Rachel Rosovsky: Hello. My name is Rachel Rosovsky. I'm a hematologist from the Massachusetts General Hospital. I am thrilled today to be chairing this discussion on *The Challenges at the Intersection of Venous Thromboembolic Disease and Obesity: Defining the Issues*.

Rachel: Today, it is my honor and privilege to have two of my friends and colleagues here and I will have them introduce themselves.

Stephan Moll: Rachel, thank you very much for having me on the program. I'm Stefan Moll. I'm an adult hematologist and coagulationist at the University of North Carolina in Chapel Hill.

Rachel: Thank you.

Bishoy Ragheb: Thank you, Rachel. I am Bishoy Ragheb. I am a clinical pharmacy specialist practitioner at the VA in Eastern Colorado. I am thrilled to be here with both of you.

Rachel: That's wonderful. Well, it's great to have you and we are going to use first names throughout this talk.

Learning Objectives

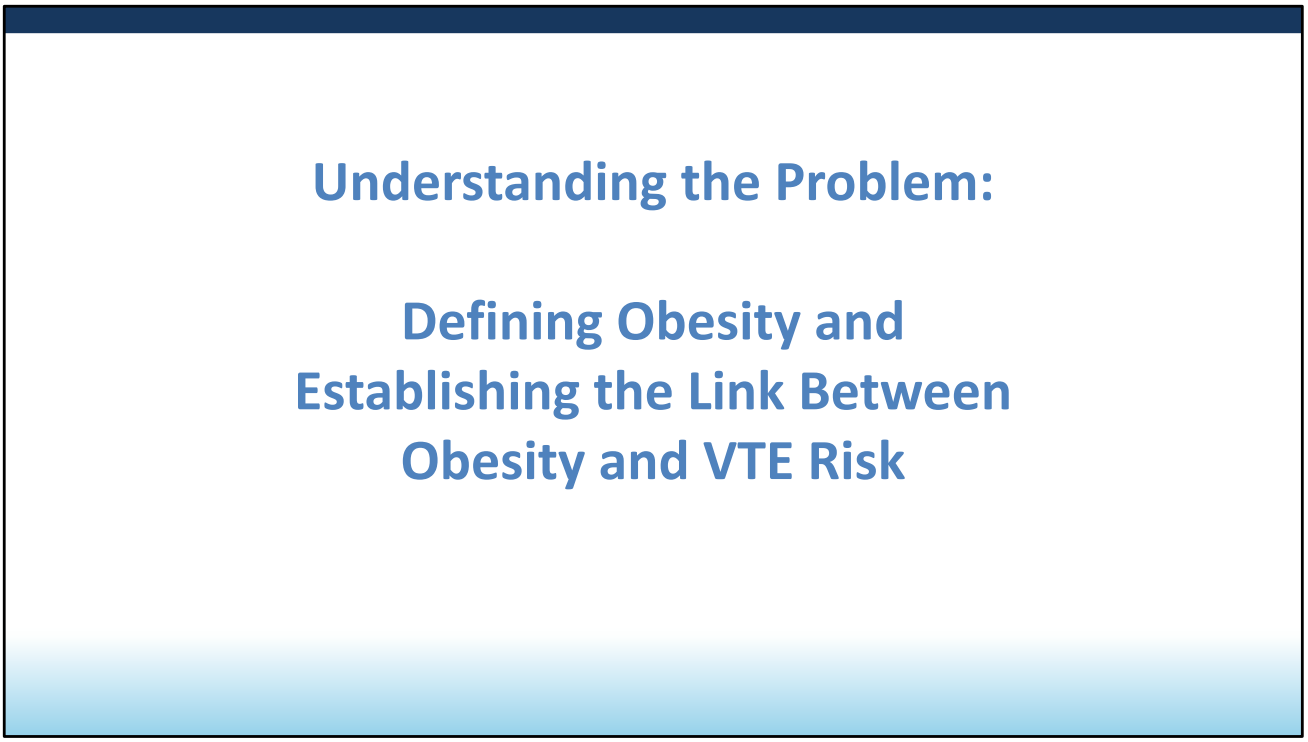
- Identify the impact of obesity on VTE pathophysiology
- Review DOAC absorption, distribution, metabolism, and excretion in obese individuals
- Explore ongoing anticoagulation management strategies for obese patients with VTE
- Educate patients regarding key aspects of anticoagulation management

Rachel: I will go ahead and start with our learning objectives, as you can see here. We really want you to leave this conversation really understanding the impact of obesity on VTE pathology, learn about DOAC absorption, and explore different anticoagulation management strategies for obese patients, and think about how to educate our patients regarding the key aspects of their management.

Case Presentation

- 29 year old female patient
- Weighs 132kg, BMI 50
- PMH DM, hyperlipidemia, HTN
- Presenting for first physical to establish care

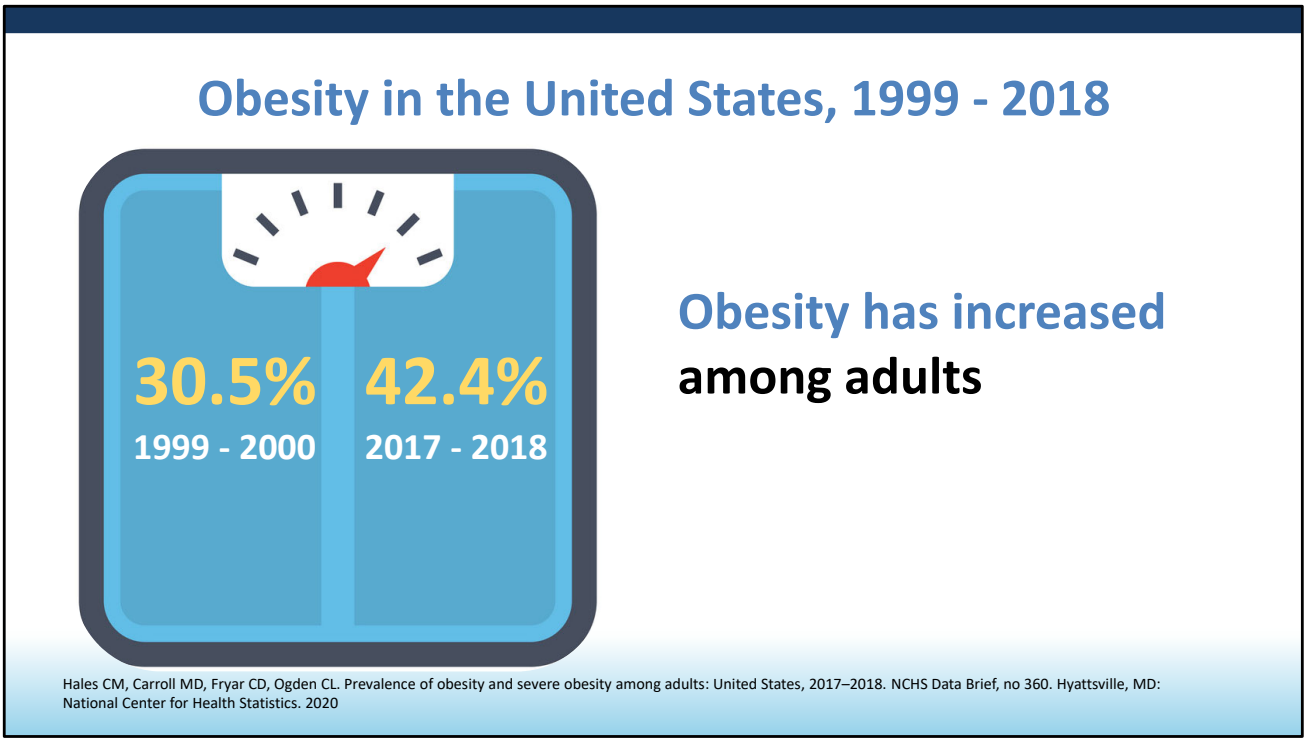
Rachel: We're going to start with a case. This is a 29-year-old woman who has a weight of 132 kilograms and a body mass index of 50. She has a past medical history of diabetes, hyperlipidemia, and hypertension. She's presenting to you, her primary care doctor, for her first physical exam to establish care.



Rachel: So before we get into that, I'd like to just briefly mention the scope of the problem. We know venous thromboembolic disease, which includes deep vein thrombosis and pulmonary embolism, is a major cause of morbidity and mortality. In fact, data from the CDC reveals that up to 900,000 men, women, and children each year suffer from VTE with over 100,000 deaths.

When you look, you can see that the prevalence is increasing. When you look at the risk factors, one of the major ones is obesity. Stephan will expand on this shortly. I also just want to define obesity in that problem. Obesity is a body mass index of greater than 30 kilograms per meter squared or higher is considered obesity. Severe obesity is a BMI greater than 40.

BMI is a measure of an adult's weight in relation to his or her height. It's calculated by using the adult's weight in kilograms divided by the square of his or her height in meters.

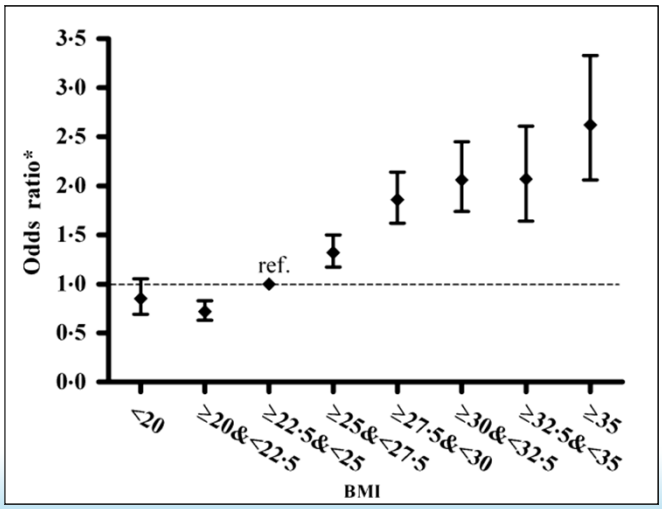


Rachel: We know that obesity is a major crisis in the United States. The age-adjusted prevalence obesity has increased steadily over the past decade. As you can see here from this slide from 30.5% in 1990 to 2000 to 42.4% in 2017 to 2018. By the end of this decade, nearly 50% of adults in the United States will be obese.

Stephan, I'd like to ask you the first question. Compared to patients of normal weight, how does obesity impact the occurrence rates of DVT and PE?

Obesity and VTE Risk

Relative risk of venous thrombosis by categories of BMI
* Adjusted for age and sex



Pomp ER et al., *Br J Haematol.* 2007;139: 289–296.

