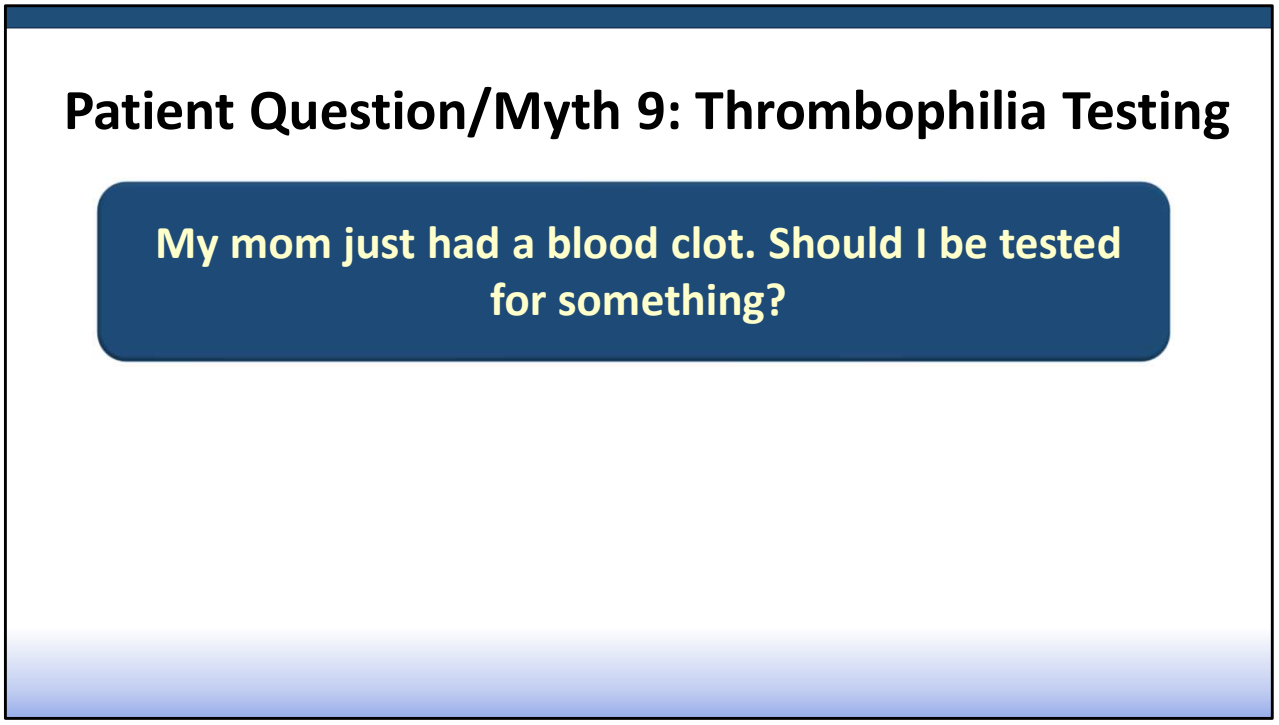
And that needs to factor into the advice that you give the asymptomatic individual then too. And then it comes down to eventually I say, well, to the asymptomatic person, your personal risk factors are A, your body mass index of 33, B, it sounds like your sister did have a PE, C, you have a long distance flight coming up, etc. and then I hold against it, well, but

Stephan Moll: you're not a clotting nightmare. You had four pregnancies, four C-sections and you didn't clot. You've had an arthroscopic knee surgery and you didn't clot. You had cholecystectomy and open surgery and you didn't clot. So, even though you have a family history of clots, you personally have shown us that you're not a clotting nightmare. And I take it from there, then.

Jori May: That's really helpful language to use, just how to phrase it to folks to help them understand because it makes sense that having a family member truly affected by a pulmonary embolism or a DVT can generate so much anxiety. So, I think really understanding the details of the event and then assessing the individual for their risk factors are the take-home points.

Stephan Moll: Yeah. And if it's true, if it's truly that you think the 25-year-old sister had a PE and died from the PE and now you're seeing the 23-year-old sister, then obviously I wouldn't say you're not a clotting nightmare. I'm concerned about you because you have a family with an unprovoked clot that led to death. And then we start to think, what's going on in the family and thrombophilia. So, this pre-testing assessment, how likely is it that there's really something in the family then also plays into potential thrombophilia testing.

