

Scott C. Woller, MD:

Well, hello everyone and welcome to this podcast sponsored by the American Heart Association on optimizing the diagnosis and treatment of venous thromboembolism. My name is Scott Woller and I'm a thrombosis physician here at the Intermountain Medical Center in Salt Lake City, Utah, where I also serve as the chair of medicine. And I'm delighted to be with you today to discuss how to approach patients when we consider the diagnosis and treatment of venous thromboembolism. Throughout the course of this podcast, we hope that objectives that you as a listener will be able to take away will include being better positioned to recognize, treat, follow up, or refer patients with venous thromboembolism. And we hope that you'll be best positioned to practice effective identification, diagnosis, and management of those VTE patients. I couldn't be more delighted to be joined today by Dr. Lisa Baumann Kreuziger. Lisa, would you like to go ahead and introduce yourself?

Lisa Baumann Kreuziger, MD, MS:

Thanks so much, Scott. So, hi, I'm Lisa Baumann Kreuziger. I am a hematologist that specializes in thrombosis. I'm an investigator at the Versiti Blood Research Institute and Associate Professor of Medicine at the Medical College of Wisconsin. I had the pleasure to work with Scott on the most recent CHEST guideline panels for the treatment of venous thromboembolism, and we'll be discussing and referencing those guidelines today. Both Scott and I have no potential conflicts of interest to disclose.

Scott C. Woller, MD:

Lisa, thanks so much. Let's just go right ahead and kick things off and permit me to sort of set the stage by way of recollection for our audience why venous thromboembolism is a common disease, and we tend to think of VTE as being the aggregate of deep vein thrombosis, admittedly most frequently presenting in the lower extremities and also pulmonary embolism, PE, [inaudible 00:02:01] blood clots in the lungs. And throughout the course of today's discussion, you'll hear Lisa and I refer to VTE as the aggregate when evidence surrounding the guidance for a diagnosis of deep vein thrombosis and pulmonary embolism together is appropriate.

Venous thromboembolism represent the third leading cause of preventable cardiovascular death, and it's true that patients have variable risk for VTE based on age and health conditions. And then of course, situations such as medications they might take, surgeries, or cancer and other diseases.

Oftentimes it's helpful to think about venous thromboembolism in the context of a clinical case. And so Lisa, let me pitch this clinical case to you and you can help us think through how you would manage this patient. So this is a 52-year-old woman who has really only a history of hypertension, taking lisinopril 10 milligrams daily, but she also takes a second generation oral contraceptive pill, and she calls the clinic complaining of left leg swelling after returning from vacation with her husband. They were in Australia and it was a long flight home. She's now calling and asking, "Gosh, what should I do with this symptom of new leg swelling?"

Lisa Baumann Kreuziger, MD, MS:

Thanks, Scott. I think both you and I probably have received phone calls like this already this week. And really what we try to think about any time a patient is wondering about any VTE, whether that's a clot in the legs or a clot in the lungs, is what's the risk factors for that patient? So Scott, you already mentioned a couple of those things including age and if they were recently in the hospital or recently had surgery. We know that younger people, especially younger females, are at higher risk both because of hormone therapy as well as pregnancy. And surprisingly, about 1 to 2% of pregnancies will have a clotting event

happen with it. In older ages, male sex is actually a higher risk for thrombosis and which may not be expected.

Some in medical conditions, you had mentioned cancer already, but other inflammatory disorders, rheumatologic disorders are also associated with thrombosis. We, of course, take into consideration somebody's family history. So if somebody's had a first degree family member like a father or a mother or a sibling that's had a clot, they're at higher risk as well.

So for this patient, the risk factors that she has had include the oral contraceptive pills as well as that flight to Australia that really put her at a risk for a clot. So Scott, when we're thinking about a potential diagnosis of VTE, what tools are available to help us understand that risk for the patient?

Scott C. Woller, MD:

Thanks, Lisa. Yeah, this is one of those conditions where, and really considering the likelihood that the patient has the disease, most of our audience is used to thinking about this in terms of the pretest probability is really helpful. And we have well-validated pretest probability assessment tools such as the Wells' score and its variations, the simplified Wells', the modified Wells'. And then for pulmonary embolism, the revised Geneva score in the YEARS criteria represent other ways that we can take our suspicion for venous thromboembolism in the form of a pulmonary embolism and better understand the risk for that individual patient.