Obesity and OCP

BMI (kg/m²)	OC use	Patients	Control subjects	OR*	95% CI
<25	No	51	167	1	
≥25 & <30	No	27	34	2·52	1·38–4·57
≥30	No	28	30	3·04	1·66–5·57
<25	Yes	260	233	4·15	2·85–6·03
≥25 & <30	Yes	178	55	11·63	7·46–18·14
≥30	Yes	132	19	23·78	13·35–42·34

Obesity and thrombophilia

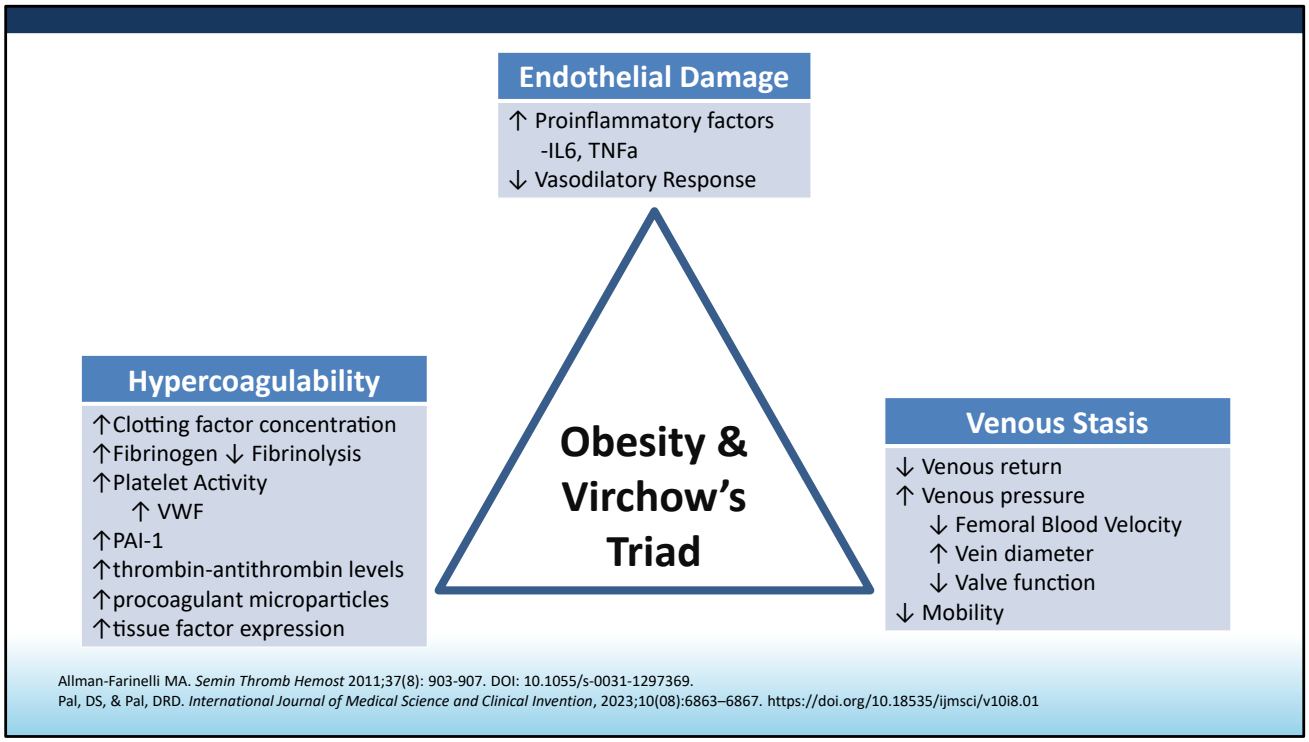
BMI (kg/m²)	FVL	Patients	Control subjects	OR*	95% CI
<25	No	1077	1631	1	
≥25 & <30	No	1289	1244	1·72	1·54–1·93
≥30	No	643	423	2·48	2·13–2·88
<25	Yes	217	69	4·18	3·12–5·61
≥25 & <30	Yes	250	58	5·77	4·20–7·93
≥30	Yes	124	18	7·86	4·70–13·15
	FII 20210A				
<25	No	1225	1803	1	
≥25 & <30	No	1455	1351	1·72	1·54–1·91
≥30	No	735	477	2·45	2·12–2·82
<25	Yes	70	18	4·39	2·56–7·51
≥25 & <30	Yes	84	20	4·51	2·64–7·72
≥30	Yes	32	4	6·58	2·31–18·69

Stephan: The BMI as it increases the risk for venous thromboembolic disease goes up. If you say a BMI of 20 to 25 or 30 is a relative risk of 1, if the body mass index is above 35, the risk is increased threefold to develop DVT PE. It's a curve that continues to go up. Above a BMI of 40 probably, and those data are somewhat limited, the risk may be increased by four or fivefold. The higher the BMI, the higher the risk for VTE.

Rachel: Well, thank you for sharing that. That's very clear.

Stephan: Rachel, if I may just add to that also, while we think about BMI as a risk just by itself, it's typically with the blood clots, the multifactorial nature of blood clots, so if an obese patient, for example, takes a birth control pill, that's not just additive, but it's a multiplicative risk. The risk has been known with a BMI of let's say 35 and I mentioned the risk is threefold increased due to the obesity. If that woman were to take the birth control pill, the risk goes up to about 20 or even 25-fold depending on which pill they take. Then similarly, if there's underlying family history of, or the patient is a smoker or advanced age, or there's a known thrombophilia, the risk is often not just additive but multiplicative. Obesity does play a significant role then, particularly with multiple other risk factors present.

Rachel: Thank you for sharing that. I think that's really important for primary care doctors to know that because it's not just one risk factor, it's that kind of multiple factors that can increase the risk. Thank you for sharing that.



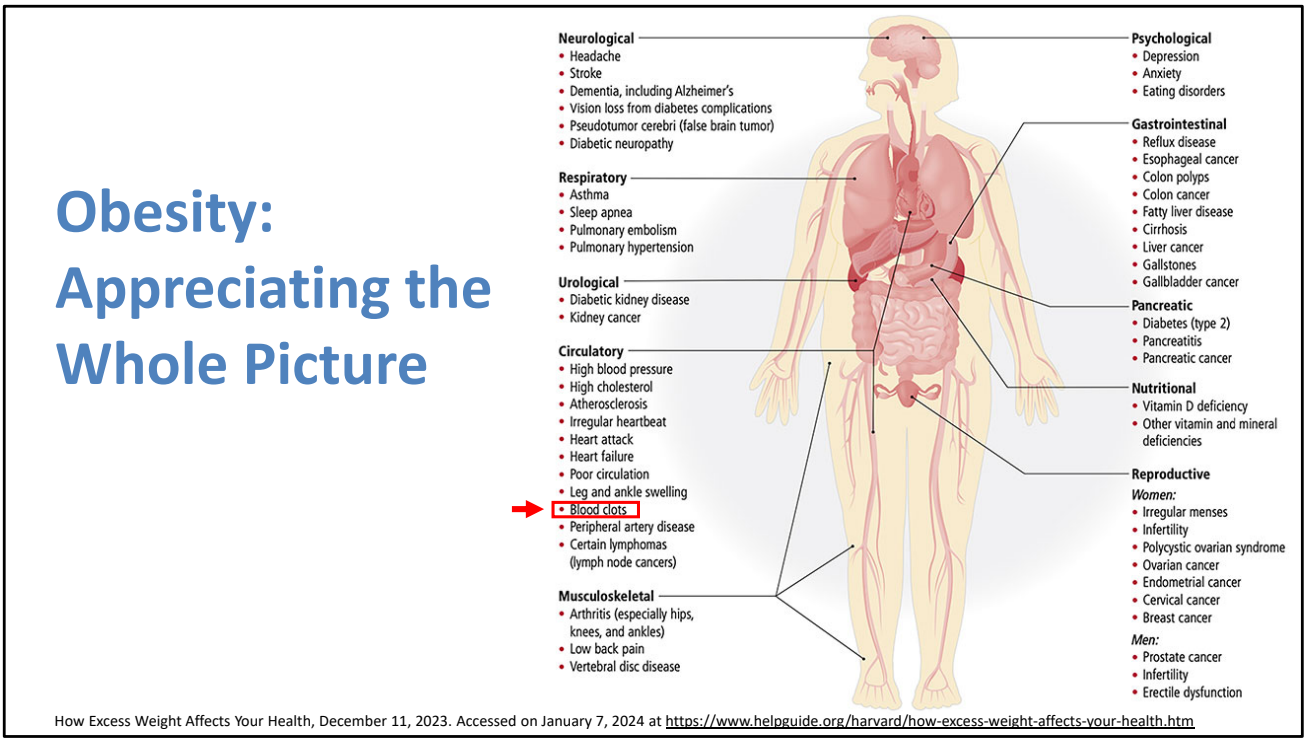
Rachel: Bishoy, I'm wondering why does obesity increase risk of VTE. Can you walk us through that?

Bishoy: What would a talk about VTE be without first talking about Virchow's triad? There are 3 factors within Virchow's triad where if 1 or more of these are present, your risk for a clot increases.

The first one would be endothelial damage. As is well-known, obesity produces an underlying low-grade inflammatory condition or state. Within that, these pro-inflammatory factors, such as interleukin 6 and tumor necrosis factor, increase the risk of endothelial damage, thereby increasing the risk of VTE. This then reduces also your vasodilatory response.

After that, you have hypercoagulability. What's been found is that patients who are obese, their clotting factor concentration is increased. They have increased fibrinogen and reduced fibrinolysis. Their platelet activity is enhanced due to increased Von Willebrand factor and some other things.

On the other side, you also have venous stasis. Venous return is typically lower in patients who are obese. Venous pressure specifically intra-abdominal is increased. That then gets believed to be passed down through the femoral blood velocity, which is why we typically will see blood clots in the femoral vein. Vein diameter is thereby also increased, so viscosity is increased. It helps promulgate the overall blood flow and valve function is also reduced. Typically, obese patients will have a lower mobility. As we see here, all three points within Virchow's triad is hit, so thereby increasing the risk of VTE.