Paul Lewis: Yeah, and I would say this is a great example of again, is making sure that we always remember to assess the patient's understanding of the disease process and what we're trying to tell them because we all have different definitions of things, different understandings, so it's great to say, tell me what you know, what you understand about thrombosis or about a clot, and then you can at least see where they're at in terms of their knowledge base.



Jori May: Let's venture into that topic of thrombophilia testing. So, you know, what are those patients, Stephan, where they come to you and say, well, you know, my family member had a blood clot where you are considering sending blood testing for an inherited thrombophilia.

Stephan Moll: So, I have to tell you, Jori, I barely ever see somebody, not barely ever, but not that often, who's never had a clot, who then wonders, should I be tested for something? It happens. But more commonly, and that we probably should address first, is a patient with DVT-PE who then wonders, should I be tested for a clotting disorder? And we've discussed it in one of the previous podcasts.

Stephan Moll: The thrombophilia testing for me is typically reserved for patients who have this intermediate risk for recurrence, where they don't know, should they be on long-term blood thinners or should they come off? And then finding a strong thrombophilia that increases the risk for recurrence if they were to come off, finding strong thrombophilia is one reason to continue anticoagulation . Now, I would not think about thrombophilia testing in a 70-year-old who didn't clot in the past with two pregnancies and colon surgery, who at age 70 then develops an unprovoked clot. Number one, the likelihood for a strong inherited thrombophilia is so low that that's not worthwhile. The patient should be on long-term blood thinners anyway if they tolerate it well because it's an unprovoked clot. If anything, one may want to test for an acquired clotting disorder, antiphospholipid antibodies.

So, we need to be clear why to test a patient who had a VTE. In the asymptomatic family member, which every so often comes up, it more so comes up if the patient with VTE then asks, should my sister or my daughter be tested?

Testing of Family Members

Proband's Thrombophilia	Male Family Member		Female Family Member	
	Sons	Brothers	Daughters	Sisters
Hetero FVL or hetero prothrombin 20210	No	No	No	No
Homo FVL or homo prothrombin 20210	No	Reasonable	No	Yes
Double hetero	Reasonable	Reasonable	Yes	Yes
C, S, AT	Reasonable	Reasonable	Yes	Yes

"Reasonable" Consider DOAC or LMWH with airline travel, cast, non-major surgery; prolonged after major surgeries.

"Yes" Advise against estrogen contraceptives/hormone therapy; give ante- and postpartum anticoagulation.

Stephan Moll: If the proband with a VTE has a strong thrombophilia, the 35-year-old who had a clot in a test for a thrombophilia, and they have a strong thrombophilia, protein C, protein S, antithrombin deficiency, or homozygous V-Leiden, or double heterozygous V-Leiden plus prothrombin, if they have a strong thrombophilia then it might be worthwhile to test the female family members, if they have a strong thrombophilia as well, you may give different advice, or I would give different advice about birth control, use pregnancy management.

But also if the proband has a strong thrombophilia, I might also suggest that the male family members be tested because I may give a recommendation to be more aggressive with even non-major surgeries. Like you have homozygous factor V-Leiden, you have an arthroscopic knee surgery coming up. Typically, we would not give prophylaxis, but if you have homozygous V-Leiden, I probably would give it.

Stephan Moll: Now you could argue, and this is...it's definitely, you could argue, well, they have a family member at a young age with clots, so the asymptomatic individual automatically has a higher risk because they have a first degree relative, so they should get maybe DVT prophylaxis even if they don't have a strong thrombophilia. Maybe that's too much, Paul, for the general internist to think about.

Paul Lewis: Well, I was going to say again, it strikes home for me, if you're not sure what to do with the results of the test, don't order the test, right? Because then you open up a can of worms. And so again, if you do have access and you think there is an intermediate risk patient who may have a hereditary thrombophilia, if you have access to a hematologist to help you interpret, because sometimes you get some confounding data, especially if it's anywhere near the acute event, and so, just always have to be cautious once we open the thrombophilia can of worms so to speak.

