PREVENTING AND TREATING VENOUS THROMBOSIS IN ONCOLOGY

Rowena Schwartz, PharmD, BCOP, University of Cincinnati

MODERATOR All right. Everyone, welcome back from that nice break. Hopefully, you got to stretch a little bit, get some coffee and so you're nice and awake for our next session. So, it's my pleasure to introduce one of my first bosses, one of the first people who really inspired me to get excited about oncology, Dr. Rowena Schwartz. For those that know her, she goes by Moe. So, she's at the University of Cincinnati, now. And, she's going to be presenting today on Preventing and Treating Venous Thrombosis in Oncology.

DR. SCHWARTZ Well, good morning, I guess. I want to tell you I love the theme of this program, of bringing clarity to complexity. It seems like in oncology, things are changing so fast that there is really a need to take a lot of data and clarify how we use it in patients. Unfortunately, making things clear does not mean that we always make things simple. And so one of the things that I will emphasize throughout the 45 minutes when I'm talking, is the fact that even though there are more options that may be easier to use for the treatment of VTE in cancer, there is a real need to make sure that we don't simplify it so much that we miss some of the big risks and potential problems in this population. So, if you look at what we really will focus on, we're going to talk about the data that has come out finally, that we're excited about, looking at the direct oral anticoagulants and how they are used in the oncology population. We'll look at risk and benefits, and we'll look at how we can approach management strategies.

Important to realize, is there are a number of clinical guidelines available that address not only how to use anticoagulants in VTE, but even within their subset of cancer-associated thrombosis. Important, also to realize, is that when these guidelines were updated, were before, most recent updates, are before the trials that came out that we're going to talk about. So, if you pull that data, it may not reflect the newer data that's available. Now that they're published, there is certainly a lot of review papers, but guidelines you may go to such as the CHEST guidelines, ASCO guidelines, even sometimes the NCCN may not have that new data. And I think that's important to realize.

I have nothing to disclose. That sounds kind of bad. I have a lot I could disclose – never mind. I have nothing to disclose.

If you look at the broad issue of VTE in cancer, I think it's broader than just the management. We're going to talk a little bit about prevention if we have time. We're not going to talk about diagnosis. And the key thing we're going to talk about is management. There's a lot of different topics. It's not just what agent do you pick, but it's also how you approach the patient with the therapy that we decide upon.

So this is my sign to – if you guys ever watch “Long Island Medium,” she always says, "This is my sign that," and of mine. I thought that was pretty cleaver, in my head. Anyhow, this is my sign to say that even though we really like to believe that we focus our decisions on evidence, and that would be the scientific evidence, the reality that you all know is that we spend a lot of our life in the art of practicing care. When we look at this right now, we have more

evidence, but with that evidence, there are also questions that have not been answered. So, although we'll spend the bulk of our time talking here, there's a lot in here that we need to talk about. And I thought this was a great slide and if you guys don't, then, well, that's just too bad, isn't it? So, just keep going. I can't believe I just said that. So, okay. You know what it is? I'm really freaking out. When you see me up close, I really don't like that. I was thinking that maybe if I was like the Wizard of Oz, behind the screen, it would be a little bit better. And, I'm thinking I'm going with that next time.

The other thing that I think is the most important consideration that you should have today, as we talk about the data, is the fact that when we talk about data, we're often talking about the results of clinical trials that include a population. But when you and I go into practice, it is the individual that we're actually looking at. And I get really worried if we look at just the data from studies and in the population when it doesn't fit the unique aspects of the patients we deal with. And I think that's important as we go through the results of clinical trials, but also as you think about the strategies you use in practice, and let me make one more plug. If you work in a specific disease site, it is really appropriate to consider developing a strategy for that disease site in terms of approach to managing VTE.