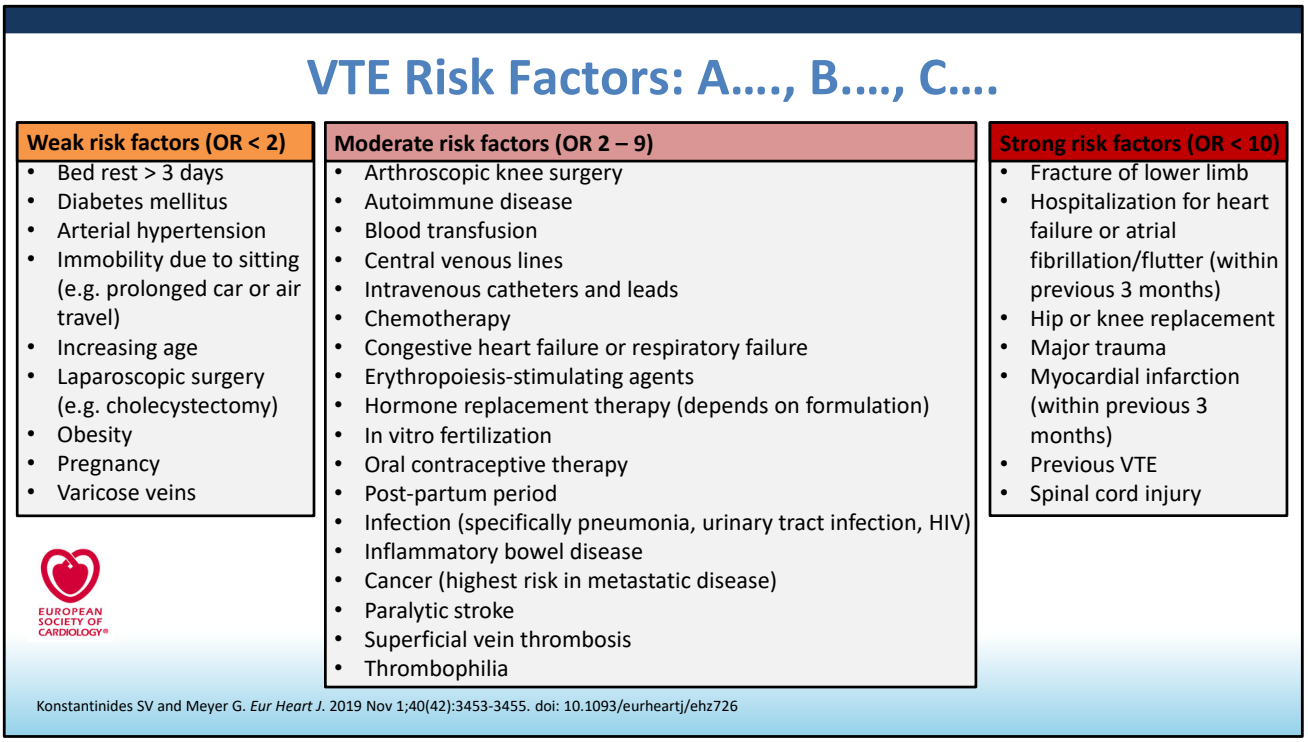
Rachel: Thank you for sharing that. I think that makes a lot of sense and it is on all fronts it looks like. So this is really important for PCPs to know. They are really the front-line clinicians that are communicating with patients about their risk of VTE.

I'm wondering, Bishoy, if you can talk about how can PCPs talk to their patients about these issues and weight loss. What you talked about is something that I think clinicians can understand. How can PCPs talk to their patients about this?

Bishoy: I think when we talk to patients if I'm coming at it from a patient's angle, I need to understand the risks. For this particular talk, we're focusing on blood clots. If we use blood clots as a gateway or an avenue to say your VTE and overall thrombotic risk is increased because of obesity, but here is also a slew of other things that the risks are increased because of obesity.

Some things will resonate more with patients but the fact if we can use it as a gateway and share other risk factors as a whole, it might motivate patients to focus on it. What may work today or what's not working today, may resonate later.

Rachel: I also think it's important to frame it as just another medical condition, right? That there's not a lot of stigma associated so it's like high blood pressure, it's like hyperlipidemia. You need to talk about these issues to think about how to decrease that risk. Again, the PCPs are front-line clinicians so imperative to have that conversation.



Rachel: Thinking back, Stephan, to what you were talking about the more risks you have, the higher your risk. I think another really important aspect of this is that PCPs need to ask about family history for patients because we know that patients that have a first-degree relative that have had a blood clot, they're about a twofold higher risk of getting a blood clot themselves. I think that's an important question.

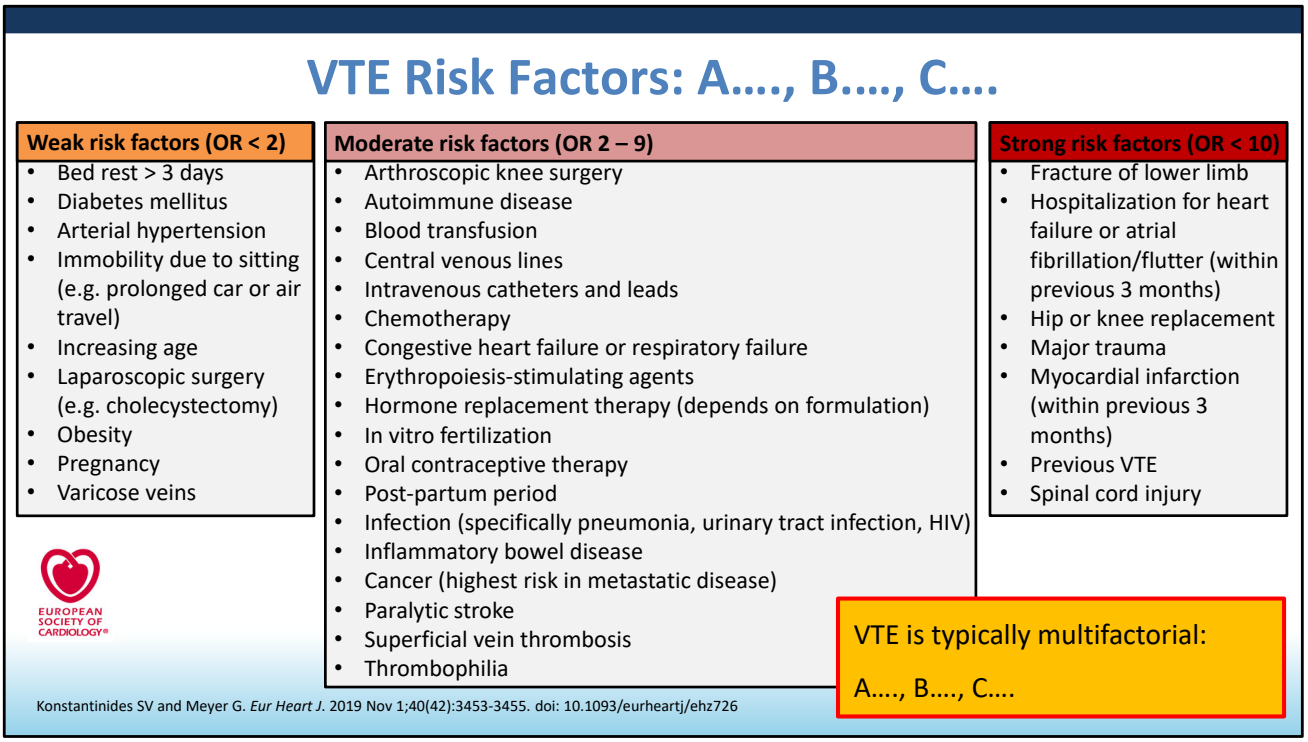
Stephan, you'd mentioned thrombophilia and you'd mentioned oral contraceptives. The more risks you have, the higher they are. Are there other risk factors that PCPs should be aware of to think about that more risk?

Stephan: Yes, absolutely. I would think most primary care physicians or providers know about that.

If you think about some weak risk factors such as partial immobility for two, three days, maybe at home when they're sick or even in the hospital, those are not strong risk factors. Obesity, as I mentioned, threefold increased risk is not a strong risk factor for venous clots, but it is a risk factor.

Then people are aware that strong risk factors such as hip replacement, knee replacement, hysterectomy, colon surgery, major trauma, those are big risk factors.

Then these in between, the arthroscopic outpatient surgery, patients with cancer. Chemotherapy cancer can be a significant risk factor. Oral contraceptives, you've mentioned, inflammatory disorders, ulcerative colitis, rheumatoid arthritis, but also infections that increase the inflammation.



Stephan: The key point really is to realize that when a DVT or PE happens, it's not typically one thing that happened, but to identify all the risk factors that played a role, the obesity, the immobility, the family history, the smoking, the hormonal therapy, because then eventually the question will come up and we'll get to that. The question will come up, "Do we treat short-term because the risk factors have resolved, or do we treat long-term because certain risk factors are permanently present?“

For that point, it's really important to realize VTE is multifactorial, identify all the risk factors in an A, B, C manner.

Rachel: I completely agree. I think the other thing for primary care doctors to think about is we do know that your risk of VTE goes way up as you get older. In addition to all these risk factors, really addressing those risk factors at each visit. Usually, people come at least once a year to see their PCP hopefully, but as people get older, we know your risk of having a blood clot in your 20s is pretty low, on the order of 1 in maybe 10,000, but as you get into the 80s, it's much higher, more like 1 every 200, 300 patients. So I think as people age, we need to keep that in mind too.

Key Definitions

- **VTE:** venous thromboembolism, when a blood clot forms in a vein
- **DVT:** deep vein thrombosis, when a blood clot forms in a deep vein, usually in the lower leg, thigh or pelvis
- **PE:** pulmonary embolism, when a blood clot breaks loose and travels through the bloodstream to the lung

What Is Venous Thromboembolism? September 19, 2022. Accessed on January 7, 2024 at https://www.nhlbi.nih.gov/health/venous-thromboembolism

Stephan: Rachel, a point to make though, is while you talk about, or we talk about blood clots, often patients think blood clot, arterial clot, venous clot, they don't know the difference, so when we talk about family history and when we educate, particularly the obese patient or the one with other risk factors about blood clots, we need to talk about DVT. What are the risks, what are the symptoms, PE what other symptoms, and how does it differ from an arterial event that people have some understanding of that so they recognize the symptoms if they come up.

Rachel: I think that is so important. Thank you for bringing that up. I think the awareness of what a DVT and PE is shockingly low. In fact, the World Thrombosis did a survey, I think this was a while ago, maybe 2014, where they asked people, just everybody, "Do you know what a stroke is?" I think 90% of people knew what that was. "Do you know what a heart attack is?" About 90% of people knew what that was. When they asked people, not necessarily patients, if they knew what a DVT or PE was, only 50% knew.

I think it's so important to clarify what that is, that what a DVT is, what a PE is, not only the risk, which is what we've been talking about but also the signs and symptoms because, Bishoy and Stephan, you know how many times PEs are missed in the emergency room and on the wards, there's been several studies about that.

So, really educating people chest pain, chest pressure, shortness of breath. You used to be able to work out for 30 minutes, no problem, and now you have to stop after 10 minutes. That's concerning. Or leg pain, leg swelling, things like that, so I think the idea of raising awareness is so important.

Rachel: Actually, the National Blood Clot Alliance is a great patient advocacy group that actually has a lot of information for patients and providers and family members about the signs and symptoms and even about risks and how to talk to your primary care doctor about risks.

Stephan: Rachel, that organization is @stoptheclot.org. That's a good one for patients to know @stoptheclot.org.