Using that risk and that assessment, if a patient is of low or intermediate risk for venous thromboembolism, then it's often helpful to use that simple blood test, the D-Dimer to further assess than the post-test probability of venous thrombosis being present.

Now you'll remember that the value of a D-Dimer being a highly sensitive test is that when it's negative among individuals who have a lower intermediate pretest probability of disease, we can actually refute deep vein thrombosis and pulmonary embolism. So that's really a pearl to take away that the D-Dimer, being a highly sensitive test, why if it's negative, we can rule out DVT or PE among individuals who have a lower intermediate pretest probability.

It's important to remember that D-Dimer cutoff values and the assays vary. So you need to have awareness of your individual institution's labs and lab results. And it's also been advised that in fact, D-Dimer can likely safely be adjusted for age, whereby you take the patient's age over 50 and then use the multiple of that. So using a scale where a cutoff of, for example, 500 would be considered negative for an individual who's 65, their cutoff would be less than 650 and you could in fact still refute venous thromboembolism based on that DDI and the pretest probability as we've advised.

Oftentimes if the diagnosis of pulmonary embolism in particular is considered among patients that present to the ED, but the initial clinical suspicion is low, we have an additional tool and that's the pulmonary embolism rule out criteria or PERC score. That score can be easily calculated at the bedside. And in fact, if that PERC score is negative, then the post-test probability of having pulmonary embolism is less than 2% and you can safely refrain from any further workup for pulmonary embolism among those patients with a negative PERC score. So lots of information there about pretest probability, the likelihood of the disease being present perhaps for pulmonary embolism, first assessed by the PERC score and then otherwise the Wells' or other pretest probability scores that we had discussed, plus or minus D-Dimer.

So Lisa, going back to our clinical case, you very astutely applied the Wells' score to that patient that presented to you. In fact, she was reporting that her leg was swollen, gave her a point for that modified Wells' making that positive pretest probability assessment. The D-Dimer that you sent came back at 860, over that threshold of 500 for her, you obtained a whole leg ultrasound and lo and behold, she had deep

vein thrombosis that was observed in the femoral popliteal and gastrocnemius veins of that left leg. So can you talk us through how you would think about the appropriate initial management of this patient?

Lisa Baumann Kreuziger, MD, MS:

Thanks. So really we've got a patient with a new diagnosis of DVT in both the proximals, so above the knee veins as well as the distal circulation. So anticoagulation is the initial treatment of choice and both guideline panels of the CHEST 2021 guideline that you and I were a part of as well as the ASH 2020 guideline do recommend anticoagulation. And when we're choosing between which anticoagulant to use, we recommend a direct oral anticoagulant, sometimes what we call a DOAC. And the medications available there are either apixaban, dabigatran, edoxaban, or rivaroxaban, and it's recommended to use one of those over warfarin therapy.

Now, we don't have a recommendation to use one specific DOAC over another specific DOAC, but there are some different aspects of the treatment that may have us prefer one agent over another. So first is both apixaban and dabigatran were studied with the use of a parenteral, so either IV heparin or low molecular weight heparin first prior to the DOAC therapy, whereas apixaban and rivaroxaban can be used just with the oral medication. So that may be a defining factor in which to choose in those. Some are once a day, so like apixaban after the first three weeks and some are twice a day like a apixaban, then that may play a role in your patient's choice and your choice as well.

Everybody's insurance as we know is different and there are some preferences for different medications, so that needs to be considered.

There are much fewer drug interactions for the DOACs in comparison to warfarin, but there are some limited situations such as anti-seizure medications or antiviral medications that may be a factor for a limited number of people.

A couple of other kind of pearls to take away when you're prescribing a DOAC is that rivaroxaban needs to be taken with food. So please remind your patients to do that because the absorption of the medication is better when taken with food. And people should avoid other things that may put them at risk for bleeding, including heavy alcohol, use of non-steroidal inflammatory medications. And then with any blood thinner, you would want them to ensure that they're asking if any new medication is being prescribed, if there is any drug interaction. So now that we've decided that the patient needs a direct oral and anticoagulant to be treated for this, where should the patient be treated? Scott, what do you think?