So, I thought I would start with a little scenario. PL is a 67-year-old woman with adenocarcinoma of the lung, metastatic lung cancer. She's receiving carboplatin, pemetrexed, and pembrolizumab. She's seen in clinic today, prior to her cycle 3. She has shortness of breath; she is worked up. It's found that she

has not only a PE but also a DVT in her leg. If you look at the past medical history, which is in the chart, it states that she has had recent weight loss because she's had a decrease of appetite since she was diagnosed with cancer and when she started therapy. She has AFib and is on carvedilol, a P-glycoprotein inhibitor, just to keep in your mind. And if you look at that, you might be thinking, she's got AFib and she's on carvedilol, does she have some heart failure there that's not listed on her problem list. So, one of the key things I'm going to say is, as you look at patients and look at treatment options, look beyond the documented problem list, which often does not include key factors that we would need to consider when we're selecting therapy. And she has a history of GERD and she is on my favorite PPI, pantoprazole. Less drug interactions, not because anybody paid me to say that's my favorite PPI. As soon as I said that, I thought that sounded really bad, but it is my favorite PPI.

Okay. So, if you look at risk factors for VTE in the individual with cancer, and we focus a lot on what it is related to the cancer. So, if you look at cancers, we talk about specific cancer types. But one of the key things is active disease. And we'll talk a little bit more about that. As important is the treatment, so whether it's a post-surgical patient or somebody getting chemotherapy, somebody getting targeted therapy. And one of the things I heard, even sitting in the last session, is the number of new agents that have VTE as a risk, really needs to be considered, especially if you work in one specific disease type. As important as the CAT risk, or the cancer-associated risk, we really need to look at patient individual factors. So, the lady – the case I gave you – is somebody who

has AFib. We know that is a risk factor for clotting. So, looking at those other factors, such as – and they're listed again – age, obesity, immobility, drugs, history, genetic predisposition, those also need to be considered. So, that's where when you look at a guideline or a pathway and it says do this and this, if you don't consider those other factors, you may not be treating that patient appropriately.

This is a relatively old study that was reported that looked at the relative risk of VTE in patients with specific types of cancer. Now, I work a lot in head and neck cancer right now. And, if you look, that's one of the ones that has the lowest risk. Last Tuesday, when I was in clinic, I had two patients diagnosed with VTE. Now we have a busy clinic, but that statistically does not sound right when you look at the risk with head and neck cancer. So, there are certain populations, certainly we are aware of, pancreatic cancer, patients with CNS malignancies, but even in those cancers where there's not a known increased risk because of other factors, you certainly can see VTE.

This looks at a more colorful diagram of the reasons that we see with cancer, increased risk of VTE. And as you look here, you will see that there are many potential pathways that can impact. Now the reason I show this is because I like the color, but the other reason that I show this diagram is because one of the things that is really interesting, is the investigation within tumor subtypes, to look at somatic mutations related to specific cancers that may make patients at increased risk of VTE. So, instead of thinking increased risk just with metastatic cancer, we may be able to tell that this population with this genetic mutation, or –

I'm not saying those words together again, with this genetic mutation, and I just did, they may be at increased risk of having VTE. Why does this become important? Because when we talk about prevention, that may be the population that we would want to look at, preventive strategies to decease risk of VTE, say, with immobility.

Treatment-related risks. These are the ones that always listed in guidelines. The key thing I would say about this is that this is a short example of the types of treatments that have been associated with VTE. There are a number of different agents that have VTE risk. That as we see new drugs being approved and used in practice, one of the things we should look at is what's the risk with VTE.

Okay. So, this is added for one reason and one reason only. One of our major goals should be with VTE is to prevent. And so we can talk about lifestyle strategies, but one of the things we really need to know is when the benefit of an anticoagulant outweighs the risk of the anticoagulant in terms of prevention. And this is one of the examples in myeloma with certain treatments where that risk has been weighed and there are guidelines available. There are not these types of guidelines available in most cancers. There has been some work looking at some of the clinical determinations of increased risk. So you can see in this list, where you look at primary site of cancer, chemotherapy, hemoglobin, pre-chemotherapy leukocyte count, BMI, to help determine by looking at the risk score, patient's increased risk. Where this may become really important when we get to the point where we're looking more aggressively at preventive strategies

for VTE. So, even though we're going to talk mainly about treatment, prevention really is something that is needed in certain populations.