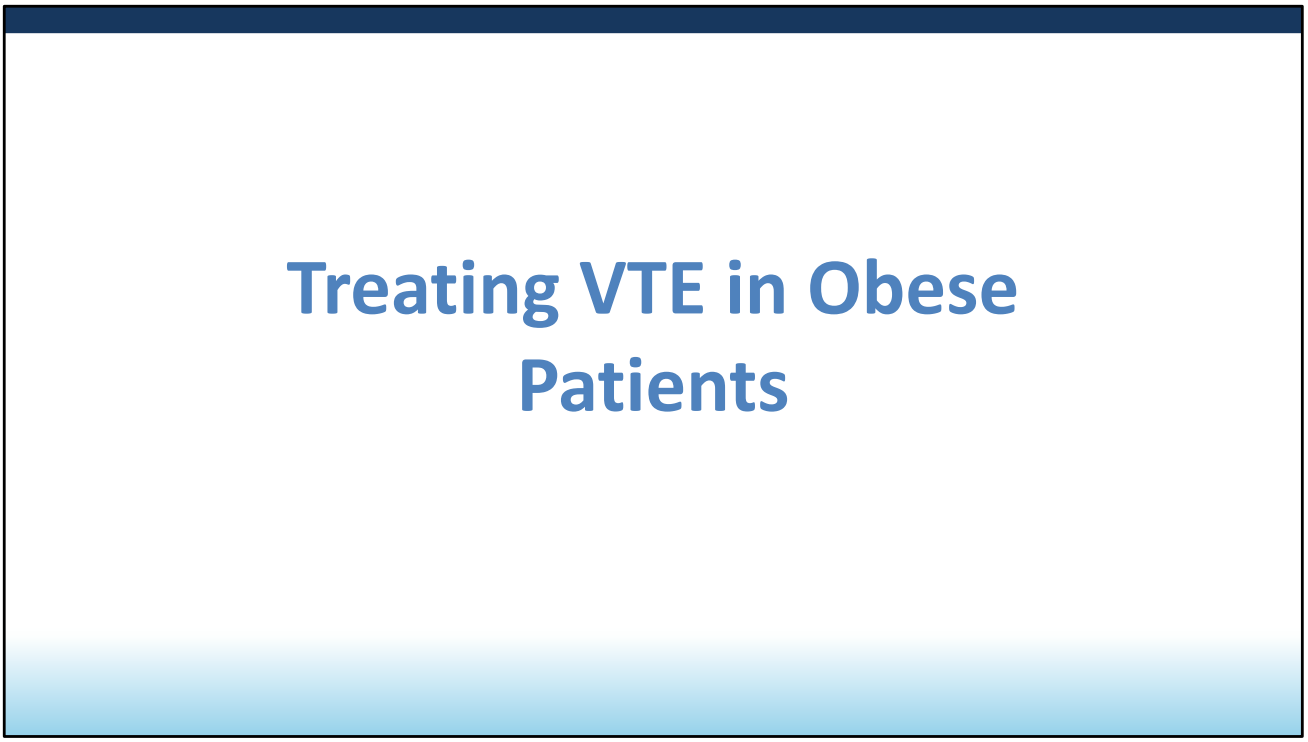
Rachel: Yes. We'll get to more resources later on. Bishoy, any thoughts about what we've talked about and risks?

Bishoy: I was just going to echo what you were saying, especially for raising awareness, especially since at one point, I'm not sure if that's still the case, but PE was considered to be the second leading cause of sudden death in the United States**.** Just raising that awareness with the patients as we have our visits is very important.

Case Presentation

- Patient is now 31 years old
- She presents as a walk in and informs the PCP she has been on an anticoagulant for 3 month for an LLE DVT that developed after broken leg
- Records show an occlusive thrombus in the left popliteal vein
- No other relevant changes, although the patient now weighs **160kg, BMI 60**

Rachel: Let's fast forward a few years. Our patient is now 31 years old, and she presents as a walk-in and informs her primary care doctor that actually she's been on an anticoagulant now for three months because she broke her leg and in that setting developed a left lower extremity DVT. In fact, she had a thrombus in her left popliteal vein, which is right behind the knee. No other relevant changes except for the fact that she's actually gained a lot of weight since our last visit that we talked to her. She's now 160 kilos and her BMI is now 60.



Rachel: In terms of treatment for patients, just to take a step back, know that there's direct oral anticoagulants, DOACs. Those were FDA-approved over a decade ago. The reason they were approved is they were compared to the standard of care at that time which was warfarin or coumadin.

All of the DOACs at that time, and we'll go into what those are in a minute, show that they were just as efficacious and just as effective as preventing recurrent blood clots but they all had less bleeding. They're now considered what we call front line or first line.

When people come in and they get diagnosed with a DVT or a PE, we will often choose a direct oral anticoagulant as the initial therapy, and even potentially long-term therapy, as long as it's for the right patient and patients can afford it. We'll get a little bit into adherence and compliance in a little bit.

So I'm wondering, Stephan, if patients do get these DVTs and they're treated with anticoagulants, how does their obesity impact or change their initial management?

Stephan: Good question. What you refer to with the FDA approval of these drugs, you say 10, 12 years ago or so, many of those studies did not include the very obese patients. The standard of care initially was we think it can be used in most patients, but we don't really know how these drugs behave in the very obese patients. There was hesitation initially, appropriately, to use it in the very obese patients with a BMI above 40.

Stephan: The International Society on Thrombosis and Hemostasis, the ISTH, recognized that there are a number of these patients out there and the question comes up, can we treat them safely with a DOAC?

In 2016, they had an expert panel review the data and came up with recommendations. At that time, based on these early or the initial phase three clinical trials, the recommendation was up to a body weight of 120 kilos or up to a BMI of 40, it's okay to use either warfarin or a DOAC, and the DOAC, as you say, would be preferable because of lower risk of bleeding. Above that weight or that BMI, it wasn't clear whether the DOACs would be safe. Was it a shorter half-life, lower peaks, etc.? The suggestion was to use warfarin in the more heavy patients. That was 2016.

Obviously, seven years have gone by since that time. The ISTH recommendation triggered a number of additional studies that came out, typically retrospective data analyses from either institutions or from health insurance databases, but also some subgroup analyses of the initial trials.

The ISTH group came out with an updated guidance document in 2021 and that's been published. In that one, now the two drugs, the apixaban and rivaroxaban, can be used in patients above a BMI of 40 and a weight of 120 kilos because there were additional data. For dabigatran, which is not used much widely in the US for various reasons, dabigatran are no good data on the very heavy patients, but at least for rivaroxaban and apixaban can be used in the very heavy patients.

In 2021, 2 years ago, when this ISTH guidance document was documented, there were more data for rivaroxaban and less for apixaban but that has really changed in the last 2 years, there have been additional studies. At this point in 2023, either one of these 2 drugs can be used appropriately, safely, and effectively in the very heavy patients. It remains that in the extremely heavy patients, the BMI above, what is it, 50, 55, 60, 65, we have very limited data and it's a little bit of is this okay to use and there are different approaches. Some people use and maybe you want to talk about this a little later on. The very heavy people use trough levels or peak levels.

For myself, it's a BMI above 55 where I feel a little uncomfortable and I do want to make sure that they absorb the drug well and that appropriate levels are reached above a BMI of 55. I tend to do a trough level, but that's not universally that everybody does that. The guidance document from the ISTH says drug-level testing should not be routinely done in the obese patients and I agree with that. It's not routinely needed, but it makes me sleep a little better in extremely heavy patients if I've tested BMI above 40. 55, I've tested and I know yes, they're in the roughly expected range.

Rachel: I think you've brought up a lot, and I think the key here is that at this time, in 2023, that it's both safe and effective to use either rivaroxaban or apixaban.

REVIEW

THE AMERICAN JOURNAL of MEDICINE

Direct Oral Anticoagulants in Obese Patients with Venous Thromboembolism: Results of an Expert Consensus Panel

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[a]Department of Medicine, Massachusetts General Hospital and Harvard Medical School, Boston; [b]Frankel Cardiovascular Center, University of Michigan, Ann Arbor; [c]National Blood Clot Alliance, Philadelphia, PA; [d]Department of Veterans Affairs, University of California, San Francisco; [e]Division of Cardiovascular Medicine, Department of Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, MA; [f]Department of Veterans Affairs, Tennessee Valley Healthcare System, Nashville; [g]Independent Patient Advocate; [h]Department of Pharmacotherapy, University of Utah College of Pharmacy, Salt Lake City; [i]Department of Medicine, UNC School of Medicine, Chapel Hill.

ABSTRACT

In clinical practice, direct oral anticoagulants (DOACs) are increasingly used for venous thromboembolism treatment and prevention. A substantial proportion of patients with venous thromboembolism are also obese. International guidance published in 2016 stated that DOACs could be used in standard doses in patients with obesity up to a body mass index (BMI) of 40 kg/m^2, but should not be used in those with severe obesity (BMI >40 kg/m^2) owing to limited supporting data at the time. Although updated guidance in 2021 removed this limitation, some health care providers still avoid DOACs even in patients with lower levels of obesity. Furthermore, there are still evidence gaps regarding treatment of severe obesity, the role of peak and trough DOAC levels in these patients, use of DOACs after bariatric surgery, and appropriateness of DOAC dose reduction in the setting of secondary venous thromboembolism prevention. This document describes proceedings and outcomes of a multidisciplinary panel convened to review these and other key issues regarding DOAC use for treatment or prevention of venous thromboembolism in individuals with obesity.

 • The American Journal of Medicine (2023) 136:523–533

KEYWORDS: Anticoagulation; Direct oral anticoagulants; Obesity; Venous thromboembolism

Rosovsky RP, Kline-Rogers F, Lake L, et al. *Am J Med*. 2023 Jun;136(6):523-533. doi: 10.1016/j.amjmed.2023.01.010. Epub 2023 Feb 16. PMID: 36803697.

Rachel: Both Bishoy and Stephan, I had the pleasure of working with them on an expert panel that we did, where we brought together some experts to really think about "Are DOACs being used in obese patients and if not, what are the barriers?" and "Are people checking peaks and troughs and what is really the concern about using these in the obese patients?" In that expert panel, we actually did explore all of the trials from when the ISTH finished their guidance document in 2021 until 2022.

In fact, Bishoy was the one that collated all those and there's a beautiful chart in there showing all of those and there now is enough data to say that apixaban and rivaroxaban can be used, both of them, and there's equal amount of data. I think there's still not enough for edoxaban and dabigatran. I think most of the people on that panel, I would say most experts are not using those two drugs in the obese population. I think the question about DOAC at the peak and trough levels is really interesting.

Before we delve into that a little bit more, I'm just wondering, Bishoy, if you can talk about the absorption and distribution and whether or not you should be checking those levels based on that.

DOAC Pharmacokinetics & Obesity

	Apixaban (Eliquis ®)	Dabigatran (Pradaxa ®)	Edoxaban (Savaysa ®)	Rivaroxaban (Xarelto ®)
Target	Factor Xa	Thrombin	Factor Xa	Factor Xa
Time to peak-effect	1-2 hours	1-3 hours	1-2 hours	2-4 hours
Half life	12 hours	8-15 hours	10-14 hours	7-11 hours
Renal Clearance	25%	80%	50%	35%
Hepatic metabolism	75% Mainly CYP3A4	20% Via conjugation No CYP	50% Mostly conjugation, ~10% CYP3A4)	65% Mainly CYP3A4
Bioavailability	60%	6%	62%	60-80%
Volume of Distribution	21 L	50-70 L	107 L	50 L
Protein Binding	87%	35%	55%	92-95%

Zhao Y, Guo M, Li D, et al. *Clin Appl Thromb Hemost*. 2023;Jan-Dec;29:10760296231153638. doi: 10.1177/10760296231153638.