Scott C. Woller, MD:

Yeah, thanks Lisa. Well, this is a really important question for a couple of reasons. Firstly, we always want to assure that our patients are safe and they're receiving appropriate care in the appropriate location. Broadly speaking, if patients are unable to care for themselves or if they do not have adequate support for their care in the setting of new venous thromboembolism, why, then they are absolutely candidates for admission to hospital to assure that they receive appropriate timely therapy for their disease.

Broadly speaking, even since the late 1990s evidence has existed that patients with isolated deep vein thrombosis can in fact be treated safely and effectively in the ambulatory setting. That is to say not being hospitalized but rather sent home from either the emergency department or their clinic.

Likewise, most recent guidelines that you alluded to in fact recommend as opposed to even suggest that if a patient has a deep vein thrombosis or pulmonary embolism for that matter and their home situation

is safe and appropriate, their clinical condition is adequate, that in fact they preferentially be treated at home as opposed to being admitted.

Now that that's admittedly placing high value on patient satisfaction on a patient safety. When we think about exposing folks to a hospital when they may not necessarily need that care.

And invariably, expense. It's been estimated that up to 25%, one out of four pulmonary embolism patients admitted to the United States today, in fact could be safely treated at home. Doing so, electing early discharge among those appropriate patients who meet those criteria for being treated at home, could save up to a billion dollars a year.

So when we think about the overarching wellbeing of our patients, of course, first and foremost, their health and their healthcare state, but also their financial wellbeing. If they are candidates for home treatment, being identified as having low risk with their venous thromboembolism, then it has been recommended that those patients be preferentially treated at home.

So Lisa, a patient that you are caring for here who just arrived back from Australia, had deep vein thrombosis in her femoral vein, but also in the isolated distal circulation. I know there are circumstances where we'll approach treating patients differently depending upon the distribution of their blood clots, and it's my recollection that one of those circumstances is if they have deep vein thrombosis isolated to those distal veins. Can you tell me about how you think about treating patients with isolated distal DVT and maybe a couple of other unusual or less common circumstances?

Lisa Baumann Kreuziger, MD, MS:

Definitely, and we do find that in the United States that we will find an isolated distal DVT more commonly because, like this patient, we did a whole leg ultrasound. So please know that in some other countries, they only do an ultrasound of the proximal parts of the leg and so may not have an understanding if there is a distal DVT or not. But in the United States, we definitely most often will do the entire leg so we will find an isolated distal DVT.

It really depends on the risk of progression of the clot to a proximal clot, which happens about 15% of the time. And so if somebody is at low risk of propagation of the clot or at a high risk for bleeding, we may elect to just do cerebral ultrasounds. So we would do an ultrasound once a week for two weeks to watch and see if the clot actually extends into the proximal deep veins.

But if somebody has severe symptoms or they have risk factors for extension, a suggestion for anticoagulation is there for those patients. So of course this does place a high value on avoiding the inconvenience of repeat treatment, and you of course would need a patient to be able to do that repeated imaging if you favored more of an imaging strategy over an anticoagulation strategy.

Now, if we do decide to use anticoagulation, it is recommended that anticoagulations continued for 12 weeks as that has been shown to be superior than six weeks of treatment.

So analogous to isolated distal DVT is sometimes when we see an isolated subsegmental pulmonary embolism. So these don't involve the more proximal pulmonary arteries, and we think about them the same in trying to understand the risk for recurrent events as well as the risk for bleeding. And there was a very important study though that has come out by Dr. Lagal that did not show the safety of refraining from anticoagulation in isolated subsegmental pulmonary embolism. And the thought is that there in a subgroup of people over the age of 65 or if multiple segments were involved with the pulmonary embolism were the patients that really probably pushed the risk towards favoring anticoagulation. So that is a patient population that we're still studying and still has lots of questions involved.

So another situation that we find are in people where clots are found incidentally. So sometimes we're scanning the chest for other reasons and we find a pulmonary embolism. So we know that the natural history of having a recurrent venous thrombosis is the same for people who have symptomatic and incidentally found thrombosis. So therefore we treat those events the same.