Okay. Let's talk about treatment. So, if we look at treatment there's a couple ways that we can approach it. We're going to start by looking at the options that are out there. And the reason I'm going to go broad-option instead of looking at the new studies that are out there first, is because the broad-options are important because the new treatment, the DOACs that use in VTE, is not the answer for everyone. And I am really concerned in practice, as I see people embrace those direct oral anticoagulants. That people are losing the ability to use some of the older agents effectively. I say that because I see people come to the clinic on warfarin, not getting the management they would have gotten 5 years ago, where they would be having great oversight because people are getting a little comfortable with anticoagulants that don't need as aggressive monitoring. That I worry that we're going to lose that ability to monitor appropriately for those agents that do need aggressive monitoring.

We're going to talk about treatment considerations, when we would use one agent versus the other. There's not great studies that tell us when we would use one agent versus another. There was a report recently published where they went to a group of anticoag specialists and gave them case scenarios and said, “What agent would you use?” And that was published and it was interesting. The different approaches people do take based on the literature that's out there now. We'll talk about strategies and then when to discontinue therapy.

Okay. So let's talk about options. So, as every talk about VTE management should begin, here is the overview of hemostasis. So, we know that when you get vascular injury, we get platelet adhesion, which starts the coagulation cascade, which then causes thrombin, deformed fibrin, get that clot and then you get the clot formation. If you look at this picture – let's see if I can do this, all right – if you look at this picture, you can see that there are activators of hemostasis and there are inhibitors. And the reason I show this is that it fits really nicely into the coagulation cascade, which all of us have seen in our life and probably have a little bit bad memories of. The key thing I really want to focus here, is again, really nice colors if you take a look at them. I did this one myself, I didn't copy this from anybody. Anyhow, let's keep going. So, you can see that we have the extrinsic pathway and the intrinsic that we all learned at some point, but the key factors I want to go to is this Factor Xa that with Factor Xa is so essential and pivotal in bringing the intrinsic and the extrinsic pathways together. If you look at this, you see the potential for targeting very different aspects of the anticoag – of this coagulation cascade. And indeed, some of the older agents we have, target different aspects and multiple aspects. Where we are looking now, are agents that target Factor Xa, or thrombin. And this is where I start with one of the key things I think that you should take home. I hate the term “direct oral anticoagulants.” And one of the reasons I don't like that term is because it doesn't tell me how those drugs work. So, when I talk about this, I'm going to separate them out and not put them together. I'm going to talk about Factor Xa inhibitors. I'm going to talk about direct thrombin inhibitors. They're not

the same. They have different effects, but more importantly the data is different that we have right now.

So, if you look at natural anticoagulants, just to make sure that we can talk about this a little bit later, protein C and S, natural anticoagulants. The older oral anticoagulants are warfarin or vitamin K antagonists. They inhibit vitamin K–dependent clotting factors, but they also inhibit vitamin K–dependent natural anticoagulants. And so we'll talk about that a little bit. We'll talk about antithrombin III and how that's the target for heparin. So, that's why I wanted to at least mention those.

Okay. So, now let's look at our options that we have. And I categorize them mainly based on how they work. So, if we look, we have the heparins, which we're going to talk a little bit about. And the reason it's so important to talk about the heparins, especially low-molecular rate heparin, because in oncology with cancer-associated thrombosis, this is our gold standard, at least for this moment in time, when we're looking at agents. We look at Factor Xa inhibitors. We focus a lot on the oral agents, but remember fondaparinux had a brief claim to fame when we used it, and we'll talk a little bit about that. Warfarin – we'll talk a tiny bit about and then the direct thrombin inhibitor and the one that we really focus on is the dabigatran.