Bishoy: Sure. Absolutely. I think as clinicians, we're very inclined to check levels specifically for anticoagulants because that's what we've been doing for the past 60, 70 years, regardless from heparin to low molecular weight heparins, to warfarin.

Along come these new DOACs and we want to treat them like we were for warfarin and heparin.

DOAC Pharmacokinetics & Obesity

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Bishoy: Overall, renal clearance for these apixaban has the least at 25%, then moving to rivaroxaban at 35%, then edoxaban at 50, and dabigatran at 80.

DOAC Pharmacokinetics & Obesity

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Bishoy: Hepatic metabolism is actually the inverse of that. The one that is least renally cleared is most hepatic metabolized and so on as seen in the slide. Specifically speaking here for then when we get into obesity, the things that we typically start to look at in terms of how lipophilic agents, which these DOACs are, how they're affected.

Volume of distribution is one of those things. Obviously, when a patient has more mass and more volume that then is affected, and protein binding was also seen as a factor that plays into how these drugs are taken in systemically, and renal clearance being the last.

DOAC Pharmacokinetics & Obesity

↓ Renal Clearance ↓ Volume of Distribution ↑ Protein Binding

	Apixaban (Eliquis ®)	Dabigatran (Pradaxa ®)	Edoxaban (Savaysa ®)	Rivaroxaban (Xarelto ®)
Target	Factor Xa	Thrombin	Factor Xa	Factor Xa
Time to peak-effect	1-2 hours	1-3 hours	1-2 hours	2-4 hours
Half life	12 hours	8-15 hours	10-14 hours	7-11 hours
Renal Clearance	25%	80%	50%	35%
Hepatic metabolism	75% Mainly CYP3A4	20% Via conjugation No CYP	50% Mostly conjugation, ~10% CYP3A4)	65% Mainly CYP3A4
Bioavailability	60%	6%	62%	60-80%
Volume of Distribution	21 L	50-70 L	107 L	50 L
Protein Binding	87%	35%	55%	92-95%

Zhao Y, Guo M, Li D, et al. *Clin Appl Thromb Hemost*. 2023;Jan-Dec;29:10760296231153638. doi: 10.1177/10760296231153638.

Bishoy: Typically, the profile of a medication that we're looking for, for a DOAC that seems to perform the best in the sense of drug levels not being as affected are medications with low renal clearance, a low volume of distribution, and a high protein binding.

DOAC Pharmacokinetics & Obesity

↓ Renal Clearance ↓ Volume of Distribution ↑ Protein Binding

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Bishoy: As you can see in the slide in front of you, apixaban has the lowest renal clearance and volume of distribution with a pretty high protein binding with rivaroxaban not that far behind, but with the highest type of protein binding.

With all that in play, the issue I think that many will run into and we say, okay, do we check levels? Well, when you look at the reference ranges for those levels, they are wide, which speaks to the wide therapeutic index.

I agree with Stephan that sometimes it's good to have it there as a tool, but not as a driver for certain decisions that I'm sure we'll get into later.

Rachel: Well, both of you said that you would check it, and personally I would too. What is that upper limit of normal? Is it A BMI 50, 55, 60? Do you just check the troughs, or do you also check the peaks? I want to challenge you both also, and if you get a level and Bishoy, you just said the levels are all over the place and have they correlated really with what happens and risk of recurrence and things like that. So, if you get a level that's out of range, what are you doing with that? Are you changing the dose? Are you changing to a different drug? Are you ignoring it? I know I threw a lot of questions at you, but I guess the first one is peak and trough. First, do you check peak and trough, or just trough?

Stephan: Rachel, that's clear for me. It's a trough level because the time to peak, there's a lot of inter-individual variability. You know the trough level is always at trough just before the next dose is due. There are reference ranges for where the trough typically is, but you're correct. It's pretty wide.

Now, if the level in the individual patient, let's say, a BMI of 60, and we've done this, and the trough level is lower than expected, I would clearly not, and I don't think that should ever be done, increase the apixaban or rivaroxaban dose.

The question then, rather is, is the patient taking it reliably? It's an initiation of talking about drug intake, or one could consider switching to a different anticoagulant such as warfarin. I have to say I'm getting less levels as time goes by because I'm getting a little more comfortable using the drugs in the severely obese patients. If it's lower than expected, it does worry me at times, even though I may continue the same DOAC. What I really want to look at is the level in the expected range, and then I feel comfortable, "Yes, you are on a good dose, and I don't worry about you."

Rachel: I agree with you. You can't start making up your own doses for the DOACs, right? If you're at the 5 milligrams twice a day, for example, for apix or 20 for rivaroxaban, you can't really go up on that because there's no data of safety and efficacy for long-term that's higher counts.

Rachel: Bishoy, how about you? What are you doing?

Bishoy: I think it's important to clarify for our listeners that the levels that we're checking are on target therapy levels. In other words, when they check them in the trials, this is just where they found the drug levels to be and the dosing that was given. It is not a level like in INR, where I have a therapeutic level, and I have a correlation there. That's why if the levels are off, all that means it's now, we have even more question as to where this really lies. The trials assessing the efficacy of DOACs were dose-based. I give you a 5-milligram dose of apixaban or a 20-milligram dose of rivaroxaban, and this is the effect. That's a clear thing.

I will say the ISTH guidelines recommend using trough. There was also recommendations for laboratory measurement for DOACs I think from 2021, it was the International Council for Standardization and Hematology. They also put out a recommendation saying use trough in those patients as well.

Stephan: Rachel, if I may just highlight that for the audience, I think this only applies to the very severely obese patients beyond the BMI, and that's not well defined, maybe 50 or maybe 55 and above. For the majority of obese patients, even the ones with a BMI between 40 and 50, we shouldn't be thinking about trough levels.

Bishoy: Yes. Even the BMI is an arbitrary cutoff.

Rachel: Stephan, what is your limit that you test for? BMI 50?

Stephan: Roughly 55, but it's not written in stone.

Rachel: Okay. Bishoy, what's yours?

Bishoy: It's been about 50 is where I start to feel uncomfortable.

Rachel: Okay. 50, and 55. Bishoy, I did want to ask you, Stephan said he would not change management if the trough level was below the range. You so nicely explained what that range actually means. What would you do if the patient was below range?

Bishoy: I think for me, it's a shared decision-making at that point. "We are outside of the range. Here's what it could mean. How do you feel?" I know Stephan is going to get into the idea of the hate factor.

I think it becomes a piece in the discussion that we then come to have with the patient.

Rachel: Yes, and Stephan, before I interrupted you. You first started to talk about the primary care doctors and this is a good question because what do PCPs, what are they supposed to do? Because a lot of times patients who come in with, let's say, a low-risk PE or DVT, they're not being hospitalized. They're being followed by the primary care doctor. The primary care doctor very well may be the person prescribing these medications and so what should a PCP do? What advice would you have for them? How should they make this decision with their patients?

Stephan: That's a good question and it really depends somewhat on the healthcare system but a patient who's obese who gets diagnosed with a DVT PE may be started on whatever blood thinner, not by the PCP initially, but by the emergency room or wherever they were seen first, maybe in the orthopedic office or by the surgeon if it's post some other surgery.

I think the PCP who then sees the patient, or even if the PCP sees the patient a priori as a first newly diagnosed, as long as the PCP knows an obese patient can be safely and effectively treated with a DOAC, I think that's the key information. Then the highly, extremely high BMIs above 50, 55, then it may be worthwhile to send the patient to a thrombosis-interested specialist if that's available, but the majority of patients can be managed by the PCP just realizing we don't need to use warfarin. If the BMI is 41, we can use a DOAC safely.

Rachel: Yes. I think that's so important. I don't think that's being adopted because people feel a little bit uncomfortable because those initial 2016 ISTH guidelines, but I think we have enough data really to let people know that it is safe and effective to use these drugs in obese patients.

Bishoy, what's your thought about PCPs and when should they refer patients? How much should they be managing on their own? What advice would you give them?

Bishoy: I think one is to also consider the alternative of using enoxaparin or low molecular weight heparin and warfarin. That comes with its own challenges and many patients either aren't able to meet their requirements for monitoring and, of course, you have increased risk of bleeding during that time and all that. So just knowing that you can use DOACs is a big thing.

For me, if this is a patient with a single unprovoked event and they're obese, PCPs should feel comfortable going with DOACs. If the patient when we're talking about recurrent events, their BMI is in the 60s and there's just stacking factors that are going there, I think it's definitely reasonable to reach out to a specialist at that point and get them involved.

Stephan: You're making a good point, Bishoy, and I think we'll talk about this a little bit more. A big decision point will be at three or six months when we think about should we discontinue anticoagulation or is there a reason to continue anticoagulation so let's keep that one in our mind to talk about.

The second thing that I think for the PCP is important when they see a newly diagnosed patient is to ask a patient or to be aware, did the patient have bariatric surgery. I see a number of patients in clinic. There may not be volunteering that they had a bariatric surgery in the past because it was four or five, six years ago, but the absorption may be changed with bariatric surgery and we'll talk about this in our second part but that's the key question to ask immediately when somebody has a DVT PE comes in with obesity, be aware if bariatric surgery was done in the past.

Rachel: Yes, I think that is very important.

Bishoy: I'm sorry, Rachel, too, another thing for PCPs to also just keep in their minds is if a patient is prescribed DOAC from an emergency department, just to make sure that the patient is taking the appropriate lead-in, that's a lot of times if-- and it becomes especially important in the obese patient because we want to make sure they're getting the right dose initially during the highly acute phase where the risk is highest.

Stephan: Bishoy, when you say the lead in, you're referring to the higher dose of the apixaban for a week before one goes to the maintenance dose and rivaroxaban for three weeks, the higher dose before one goes the BID dose, and before one goes to the once daily after three weeks.

High-intensity DOAC Therapy

- **Apixaban:** 10 mg twice daily for the first week, 5 mg twice daily thereafter
- **Rivaroxaban:** 15 mg twice daily for three weeks, 20 mg once daily thereafter
- Rivaroxaban should be taken WITH FOOD (at least 250 – 300 calories) to avoid a drop in bioavailability

Bishoy: Correct. I don't like calling them loading doses because there's nothing to load. These have short half-lives so sometimes they're thought to be loading doses, which then lead to other misconceptions down the road but yes, they're lead-in doses for the high-risk acute phase and it's exactly as you outlined, Stephan.

Stephan: The term I use, Bishoy, which I like is high-intensity therapy for the initial period.

Rachel: Yes. Then just to be specific, the two that we're talking about that are safe and effective in obese patients is apixaban, which would be 10 milligrams twice a day for the first week, and then 5 milligrams twice a day thereafter and rivaroxaban 15 milligrams twice a day for three weeks, and then 20 milligrams once a day.

I also think it's really important to make sure that patients on rivaroxaban are taking it with food. And Bishoy, maybe you can say why that's so important that they need to take it with food.