Stephan Moll: Yes, but what I agree with that, what has become clear though, is there's no indication for thrombophilia testing in the general female population who's thinking about taking birth control pills. And there have been guidelines from the American Society of Hematology that came out two years ago, 2022, that clearly states women who are considering birth control pills in general, all comers should not be tested for thrombophilia. That's number one.

Number two, I don't, if somebody was testing a patient with VTE and they're found to have a mild thrombophilia, a heterozygous V-Leiden or a heterozygous prothrombin mutation, I do not recommend family-wide testing because that's a mild thrombophilia that's common. It does not change the management of the asymptomatic family member. So, this family-wide testing, if a mild thrombophilia testing, that's not appropriate.

Jori May: Well, I think this brings up some important points and considerations because this is a difficult decision to make and I think Paul's point is really important, is that the assays themselves can sometimes be quite complicated. And so, to be careful before venturing into testing, first of all, is there an indication for testing? And second of all, making sure that we understand that the testing is happening at the right time in the right place and for the right patient.

And so, Stephan, I wonder if you could touch briefly on some pearls on thrombophilia testing, the assays themselves. What we're ordering, what we're not ordering, and if we do want to order them, the timing of that.

Stephan Moll: Yeah, so, first question is, why do we test? What's the consequence of a result? Number two, the patient needs to know that often factor V-Leiden and factor II or prothrombin, 20210 mutation testing, the insurance companies don't pay for it. So, the cost may have to be borne by the patient. Thirdly, they need to really understand what the result means, that they don't panic, I have a thrombophilia. And then from a test result point of view, one needs to know what one orders.

Stephan Moll: For Factor V Leiden, sometimes the Factor V activity gets ordered, which is wrong. The activity is normal in Factor V Leiden. It needs to be, if anything, the genetic test or a test called activated protein C resistance. And with a Factor II or prothrombin mutation, sometimes falsely, a Factor II activity is tested or ordered. That's inappropriate. That's typically normal.

It needs to be the genetic testing that gets ordered if one even thinks about that. And then with protein C, protein S antithrombin, they can be abnormal with liver disease in the acute setting, on anticoagulation, particularly on apixaban and rivaroxaban, they can be falsely normal. So, all the activity assays, one really needs to know how to interpret them.

And then if you talk about antiphospholipid antibodies, which is a topic by itself and really worthwhile to discuss further if there's interest. The two that are reliable on anticoagulants are the anti-cardiolipin and anti-beta2 glycoprotein-1 antibodies. But the lupus anticoagulant is often falsely positive, can actually be falsely negative in the acute setting, falsely positive on the direct oral anticoagulants , so the interpretation has to be taken really with care.

And the lab reports often have stuff like DRVVT and LAPTT and hex-phos neutralization. It's difficult to really, for somebody who doesn't deal with this frequently, to really know what is positive and what is negative and if it's positive, how positive is it? Is it really striking or is it just borderline? I think maybe the thrombophilia testing is probably best left over to somebody if one is even thinking about it, to somebody who deals with this more frequently.

Paul, what do you think about thrombophilia testing? Should that even play a role for a general practitioner?

Paul Lewis: Yeah. And again, I think as we started, I think most of the time, likely no. It's a great point if they have the positive of the anti-cardiolipin antibody and they were on anticoagulation, right? So, maybe there's a role to repeat it, if it was done in the hospital setting and it was positive or you, because you, at that point you said, well, it probably shouldn't have been done in the hospital setting.

I will occasionally do that because it was positive as the patient comes to me, they think they have it, but if you know they had an acute event or they were on anticoagulant, I may repeat it then. But again, as we sort of start out with, I try to be super-selective in doing this and if I think it's going to be complicated, try as much as possible to get them. And I again, try to avoid sort of, I hate to use the word just, order of everything like a whole thrombophilia panel, right? It's sort of, I see sometimes the residents doing that and it's just a can of worms you've got to be careful about opening because you've got to put that lid back on, and you may not be able to.