Okay. Let's talk heparin a little bit. So, heparin we all – okay, I say we all know heparin, but it all depends on your age if you know heparin. So, unfractionated heparin was the gold standard. Big molecule. It's a biologic. One of the key things is that it causes hypersensitivity reaction and that you can get

antibodies associated with it. And then lower molecular weight heparin, smaller, about one-third of the size and less associated hit. And I'm not going through a lot of this just because I think this stuff most of you know. The key factor is that when heparin binds the antithrombin III, what occurs is that it increases. It's the effect on thrombin and on Factor Xa causing the anticoagulant effect. Now, you'll think maybe I made mistakes with all these other circles, but in fact, no, that effect on other proteases, it R and D'd part of what we see when we use unfractionated heparin. When we go to low-molecular weight heparin, our focus tends to be much more on Factor Xa and on thrombin. So, when we look at unfractionated heparin, this is one of the key drugs, I think, that people forget how to use. So, if you're an outpatient-focused person, which I am at this point, if you said to me, how do I dose heparin in a patient with a new blood clot? I would have to look it up to see how you dose it. So, many of us have nomograms available, but because this is not the treatment of choice in many situations, we don't even have those nomograms. It's important to realize the benefit of heparin, because one of the key benefits of heparin is a short half-life and by turning off the infusion you can get rapid turnoff of the effect. Something that we need when we're doing bridging and for certain other types of procedure. So, important just to bring up to remind people.

Bleeding with unfractionated heparin. One of the key things with unfractionated heparin, like I said, is that you turn it off and the bleeding risk deceases, so just discontinuation of therapy can be very helpful. We do have protamine sulfate, and if any of you have ever used this, you know that it can be

very effective. There are guidelines because protamine sulfate is a peptide that is developed from salmon sperm. I can't believe I just said salmon sperm in front of a group of people. But salmon sperm, one of the key things that people need to worry about when you're thinking of using protamine in a patient, that you're trying to reverse the effect of heparin, is patients that have shellfish allergies and patients that have had vasectomies and then patients who have been on insulin. Protamine, insulin, there's an increased risk of allergic reaction with protamine. I thought that was really interesting. I think some of you guys should be writing that down. Write that down about the salmon sperm, because that's the last time I'm saying that in this decade.

Okay. Low-molecular weight heparin. Low-molecular weight heparin certainly took the place of heparin and depending on your age, you can remember almost exactly the day when that started to happen. Remember we talked about this as more Factor Xa. So, now we're getting into the whole concept of Factor Xa. And the reason I'm focusing so much on Factor Xa is because when we talk about reversal of Factor Xa oral agents, think about how they work because it does have effect on low-molecular weight heparin because of that Factor Xa effect. You can see the key things that made these drugs really predominate the use of initial therapy for treatment of VTE as well as initial and longer-term treatment of VTE in cancer, is the fact that it's relatively predictable. It can be given as an outpatient and – here we go – and that you can actually look at Factor Xa effect if needed. So, the key things when you look at these agents, when it took over the treatment market, is that it's clearance is not

dependent on dose and we do need to monitor it in most patients like we did unfractionated heparin. This is where they work. These are the agents that are available. There used to be a third one that was taken off the market. Some of the clinical trials that have looked at the use of low-molecular weight heparin compared to other agents did use that, tinzaparin, that is now off the market. And I show you the dosing available.

One of the key things I do want to mention is even though you look at the VTE treatment doses, based on the package insert, factors such as obesity and renal effect may be important. And this is the dose used usually for short-term treatment of management of VTE. But as we go to another agent, in the old days, maybe vitamin K antagonists such as warfarin, that – we only use these drugs short. But as we learned that we can use these longer, after the first month of therapy, sometimes the dose is decreased. We'll talk about that when we look at studies, but it's important to realize that these package insert doses are not a long-term dose used in most patients with cancer-associated VTE.

Considerations of low-molecular weight heparin – I'm going to highlight a couple key ones that I think are important. We talked a little – we can mention a little bit that you can reverse with protamine, about 60%. Relatively contraindicated in patients with HIT. Absolutely contraindicated if it's recent. But this is the part I think people don't think about and that's the osteoporosis. Heparin itself has an increased risk of osteoporosis with prolonged use. But how many people do you actually use prolonged, unfractionated heparin. So with the use of low-molecular weight heparin, using it for 6 months, 12 months, and

beyond, that risk of osteoporosis is something that we should clinically think about in patients.