Bishoy: Well, specifically for the 15 and 20 milligrams, the bioavailability of rivaroxaban is affected with food. There's a significant drop in bioavailability if the patient doesn't take it with food. By food, we mean a decent-sized meal. Anywhere between 250, 300 calories in that range to ensure that there's enough food to assist with the absorption.

Stephan: And Bishoy, that's likely important in the first few weeks with an acute clot. I get a little less diligent about that after few months because if there's less absorption, clinically that likely doesn't matter. Keeping in mind in a number of people, not necessarily severely obese patients, we know that the lower dose of the rivaroxaban and apixaban after six months is effective. If they take full dose and they don't take it with a meal, they have less absorption. They're still getting plenty of it.

Rachel: I'm going to challenge you a little bit, Stephan. If you're keeping somebody on a 20-milligram dose, we're jumping ahead a little bit as opposed to going down to a 10, which is not right now something that we talk about. If there was a reason you were keeping them on a higher dose, don't you want them to make sure that they're absorbing it?

Stephan: Yes, but as you say, we are getting ahead. Let's talk about this. We know at six months, the studies have been done, the Amplify Extension with apixaban, the EINSTEIN CHOICE Trial with rivaroxaban, the patient with DVT and PE, who is on long-term anticoagulation, after six months, they were dose reduced to the prophylactic dose and compared to the full dose and in one study compared to aspirin and the other one to placebo.

The full dose compared to the prophylactic dose after the six months was equally effective. If you have a person, even if they're obese and at six months they're meant to take 20 milligrams, but they absorb a little less, 30% less, they're still roughly at what, 15 milligrams of rivaroxaban. That's still above the typical 10 milligrams. I'd be okay with that, realizing that in the very heavy people, we don't know whether they can be safely dose-reduced to the 10 milligrams, whether they need 20 milligrams.

There's a non-evidence-based decision-making. Some people just say I hate to take it with meals, so I have my biggest meal unreliably, sometimes it's at lunch, sometimes it's dinner. I don't get too uptight about that.

Bishoy: I was going to say actually the EINSTEIN CHOICE when you look at what they consider to be a patient at clinical equipoise, or having a provoked clot, they did consider morbid obesity of a BMI greater than 30 to be a clinical equipoise.

Now, how far above that did patients get is a good question. Again, in very high BMIs, it becomes cloudy, but they weren't excluded by any means. Then the second thing I think, too, that we factor in is, was this a single event or was this a recurrent event? Obviously, if these were recurrent events, I might be pushing the food issue a little bit more. If it was a single one, I could feel like I could get away with the 20 or the 10, I'm sorry for rivaroxaban. I won't push the food as much.

Rachel: Excellent conversation. I would say in both of those trials, the clinician had to have equipoise, meaning they were okay with the patient being put on that third arm, which was either an aspirin or placebo. Exactly to Bishoy, your point, if you have somebody that's had recurrent clots or has antiphospholipid or something else, although that's a whole different conversation with APLS and DOACs, so we won't go there, but if they do have significant higher risks or multiple risks, and you don't have equipoise about whether or not you would stop their anticoagulation, those are the people that I get a little bit concerned about, and I don't dose-reduce those people.

I also think those are the people that I want to make sure that they're taking with it with food. I just want to make sure that the message we're giving to our primary care doctors, it's not that they shouldn't take it with food, that is the recommended to take it with food. But there is a lot of good data suggesting in certain populations that you can go down to that lower dose. If they're on the 20 and they're not taking exactly with a huge meal that they probably are okay as Stephan had said. I think that was an excellent discussion. Stephan, I can tell you want to say something?

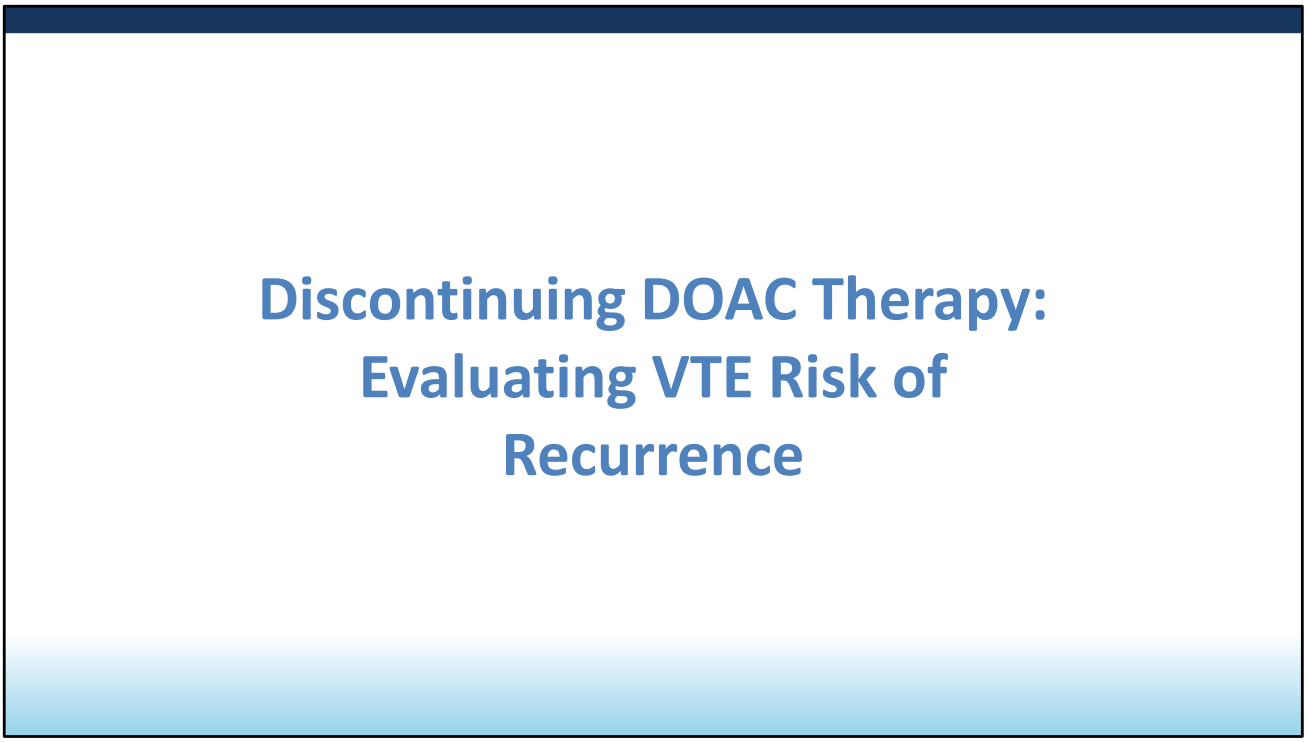
Stephan: Yes, I do. Just to summarize this for me and maybe for listeners at least my point of view. In the very heavy people, BMI above 40, weight more than 128 kilos, I typically would not dose-reduce. If they have an indication for long-term anticoagulation, I would keep them on the full dose given the lack of data with a dose reduction the very heavy people is safe and effective. They've already shown me in the last six months, I've tolerated the full dose okay I didn't have bleeding issues. I'd say, continue the same dose.

Rachel: I think that is crucially important. That's in line with ISTH guidelines that you shared, which is, BMI greater than 40 or weight over 120, that they should not dose reduce.

Stephan: At least we don't have evidence that dose reduction is safe, effective, or what can be done. It's a non-evidence-based decision and my non-evidence-based decision is, I'd rather see you on full dose anticoagulation.

Rachel: Yes, I would agree, Bishoy?

Bishoy: Also, I think it's important to understand the differences from the trials between the full dose and the half. The efficacy was the same and our minds we're thinking we're helping reduce the bleeding if we go low dose, but really what we saw was statistical significance and clinically relevant, non-major bleeding. Major bleeding was about the same specifically for apixaban.



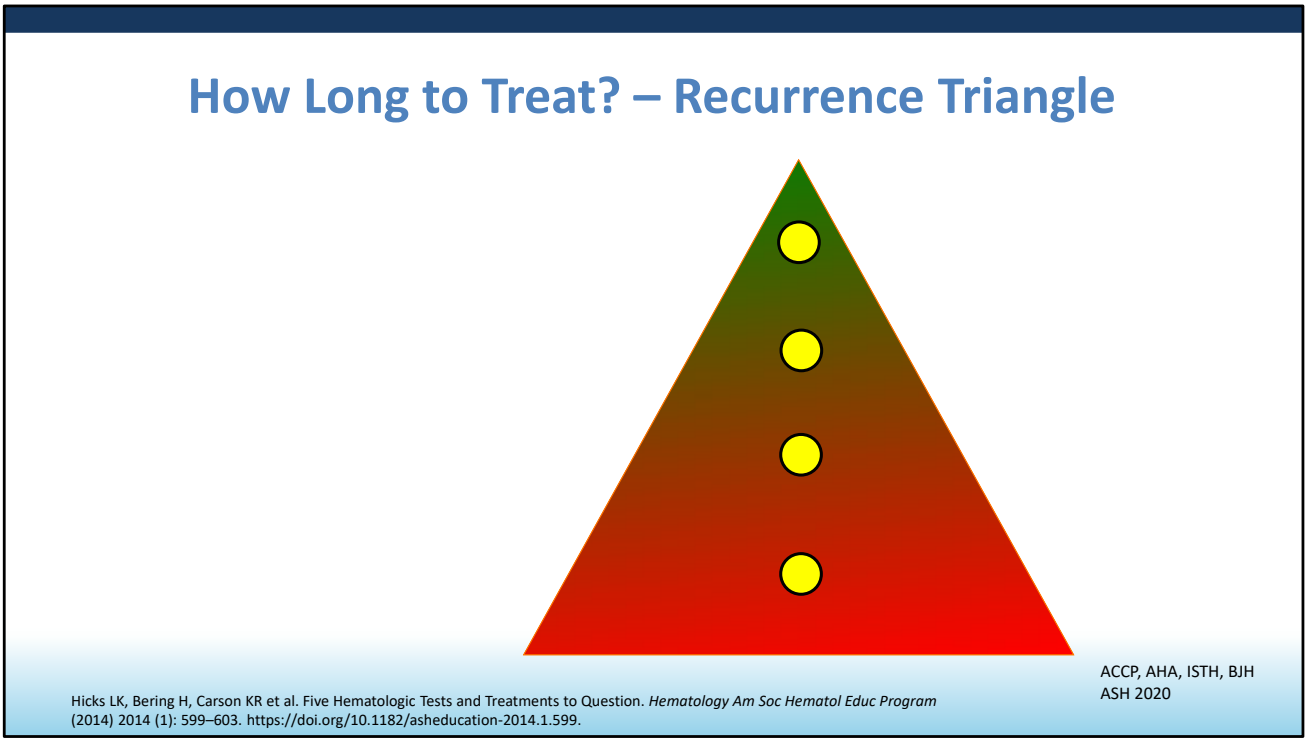
Rachel: I think this is a nice discussion that leads into actually how long people need to be on anticoagulation.

As Stephan mentioned, typically in patients that have a blood clot, we do three months. Then at the three-month, or three to six-month is when we think about, is this somebody that needs to be on long-term anticoagulation?