Stephan Moll: My summary for that would be, if I may, I have four points when not to do thrombophilia testing. Don't do it in the acute setting. It doesn't change management. Don't do it in a hospitalized patient because they're sick and sickness changes many of those thrombophilia test results. Don't do it on an anticoagulant, because the activity assays get changed by being on an anticoagulant, falsely positive, falsely negative, or low or high. And then lastly, if you don't know what to do with the results, then that's not the person who should be testing the thrombophilia, then send the patient to somebody who then can decide should we even do the thrombophilia testing.

Paul Lewis: Great points.

Jori May: Absolutely. So, you know, with that, let's touch briefly on some future directions in hematology that might be relevant to the primary care doctor. So, Stephan, can you update us on what's going on in the world of VTE? Anything new in the pipeline that you feel like will change practice for the general practitioner?

Stephan Moll: Yeah, and keep in mind that I'm mostly clinician and clinical researcher. I'm not a PhD or basic researcher. We're focusing on something that's tangible in the next two, three, four, five years or so that may change our management. I've been involved in the development of the direct oral anticoagulants over time, and Paul has seen that too. Jori, you're up a little bit, but given your age, less so, but the change really was from warfarin to the direct oral anticoagulants.

And if used correctly, they're quite safe and quite effective and so much easier to use for the patients and for the healthcare professionals than warfarin. That's self-understood. But people are looking for blood thinners that are even safer. And the hope is to find a blood thinner that disconnects protection from clots and bleeding risk, i.e. something that protects from clots yet does not increase risk for bleeding. And that sounds too good to be true. It's something that you get all the benefit but no downside, and that probably does not exist.

Factor XI Inhibitors in Development

Class	Compounds	Mechanisms of action	Administration	Onset-offset
Antisense oligonucleotide A	IONIS FXI Rx Fesomersen	Reduce hepatic synthesis of FXI by inducing catalytic degradation of FXI mRNA	Parenteral	Slow onset and offset
Monoclonal antibodies	Osocimab Abelacimab Gruticibart	Suppress FXIa generation or inhibit FXIa activity	Parenteral	Rapid onset and slow offset
Small molecule inhibitors	Milvexian Asundexian	Block the active site of FXIa or induce allosteric modulation	Oral	Rapid onset and relatively rapid offset

Factor XI inhibitors will likely not be available in DVT and PE for some time, due to recent trial failures in A-fib[1]

Chan NC and Weitz JI. New Therapeutic Targets for the Prevention and Treatment of Venous Thromboembolism With a Focus on Factor XI Inhibitors. *Arteriosclerosis, Thrombosis, and Vascular Biology.* 2023;43:1755–1763. Weitz JI and Eikelboom JW. What Is the Future of Factor XI Inhibitors? *Circulation.* 2022;146;1899-1902.

[1]OCEANIC-AF study stopped early due to lack of efficacy. November 19, 2023. Accessed April 27, 2024 at https://www.bayer.com/media/en-us/oceanic-af-study-stopped-early-due-to-lack-of-efficacy/

Stephan Moll: But people are banking on the factor XI inhibitors quite a bit for various reasons. And a number of companies are developing factor XI inhibitors. They will be probably good for patients who had high risk for bleeding and yet they need an anticoagulant, because the hope is that they are safer, even safer than apixaban and rivaroxaban and dabigatran and edoxaban.

But for the general DVT-PE patient, the Factor XI inhibitors probably won't play a role for the next several years. Disappointingly, in November of last year, one of the big Factor XI inhibitors that was in development and being compared to apixaban in an AFib trial was not as effective as apixaban, and the trial had to be stopped. So, the enthusiasm about the Factor XI inhibitors has been somewhat dampened. Maybe it was a dose issue that needs to be seen, but I don't expect any big development there in the next two, three, four years for the general patient with DVT-PE.

Stephan Moll: Where is this field going? And there are a number of things to mention, but we all know healthcare delivery, we are struggling with this, with people not being able to afford certain drugs, not being able to afford medical care. I think the healthcare delivery is a struggle, not so much the tools that we have available. We have superb tools, we have superb training and education in many people.

But we're struggling with cost of drugs and cost of the health care system. Now, that's not my specialty, but that's really where I think the next five years need to really change, be it the development of generics, that they become less expensive. But that has been delayed so much by political and the companies buying one of the generic companies that's developing the generic or the patent being delayed and prolonged.