Okay. Let's talk about Factor Xa. Targeting Factor Xa. Taking out the other effects. These are the agents that we could discuss. So, if you look at this list, you see on the fondaparinux, subq. And then you have four agents, oral agents, that are anti–Factor Xa. The bottom agent was just approved but it was approved for prophylaxis, or prevention, in patients at high risk for medical illness after they were hospitalized. So, we're going to focus on these three agents. And I will even go as far as to say, that these three agents are not the same. The dosing certainly is different. One of the key things with edoxaban is that we use a lead-in of a low-molecular weight heparin or unfractionated heparin before we start the oral drug. And that is because that is how it was looked at in clinical studies. So, one of the things that I find is people get very comfortable with an agent in their practice because that's the drug they go to. Insurance companies may help us make that decision that the one agent that we like, which I'm not going to mention the one I pick, that that agent may not be the agent the patient can receive. So, that's important.

The other thing that I will mention, if this is not something you do every day, this lead-in period with rivaroxaban for 21 days or apixaban for 7 days, this can lead to a lot of confusion. So, when we see somebody who has a VTE and we throw them on these drugs and we call them into the pharmacy or, you know, send that e-prescription, and don't talk to the patient, one of the big problems is that it's not a drug like an antibiotic that they will know how to take. It really does

take the same education you would have used if you were starting them on warfarin or low-molecular weight heparin. The only difference with low-molecular weight heparin is you don't have to do that whole give-the-shot thing. That was a joke. Okay. That was a joke and I thought it was really funny because I – that's my favorite reason to use these agents is because I don't have to tell people how to give themselves injections. There is a reason I became a pharmacist. And one of them is, I do not like to make people give themselves shots. Okay. Never mind. Why did I just say that in front of a large group. Keep going, let's see how much time. Okay.

So if you look at parenteral. Fondaparinux. I just wanted to give that for time-wise. We will keep going. This is comparing the different heparins with fondaparinux. The key thing here is that deceased HIT. This is the dosing. This is all package insert, or available in guidelines, so I'm not going to go through this.

Now, let's go with the oral Factor Xa inhibitors. This is the comparing of the agents. You can see rivaroxaban, apixaban, edoxaban. You can see none of them are pro drugs, like the direct thrombin inhibitor. And if you look, some of the key things. Look at these drug interactions right here. Our patient has carvedilol, which is a P-glycoprotein inhibitor, and then we have the antidote and this has been changed because this was taken from a paper in 2016. We now have an antidote.

So, if we look at pros and cons. We're going to go through some of these. So, let's go through the data. Okay. Thrombin, I just wanted to at least mention, the direct thrombin inhibitor, and here we see the dabigatran and I mentioned

that, just so you can see that information. And then vitamin K–dependent clotting factors. Again, you should know this – the information of how they work. Key thing is that when you start the drug, because it inhibits this anticoagulant protein, it is important to use heparin or low-molecular weight heparin or fondaparinux first, till we get them up to therapeutic range. So, I put this in just for information.

So, let's go to our patient. PL is a 67-year-old woman. What are our treatment options? If you look at just the treatment of VTE, you can see that the data went from one fractionated heparin to vitamin K antagonist to low-molecular weight heparin to vitamin K antagonist, to now we're at a point where we have low-molecular weight heparin II, a direct oral anticoagulant, depending on which agent you pick, or in some agents you can just start with a DOAC. If we look at the information in cancer-associated thrombosis, this is the change. We are comparing not to low-molecular weight heparin and vitamin K antagonist, we're looking at low-molecular weight heparin as our gold standard. So, this is the study that initiated this as a gold standard. It’s the CLOT study. I bring it up for a couple key points. One, oral anticoagulant, the study was published, you can see in 2003. This means vitamin K antagonist. So, it basically looked at using low-molecular weight heparin over to a vitamin K antagonist or low-molecular weight heparin for 6 months. If you look at the initial treatment doses, these are ones that we use today. If you look at the recurrent VTE, you can see that for low-molecular weight heparin compared to vitamin K antagonist, it was better. If you look at the time patients were not in therapeutic range for warfarin, you can see

half of the time they were in therapeutic range, 25% they were high, 25 low. One of the key problems. This is the bleeding effect and you can see between the two groups.