That really depends on what the underlying cause of the blood clot was. For things that have major transient risk factors, for example, orthopedic surgery, things like that, we know that unless patients have ongoing risk factors, three months is good. Then I think patients with very high risk of risk factors that are ongoing, such as cancer or antiphospholipid, those patients are going to be on longer, long-term anticoagulation.

But there's this middle ground, this intermediate which are considered weak risk factors like oral contraceptives, traveling and in those situations, it's not so clear as to which of those people need to remain on the anticoagulation. It really has to do with what is your risk of recurrent over a year?

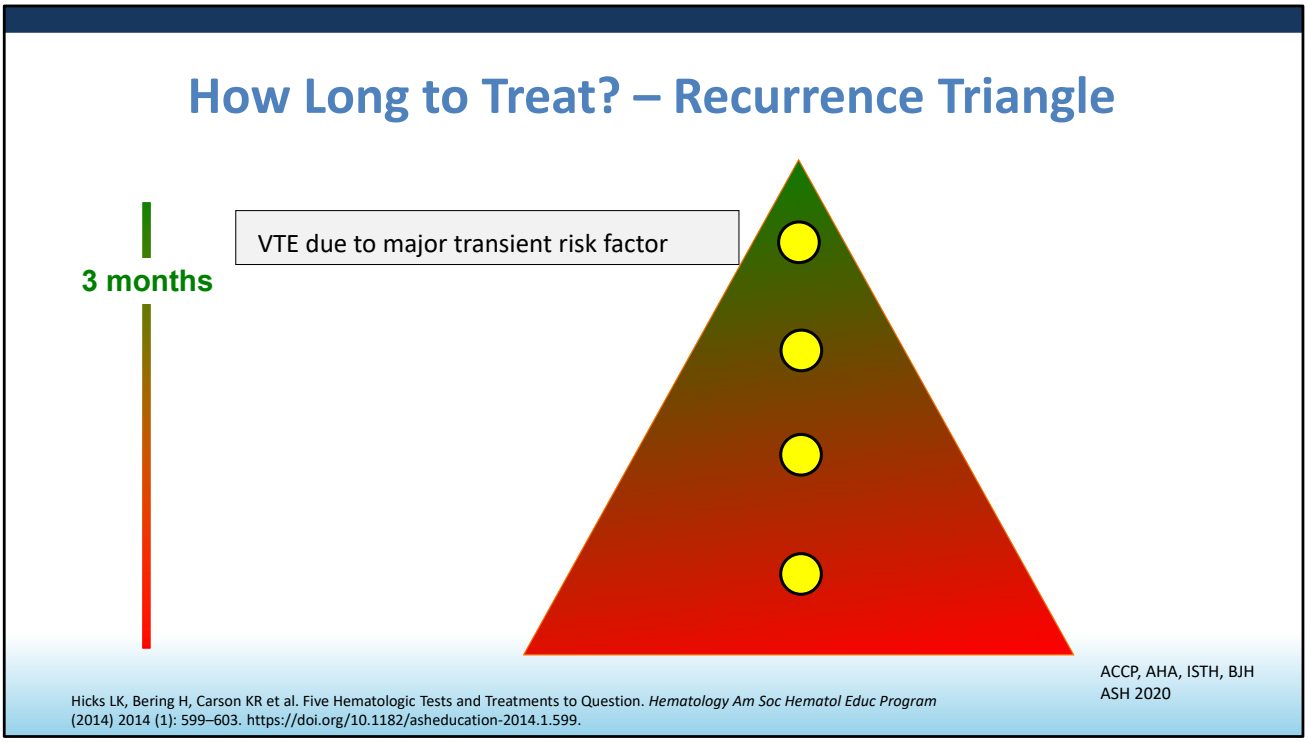
If your VTE risk of recurrence is over 5%, then we think about, oh, those people should probably stay on anticoagulation long term.



Rachel: Stephan, you are well known for your recurrence triangle and hate factor. Tell us, walk us through how you help patients decide whether or not they are someone that needs to be on long-term anticoagulation.

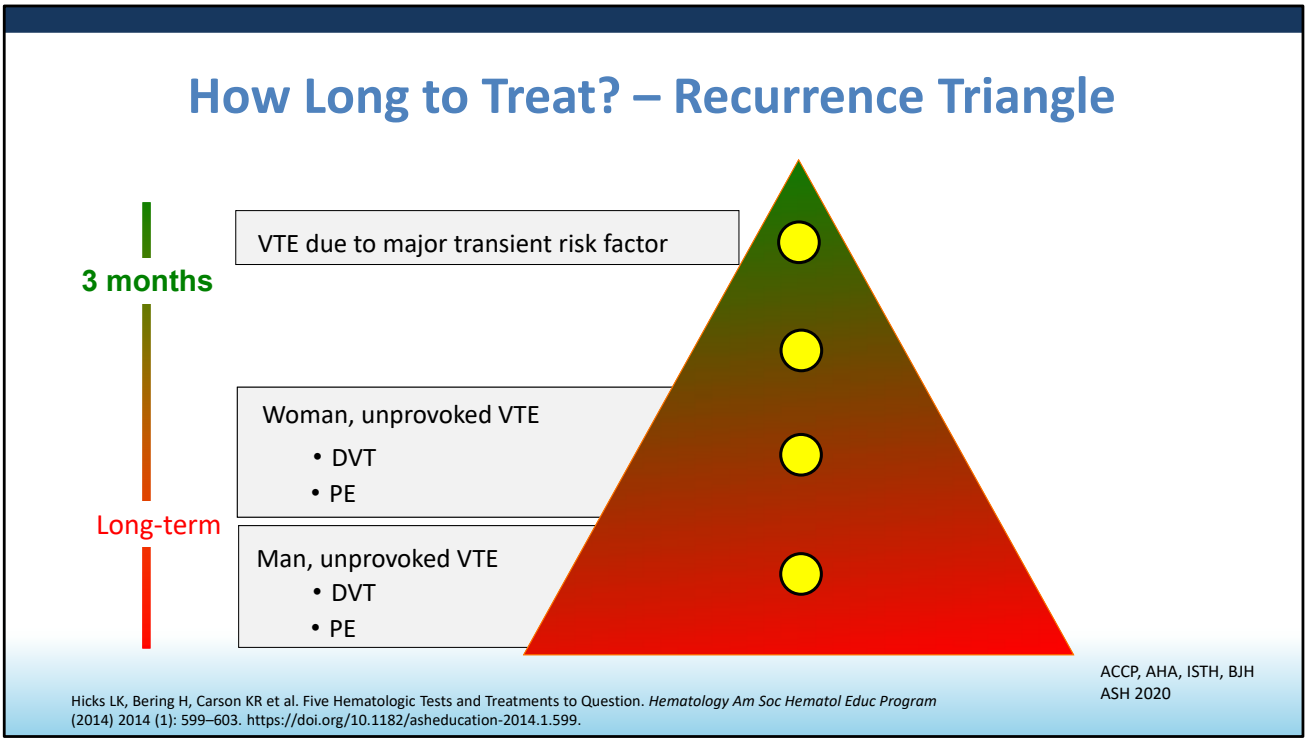
Stephan: Happy to do that. Rachel, obviously this is not just a question in the very obese patients, but the question, how long to treat is one of the main questions that patients have when they come to the hematologist. I'm sure that many of the primary care providers ask the same question.

What I use is this as a concept, is this recurrence triangle.



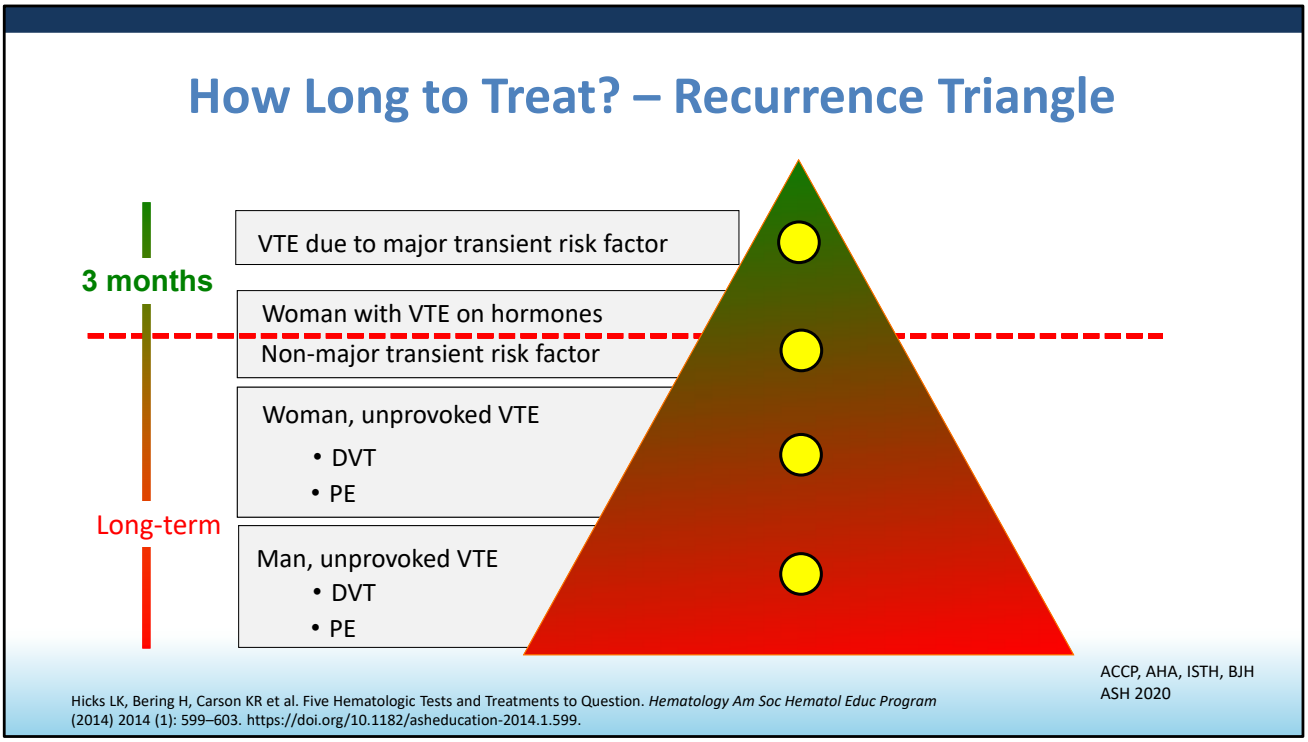
Stephan: Everybody, once they stop blood thinners after three or six months, have some risk for recurrence. If the recurrence risk is very low, I put them in the tip of my triangle, which is green, which means low risk for recurrence good. We can stop after three or six months. That's a risk of recurrence that's typically set to be less than 5% over five years. That's a low-risk and short-term integrations appropriate.

As you say, that's a person with a major transit and risk factors associated clot, hysterectomy, colon surgery, hip or knee replacement, surgery, major trauma.