Anyway, you've get me there on the negative side because in clinics so often now, the question is not about medical issues, but rather how much is your copay for the drug that you're taking? I cannot afford it or initially it's this and that. And then by the end of the year, fall into the donut hole and it's so much and I can't take it. Paul, I'm sure you deal with it a lot.

Paul Lewis: Yeah, no, I'm just shaking my head because I hear that a lot. I mean, obviously with the DOACs, other expensive medications too, and it's a struggle and it's a gap. And again, we do what we can do. I always hate to prescribe warfarin. I still have to occasionally do it in a pinch. But there are some good programs that people can access, as we've spoken about earlier, from the companies themselves and other discount programs, at least there can be a gap for some people. So, not perfect by any means, I realize that.

Stephan Moll: And on the pulmonary side, Jori, the development over the last 10 years or so, or maybe 12, 15 years by now, is the catheter-directed thrombectomy. Initially, with the catheters that inject TPA clot busters into the clot and suck out the remaining. Increasingly it seems like the development is going towards thrombectomy, mechanical thrombectomy, where the clots are macerated and then sucked out without the TPA or the fibrinolytic agent given because that increased the risk for bleeding . And while, initially this was for patients with massive life-threatening PE, then the proceduralists like to use it even for the intermediate risk PE or called sub-massive PE with some right heart strain with questionable benefit. And there are trials ongoing to see which patients with PE, with moderate-sized PE, with some right heart strain, for which patient is this procedure really beneficial.

There's a fair amount. And then there's a number of activity which I like to, with a post-PE syndrome to better define it, to define who develops it, to discover it early. So, I think that will be a much more structured approach rather than, oh, you had a PE, you need long-term anticoagulation, and then we see the patient once per year. More real assessment, how much right heart strain is it? Are they candidate at some point for referral to pulmonary, pulmonary enterectomy, medication for pulmonary hypertension, etc.

Jori May: Well, thank you for turning our future from somewhat negative to a more positive conclusion. That was a helpful turn. But with that, we are running up on the end of time. So, I hope I can go to each of you with some take-home points for the audience. And Paul, can I start with you? What are your take home points from our discussion today?

Conclusion: Primary Care

- Carefully assess the patient and their disease state
- Know the limits of knowledge relative to thrombophilia
- If you don’t know what to with the results of a test, don’t order it
- Refer to, or consult with, specialists for appropriate patients

Paul Lewis: Yeah, so from take-up points, again, listen to the patient. I think that's incredibly important too, that we are listening to the patient, we assess their disease state. Know your limits of your knowledge based on thrombosis, thrombophilia from a primary care perspective. If you don't know what to do with a test, don't order it. And don't be afraid to ask for help, right? I mean, we know in primary care, there's a lot to know. And that's why we have the benefit of our intelligent specialists to help guide us and collaborate.

Jori May: Wonderful. Thank you, Paul. And Stephan, some take-home points from you as well.