This is looking at all the data that looks at using low-molecular weight heparin compared to a vitamin K antagonist. And you can see, if you look at the time recurrent VTE and major bleeding, the benefit. It became gold standard. So that's the gold standard that we've been waiting for to compare DOACs. So, this is the first strategy people used to look at, the data with DOACs, in cancer patients. They looked at the large multicenter, randomized clinical trials that had a small subset of patients with cancer and they looked in that small subset of cancer patients, was there benefit? A lot of the complaint was, it was a subset analysis that wasn't powered appropriately. And this will just give you the data and it shows you the different agents that were looked at and how they were compared.

And then we have the study that was presented at ASH 2017, published in February after, that looked at the question we really wanted to know. We looked at using low-molecular weight heparin compared to using a vitamin K antagonist. But the vitamin K antagonist in this study was edoxaban, which meant that there was a lead-in of a low-molecular weight heparin. So, we're using a low-molecular weight heparin versus a 5-day low-molecular weight heparin then to a vitamin K antagonist. And if you look, you see the duration of treatments, 6 months to 12 months, and the primary outcome was to look at a composite analysis of recurrent VTE and major bleeding. If you look at the two treatment arms, you can

see it was 1,040 patients in the intent-to-treat arm. You can see for the vitamin K antagonist, remember they had a low-molecular weight heparin for 5 to 10 days before. And then you look at just continuing a low-molecular weight heparin. And you can see they're very evenly matched. A key thing here, look at these patients, over half of them had metastatic disease. Most patients were receiving cancer treatment. And you can see most patients had risk for bleeding.

This is the definitions that were used for the primary outcome. This is the definition that's used in many of the studies now from the International Society of Thrombosis and Hemostasis, and you can see recurrent venous thrombosis, major bleed and clinically relevant nonmajor bleeding.

So, looking at the results, you can see, now this is in your slides it says percent. This is actually 67 of these 525 and this is 71. This is not 71% had recurrent VTE or major bleeding. But you can see noninferiority between the two strategies. So, using low-molecular weight heparin, going to edoxaban, compared to using a low-molecular weight heparin. You can see, noninferior. Because this was a study of 1,040 patients, this was the data that we've been looking for. But it compares the agent, most of us probably do not use clinically, when starting patients on a DOAC.

So, that takes me to the SELECT trial. The SELECT Trial was a pilot study done in the UK that was open-labeled that looked at rivaroxaban compared to the same low-molecular weight heparin that was used in the prior study. And so this study was about 460 patients. You can see the two arms. Again, the treatment

duration was 6 months. The outcome that was the primary outcome was VTE recurrence.

And this – now I'm going to warn you, if you pull this study, which I would recommend that you do, I took the actual numbers. In the study summary, it talks about the accumulative 6-month` occurrence. I looked at the actual number incidents of VTE occurrence. So, that's why the numbers will look different if you pull the study and just read the summary. But, you can see the rivaroxaban versus low-molecular weight heparin in terms of VTE occurrence and if you look at bleeding, you can see increased bleeding. So what you'll see was summarized in a meta-analysis where they pulled the literature and basically saying that DOACs had lower 6-month recurrent VTE compared to low-molecular weight heparin, had higher major bleeding when compared to low-molecular weight heparin and associated with higher clinically relevant nonmajor bleed. What does this mean? It means that we have to look at the populations in the study. So, the bleeding that mainly occurred was GI bleeding, not that other bleeding didn't occur, but was GI bleeding in patients with GI tumors. And one of the things that you'll see in guidelines now is the warning to be cautious of patients at risk for GI bleeding. This looks at all the ongoing studies that are looking at different agents. So one of the things I would like to know that if I'm used to using apixaban, I want to know what that looks like compared. Those are ongoing.