So we've talked about more standard patients that are symptomatic but may not be severe, but there are patients that present with more profound symptoms and we may consider using thrombolysis or involve our vascular or interventional radiology colleagues. So Scott, could you talk us through patients that you would consider that consultation or the use of thrombolysis in addition to anticoagulation?

Scott C. Woller, MD:

Yeah, thanks Lisa. This is perhaps among the scariest stuff that we as physicians deal with. It often involves coordinated care involving not only the emergency room physicians where these patients will frequently present, but then coordination with, for example, critical care should they need to be taken to the ICU and/or perhaps even interventional radiology that I'll speak to momentarily. So to kind of structure our discussion, let me begin with pulmonary embolism.

And if we look at the structure of severity surrounding pulmonary embolism, the most worrisome presentation that's variably referred to as massive pulmonary embolism or life-threatening PE is when a patient presents with the new diagnosis of pulmonary embolism and in fact has a persistently low blood pressure defined by a systolic blood pressure of less than 90 millimeters of mercury for at least 15 minutes. That is the definition that's often used for which evidence exists so that yeah, anticoagulation is going to be necessary, however, this patient is in fact at a high risk for mortality and a further intervention is required. It's in those patients where it is advised to administer systemic thrombolysis preferentially through the vein.

Now of course, in the situation where interventions are available, and especially if that patient is at a high risk for bleeding, other interventions to save that patient's life may be indicated including catheter-directed thrombolysis or perhaps even a mechanical thrombectomy whereby that clot burden is extracted.

This is a super interesting field where evidence is evolving and technology is advancing quickly. And so while current guidelines advise that thrombolysis be utilized preferentially in this circumstance in a case-by-case basis, others with the proper expertise may be selecting either catheter-directed thrombolysis or a mechanical intervention that I had alluded to.

Switching gears now and talking a little bit about those patients that present with extensive deep vein thrombosis, we have had a couple of very well conducted prospective randomized controlled trials among patients that have had big blood clots in their legs, however have been vascularly intact. That is to say, good pulses, neurovascularly, without compromise. And the question has been, well, gosh, with this big clot burden, perhaps these folks would do better in the long run if we can extract that clot, get them on anticoagulants, and help them feel better more quickly. Both the CaVenT and the ATTRACT trials were designed to help answer that question.

The long and the short of it is that using mechanical or catheter-directed therapies to treat ilio femoral or more extensive large deep vein thrombosis appears to help patients feel better more quickly. However, the long term risk of post-thrombotic syndrome, which can be characterized by pain, but it doesn't have to be, it can be tenseness, swelling, heaviness, fullness, itchiness of the leg at the two-year mark, does not appear to be meaningfully different between those patients that receive catheter-directed therapy for their extensive DVT and those that receive anticoagulation alone. Importantly, the catheter-based therapies appear to confer an increased risk for bleeding.

And so the way I'll think about this with my patients is if they have extensive proximal DVT by and large, they'll end up doing is well clinically, so long as they're neurovascularly intact with anticoagulation alone. If they place high value on a more rapid resolution of their symptoms, they're willing to accept the risk of bleeding associated with catheter-directed therapy of their clot and willing to accept admittedly, the added potential expense associated with this because oftentimes, this therapy requires hospitalization and follow up. Then, in those patients catheter-based therapies may be reasonable.

I think the last thing I'll say in this section really has to do with the emerging technologies where evidence is suggesting that perhaps mechanical interventions, especially for pulmonary embolism, but also DVT without clot busting medicines may be on the horizon and may be becoming more routine in centers that have that expertise. The jury is out on whether or not these interventions will be safe and effective as those studies are just getting going, and the role for these interventions in patients without life-threatening thrombosis is to be determined.

So Lisa, in talking through our case, you had mentioned that the woman who presented to your clinic was on oral contraceptive pills. So oftentimes we'll have patients coming and presenting with new thrombosis on oral contraceptives, and our knee-jerk reaction can often be to say, "Whoa, this is an agent that appears to provoke thrombosis and increased risk for thromboembolism." Should we really stop those medicines? Does that help our patient?

Lisa Baumann Kreuziger, MD, MS:

So Scott, this is a very important aspect for this patient. So if a patient is started on blood thinners, the oral contraceptive pills or other hormone treatment do not need to be stopped immediately, and there's four reasons for that.