Conclusion: Hematology

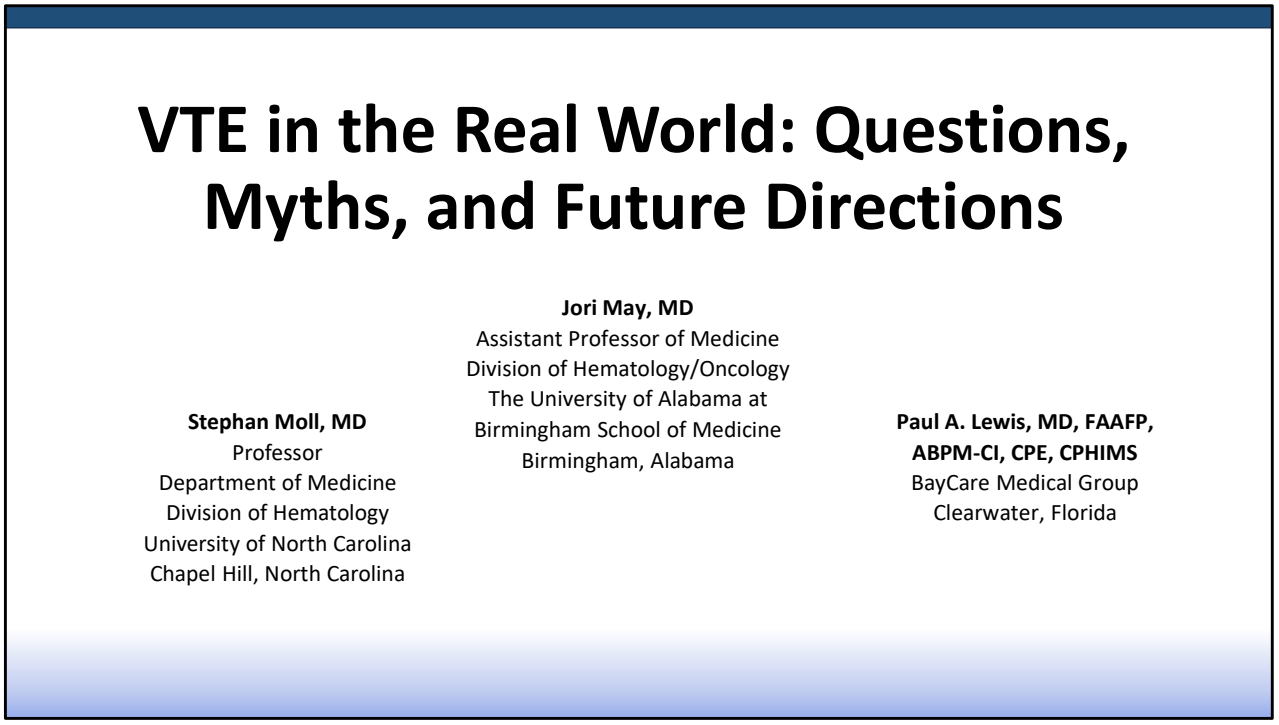
- After a DVT: no indication/need for routine follow-up Doppler ultrasound to "monitor progress/resolution of clot"
- Follow-up Doppler ultrasound when stopping anticoagulation as a baseline
- Educate patient about symptoms of DVT and PE, as well as risk factors
- When off anticoagulation after a VTE, get good DVT prophylaxis in future risk situations
- Women's health issues
  - Progestin IUD and injectable progestins are safe contraceptives
  - Avoid estrogen pills, patches and rings
  - Vaginal estrogen preparations may well be a reasonable choice
- Asymptomatic family members:
  - Talk to patients about their VTE risk factors
  - Educate about VTE symptoms and risk factors
  - There is rarely an indication for thrombophilia testing (unless a family member with VTE has a STONG thrombophilia)

Stephan Moll: Well, summarizing today, number one, we said there's no role for routine follow-up Doppler ultrasounds every so often to monitor progress of the clot, but there is a role to get a Doppler ultrasound at the end of the anticoagulation treatment period as a baseline.

Secondly, to educate the patient about symptoms of DVT-PE as well as the risk factors when they come off blood thinners to watch out for the symptoms and seek medical attention early if they develop those symptoms and seek medical attention early if they develop those symptoms, to tell the patient who came off blood thinners, if you have surgery in the future, ask the surgeon, do I need DVT prophylaxis, I've had a blood clot in the past.

And then we talked about women's health issues: progestin IUDs, if the woman is not on blood thinners anymore, progestin IUDs are a great choice, or the implantable progestin rods are safe contraceptives. Avoid estrogen pills, patches, and rings. The vaginal estrogen preparations in perimenopausal women may be a very reasonable thing to do at a lower dose.

And then for the asymptomatic family members, we discussed talking to them about the individual risk factors, their body mass index and their smoking habit and their immobility. Educate about the symptoms of DVT and PE risk factors, just like we educate patients. And then rarely there's a role for thrombophilia testing in family members, and only maybe if they have a family member with a clot who has a strong thrombophilia.



Jori May: I learned a lot from both of you today. Thank you for a fantastic discussion. This concludes our overview of questions, myths, and future directions in patients with VTE. So, I'd like to thank Stephan and Paul for taking the time to talk with me today. In our final podcast, we're going to be discussing a series of cases that will hopefully bring together all the information we've discussed across the entire series. It's going to be a tall task, so please be sure to tune in.

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