Now, the other thing I wanted to bring up, is looking at this duration of treatment. And I think one of the biggest questions we have in cancer is how long do these patients remain on treatment? In the initial study that I showed you,

looking at edoxaban versus low-molecular weight heparin, it was found that patients stayed longer on the oral agent than they did on the injection. Now, aren't you all shocked that patients actually will take a pill that, if it's not causing them problem longer, then they will give themselves self-injection? How many times do you have to do that deal with a patient? Just keep on it now. We'll look at it later and see if you need to continue this therapy. So, one of the things is that patients will stay longer on these therapies if they're tolerated.

So, if you look at the NCCN guidelines, this is what it states at this time. I think that they will even be updated more. Key things here, is that identify patients are on chronic anticoagulation. And this is the note to practice, that people when they're taking medications, kind of forget what they're taking them for. And if they're taking a lot of different therapies, it's really important that people always know they're taking an anticoagulant.

The other aspect is if we're the ones writing for the anticoagulant, every other doctor associated from that care – well, let's be real – every other health provider taking care of that patient needs to be aware that that patient is on an anticoagulant and that when they're adding drugs for different indications, that they need to consider that. It's pretty easy for people to remember they're on an anticoagulant if they're giving themselves shots. It's not necessarily as easy if they're taking oral drugs.

So, one of the other questions that have come up is what populations does this not work for. And, one of the key issues that people have identified is people at extremity of weights. So, patients that are very low weight – cancer

populations, or patients that are very high weight. Again, a significant amount of our cancer populations. Because these doses are flat dosed, they are determined in the general population. Are we going to over anticoagulate those people that are very small, or are we going to under anticoagulate those patients that are big? And what numbers you use, some people use under 50 kilos. Some people use over 120 kilos. Some people use BMI. But that's going to be one of the considerations.

Okay. Management strategies for patients with anticoagulations. I wanted to at least mention reversal. Because we now have a new reversal agent. So, when you look at what agent you're using, one of the key factors is in patients with cancer, to think about, what can I do if I need to reverse? And when do you need to reverse? Well, you need to reverse if they're bleeding. You may need to reverse if there's a procedure. Or you may need to reverse if there is thrombocytopenia. I will question a thrombocytopenia with reversal, maybe. And, I think even with procedures, I think planning is the key issue. So, I wanted to at least mention the reversal agents that are available. The FDA approval for andexanet is for rivaroxaban and apixaban, but it has been looked at for other vitamin K inhibitors. So, it's been looked at in low-molecular weight heparins, as well as edoxaban. So, if you look at this agent, it is a modified human Factor Xa decoy, that when you give it, it is a decoy for Factor Xa, and as soon as it is stopped and gone, the Factor Xa is available. So one of the big challenges with this agent, if I was going to put it in terms of like, what the challenges are – one is where do we use it? Because it is available, people are using it outside the

indications of where it was actually approved. Number two, how do we pay for it? $58,000. Number three, are we jumping in and using it inappropriately because we have the initial clinical trial, but if a patient has bad kidneys and the drug is hanging around for longer than the time we normally would treat, do we need to treat longer? What am I saying? Do we need to spend more than $58,000 in order to treat? So, I think one of the key things with this agent is to not think about using it without really having looked beforehand at what strategies you will use within your institution.

I also wanted to mention, for fair time, that when you look at – that we do have a neutralizing agent for the direct thrombin inhibitor, the dabigatran, as well. Plus, I really do like a little bit of picture up there.

These are some resources. And you see one of the key ones, right here. Institutional guidelines. And if you work in a physician-based clinic, you still should have these guidelines of when you want to think use. I had a patient that was on warfarin. We gave him one dose, one dose of a direct oral anticoagulant. One dose. He started having bleeding. He had renal cancer. He started having urinary bleeding. And so, he went into the hospital. One dose. And they were talking about whether they were going to reverse him. I was shocked, because it was bleeding that could be easily stopped, and it was one dose. It wasn't a whole lot to reverse. So, it's really important to consider how you're going to use these agents.