So first, a study of people who were treated with blood thinners did not show a difference in the risk of having another blood clot in people who either continued on their hormones or stopped their hormones. So by continuing their hormones and continuing blood thinners at the same time, we do not put them at an increase in risk for having another blood clot.

The other three reasons involve the reason why the patient was taking the hormones in the first place. So some people use hormones to control heavy menstrual periods and stopping the hormones can lead to a significant menstrual bleeding. In some circumstances, such as transgender medicine, the hormone are required for an essential component to the individual's identity and quality of life.

And then the last reason is that warfarin is associated with a risk of birth defects and miscarriage and the risk of birth defects with rivaroxaban and apixaban is not known. So effective contraception is needed while taking oral blood thinners.

So if the patient had a VTE that was associated with hormone therapy, that hormone therapy can either be stopped at the end of the three to six months of anticoagulation for the blood clot. And so patients should see their OB-GYN or primary care provider to discuss the risks and benefits of continuing their medication or switching their therapy, and that could be to a progesterone only method that's not associated with an increase in risk for blood clots or for patients who are transgender, some topical treatment is associated with less risk for blood clot as well. And so it's really an important component that people do follow up with their primary care provider or their OB-GYN regarding their hormone therapy. So Scott, mentioning that, what other follow up should occur after a VTE event?

Scott C. Woller, MD:

Yeah, thanks, Lisa. I think my overarching remark is firstly, and patients have comparatively less awareness of venous thromboembolism than they might of other diseases. For example, just thinking

about their generalized awareness, their perception of deep vein thrombosis and pulmonary embolism appears to be about half of that for their awareness surrounding, for example, breast cancer and stroke, heart attack, prostate cancer, and the like. And so it's a nice opportunity for us to remember as physicians and clinicians that while VTE is often top of mind for us, when a patient experiences a venous thromboembolic event, it's super frightening and we have a real unique opportunity to help them better understand that disease and feel better about the treatment that we're initiating, in the immediate term, helping them understand the importance of adherence to the prescriptive medicines that we are giving them signs and symptoms of what they can expect over the subsequent hours and days and weeks, and then limitations and anticipatory guidance regarding, for example, what they might be feeling and how that's either of concern or equally importantly, why, normal.

So for example, in a patient with deep vein thrombosis, while historically if you go back into the annals of medicine, we immobilized people and didn't let them move. In fact, best evidence suggests that early and frequent ambulation is indicated along with optimal adherence to anticoagulation. And so those are really important messages so our patients, of course, are educated and informed and yet don't feel as though they're necessarily walking on eggshells. You likely recall that in the quote, unquote, old days, we would talk about putting people in compressive stockings at the time they were diagnosed with DVT. Those were often 30 to 40 millimeters of mercury and they needed to recruit their son-in-law and daughter to wrestle those babies on their legs. In fact, good evidence now suggests that in most circumstances there's no need to use compressive stockings in the setting of acute deep vein thrombosis does not appear to diminish risk for a post-thrombotic syndrome in the long term.

When we think about duration of anticoagulation, why, the general rule is that a minimum duration of 12 weeks, 12 weeks is indicated to treat the clot you got, and so you should absolutely have follow up with your primary care physician shortly following your diagnosis of venous thromboembolism, and then have those discussions surrounding the 12th week mark.

Lastly, being aware of potential drug-drug interactions, just as you described Lisa, and thinking about how we would manage anticoagulants in the setting of any necessary surgeries or procedures is an important part of patient education.

So in closing, let me begin just by saying thank you, Lisa. Thank you for joining me today and discussing the approach to patients that are suspected of having venous thromboembolism.

Lisa Baumann Kreuziger, MD, MS:

Thanks so much. It's been a pleasure.

Scott C. Woller, MD:

Thanks to all of you for listening. We hope that you've found this podcast informative surrounding how to approach patients with venous thromboembolism. It's really our aim to help physician clinicians to be best informed of both in the recognition, diagnosis, and management of venous thromboembolic disease. In future podcasts, you're going to learn more about an evidence-based approach and the guidelines that exist for managing patients with venous thromboembolism. To claim credit and to get additional information, please visit learn.heart.org, and we hope that you'll be able to join us for future episodes. Thanks so much for your time and attention today.