When to consider no active treatment? I just wanted to make sure for completeness, to add, these are the absolute contraindications by NCCN. These

are relative by NCCN. When to consider filter? I want to laugh when I say this. I had worked with one physician that if you say the word filter, he has a little mini seizure. So, you can't even say it, and I used to work with another physician that like, I swear, if you could give it out in cereal, it would be. So, I think that this is something that you need to consider in your practice.

Thrombocytopenia. There are guidelines about when to hold certain drugs with thrombocytopenia. But the thing that we don't look at when we look at these charts is the duration of assumed thrombocytopenia. So, when you're talking about a heme malignancy, it's very different than you talk about a short-term thrombocytopenia in somebody receiving chemotherapy. That you pretty much know is going to resolve.

Okay. Recurrent VTE despite anticoagulant. This is going to be, probably the key thing to end with. When you have patients with cancer, who have recurrence of their VTE, what treatment options do you think? And it's going to depend a lot of what they're on. So, there are some data looking at who is at risk for recurrence. This was a really nice study looking at tissue factor levels to see if that predicted people at high risk for recurrence. This was taken from the CATCH study that looked at low-molecular weight heparin compared to vitamin K. And they looked at people that reoccurred and they looked at their tissue factor, so I added that in, if you're interested. You can look at certain populations. One of the nice ways to really approach it is to look at reoccurrence and look at, is it because the therapy wasn't optimized? And this is where oral agents become really important to consider. Are people taking them, or are they taking them

appropriately? And is the dose appropriate for that patient? You can do the same thing with low-molecular weight heparin as you can do with vitamin K antagonist, but really evaluating before you say someone has failed, to see if they're actually taking the drug, looking at the cancer to see if it's progressed and then looking at other factors. So, these are some of the options. If patients are on low-molecular weight heparin, you can optimize the dose if you haven't. And some people would recommend looking at Factor Xa levels. Warfarin, looking at the dose to see if the INR is appropriate. If it's low, putting them on low-molecular weight heparin until you get them up. For Factor Xa inhibitors, not in the guidelines yet. But many people are recommending that you would look at an alternative agent that you could better control.

Bridging therapy? Very clever. You can see – I think this is very clever. I like Google Pic Images. So, you can see, in some cases, where there's no need to bridge and other cases where there are. And I recommend you go to the NCCN guidelines, which I think have some of the best guidelines for bridging or stopping therapy before procedures. I just took apixaban and looked at it and you can see the different terminal half-life and whether it's a low-risk procedure or a high-risk. And I put that in there for you as well.

So, prophylaxis. Because of the 1 minute that I have left, I will say the key thing with prophylaxis, I just wanted to mention, a new drug, the indication for prophylaxis in medically ill patients, cancer patients were allowed. I mean, I just wanted to talk about this study for one second. There were three cohorts. The cohorts were how they looked at the data that was analyzed. The first cohort

looked at patients that had high D-dimers. The second looked at D-dimer levels that were high plus patients over 75. The third cohort is what looked at both of the first two cohorts as well as the other people in the study. So, there's a lot of debate about this study. But one of the things to look at, if you have time, is how the analysis was actually done to show the benefit.

So, I left this in, let's just go to the very end. So, when we look at management of VTE, in your patient with cancer, key thing to look at is the evidence. What data is out there right now, when you're selecting agents probably? The risk of bleeding. And then to look at individual factors. The practical things such as drug interactions, ability to neutralize. We know cost and convenience. I wanted to say with that patient case, she was on carvedilol. If you do a search with carvedilol and edoxaban, you find that there is a significant drug interaction. So, the question is, should you use a low-molecular weight heparin, or should you manage the AFib differently? Those are things to consider.

And with that, looking at just the benefits and the risk, I think I mentioned, and I have less than three seconds for questions, which is just how I like it, so

I will be around if you have questions or you can feel free to email me. And if you want any of the studies I talked about, my email is rowena, r-o-w-e-n-a, dot schwartz, s-c-h-w-a-r-t-z. Why are you all not writing this down? At uc, University of Cincinnati, dot edu. I'd be happy to send you anything I can that I didn't go over and thank you guys, very much.

[END]