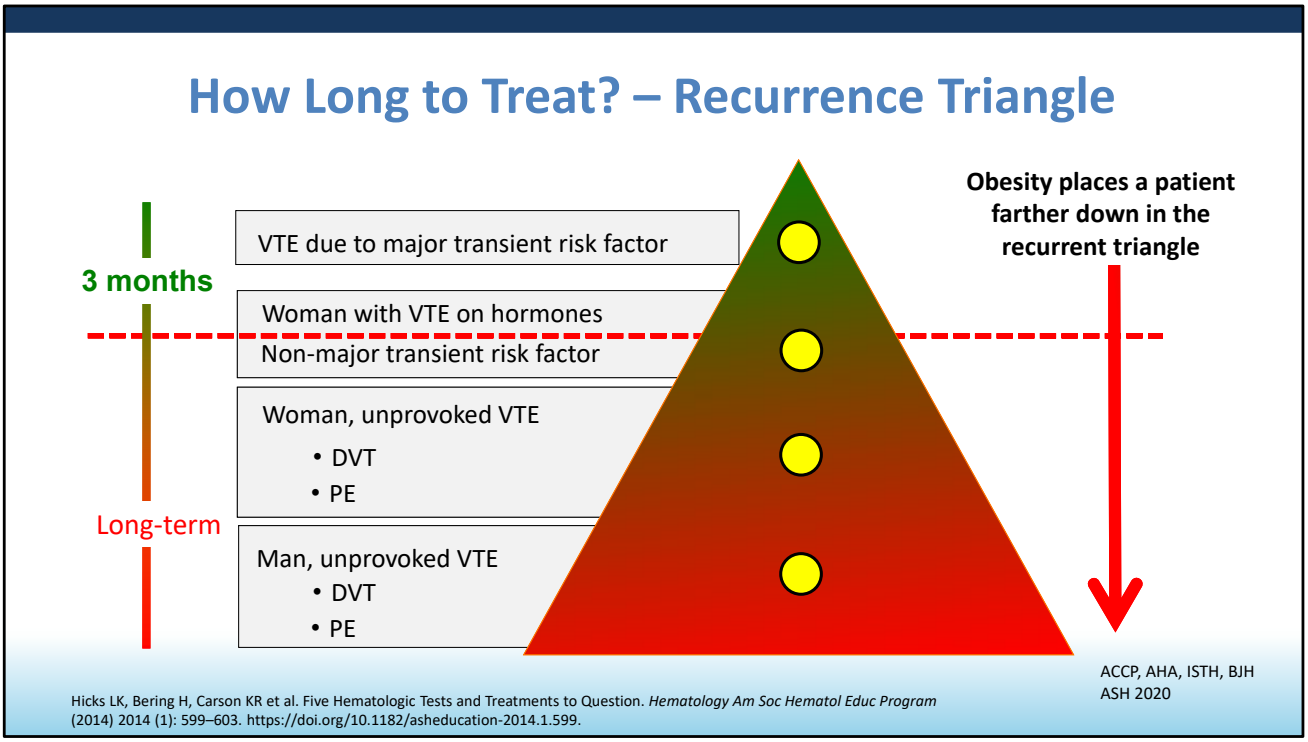
Stephan: Then we have the people at the bottom of the triangle where the broad basis, which is red. Broad base means high risk for recurrence. Red zone is bad, high risk.

Those people need to be on long-term blood thinners and those are people with unprovoked clots for example, out of the blue, idiopathic used to be or the high risk that you mentioned underlying cancer, underlying chronic risk factors. You mentioned the antiphospholipid antibodies.



Stephan: Yes, in-between patients, those are the ones where it's difficult. Birth control pill, minor risk factors such as some minor immobility. They drove maybe six, seven hours somewhere. It's not really immobility. Not long-distance travel. Is that more unprovoked, red zone? Is it in between? What do we do in those patients?

I think those are patients that are appropriately sent to a thrombosis specialist, whoever that is in an area. That could be a cardiologist, pulmonologist, hematologist, general internist. Sometimes APPs can take an interest in that. It's those people where one could consider, and I wouldn't promote that for primary care physician usage, the D-dimer or thrombophilia workup.



Stephan: The question that you will ask appropriately is, “Does obesity push the patient down in the triangle?” Let's say they're at intermediate risk for recurrence. Does the obesity increase the risk for recurrence? It does. There are data suggesting that if your obese, you have a somewhat higher risk for recurrence.

How much does it push you down in the triangle? Do you go from the intermediate zone all the way to the deep red broad base zone? That is not well defined, and it depends on some other risk factors.

If you want to talk about the patient that you introduced earlier.

Case Review

- Patient is 31 years old
- Proximal DVT
- BMI 60
- Major transient risk factor

Rachel: This is the woman who had a DVT from breaking her leg. It's a proximal DVT, so not a distal one because we know distal ones tend to not require long-term anticoagulation, unless ongoing significant factors. She has a BMI of 60, which was new. Remember she had a BMI of 50, so she's gained a fair bit of weight over the prior year.

She's got the BMI and she's got probably what you would consider a major transient risk factor. She broke a leg, was in a cast, and she got a blood clot from that. She has this ongoing risk factor of BMI of 60. How does that weigh in into your triangle and what's the conversation you'd have with her about that?

Stephan: As we mentioned earlier, the first thing I would want to do is identify any other risk factors that she had.

The fracture is one, the mobility is another one. The obesity is another one. I'd like to know, was she on hormonal therapy? Does she have a family history?

I also would like to know in the past in the first-- I forgot how old. She's 32 years. In the first 31 years, has she had pregnancies without clots? Has she had appendectomy or other surgeries without clot? Is she a clotting nightmare or did it take this major surgery to make her clot?

That also factors into where in the triangle she fits in. In general, she fits into the greenish zone, but the obesity pushes her down more into that intermediate, maybe early red zone broader base. It's difficult to decide. Should we stop or should we not?

Stephan: I cannot give you any immediate comment. That would be a discussion with the patient and the patient needs to contribute as well. I would say your risk of recurrence is probably in the order-- I'm making this up a little bit now, in the order of 5 to 10% over the next five years, is that high or low? In that case, I often think about the use of a D-dimer or thrombophilia workup. Anything else that would help me decide is she really even further down in the triangle or does she go up in the triangle?

Rachel: I would say two other things. One is, when I think about risk of recurrence, I always weigh the risk of recurrence off of anticoagulation versus the risk of bleeding on anticoagulation. I think we always need to think about that because if people at a very high bleeding risk, that's going to weigh into what we do.

Actually, there's a new risk assessment model called VTE-PREDICT, which I think you're aware of. I think that was presented at ISTH where it takes both bleeding. It's the first model that actually combines bleeding and clotting together, and tells you a risk of—you put in all these different factors, there's 14 factors. This was initially formulated looking at a collaboration of trials, about 15,000 patients. It was validated in almost 60,000 patients. It takes 14 risk factors and it churns out a number of what your risk of recurrent VTE is on full dose anticoagulation, prophylactic dose, as well as the bleeding risk. It's a nice thing to share with your patient to go through. In fact-- I think that's a nice way to think about this.

I think it's bleeding risk and recurrent clot risk. I also think another factor, and I'm wondering whether this is something either of you have patients that say this to you, and that is their mental state. I have patients that are like, "I cannot live off of anticoagulation. I will be so anxious that every 10 minutes if I have a sniffle or a sneeze or a twinge or a trickle, I'm going to end up in the emergency room.“

That's a conversation I think important to have with patients. Also a conversation you could refer them to some mental health experts to really deal with their anxiety around that because I think anxiety and depression and quality of life can have a huge impact, but it's really having that conversation with the patient and what they are most afraid about, especially in this where you have in your triangle there's that gray zone, whether it's not clear cut, yes, they should stay on, or no, they don't need to. That's where I think all these different risk factors come in.

Stephan: Rachel, please allow me to jump that in two things with a risk assessment. I'm not a big friend of these bleeding tools. It's pretty much common sense and the tools are good for clinical studies and such. But it's a question, are you on aspirin? Too many people are on aspirin plus an anticoagulant. Do you take pain medication frequently that contain nonsteroidal or aspirin products? Do you have bleeding, the hemorrhoidal bleeding, the history of GI bleed, etc.? Do you have thrombocytopenia? Do you have liver disease?

Stephan: That's a lot of common sense, but one needs to focus on the bleeding risk. I agree with you. It's the A, B, C of bleeding. Bleeding is often also multifactorial, so one needs to identify the risk factors.

Then the third point of decision-making, you mentioned either anxiety or some people just hate to be on blood thinners. You mentioned earlier that I like to use the warfarin hate factor or the rivaroxaban, or the apixaban hate factor. I do use that in clinical practice.

I ask them, on a scale from zero to 10, how much do you hate to be on apixaban or warfarin or rivaroxaban. Zero means it's just a pill, no big deal. 10 means I hate it incredibly. Then often patients spill out and they may say, "Zero. I actually like to be on it. It gives me comfort that I don't have a new clot," or they say it's 10.

With the DOACs, I ask them, what is your copay? It's often the copay, that's a major problem. Then we can discuss the copay cards that many of the companies have that grip for patients.

It's the DOAC hate factor that assesses for me what is the entry to the assessment, what is the patient preference and allows the patient to contribute to the decision should I be on blood thinners or not?

Rachel: I will just point out that that VTE PREDICT that one of the 14 factors is obesity, just because that does play a significant role in recurrence. There's another one of those the HERDOO2 score is another one that has obesity in it.

I love your idea of the hate factor. Really, I think that the key to this is that these are complicated conversations and really a lot of complexities come into it. I think really listening to the patient and what's important to them has to be critical in this conversation because if they're not on board and if they have the hate factor of 10, you might decide, yes, they need to stay on it, but they're going to go home and maybe go off of it probably.

I think bringing in the patient's perspective and really what is at the forefront of their concern is important. Bishoy, I'm wondering how you think about this with patients in terms of their recurrence. I guess my next question is, if she were to lose a lot of weight would that change your recommendation?

Bishoy: Yes, a couple of things. In terms of the recurrence triangle, I think the issue about the hate factor or when I present it to patients, I say, "What do you value," similar to Rachel, what you were saying. I think the important thing here that sometimes we see is when a patient values something, how do they arrive at that?

Bishoy: Then let's say they value being on an anticoagulant when they clearly had a provoked factor or they value coming off of it when it's clearly unprovoked and they should be on it. I feel like our jobs as clinicians is to come in and say, "Okay, here are the risks that you're putting yourself in and understanding the whole picture, of course we're going to take your value in, but when you make this decision that you're doing it with the best possible information and the most evidence that we have to do it," and many times I've seen patients, their values will start to shift because, "Oh, I didn't know that or I didn't realize that this would be my risk, and kind of bringing that into it. So of course we take the value in, but in context with everything else we come to a mutual decision.

With regards to if the patient loses weight, I think again, it depends. If weight was the major reason why we kept the patient on an anticoagulant, I would be open to maybe considering coming off or going with a lower dose at that point if we hit a good weight. To conclude that if the patient had an unprovoked clot, there was clearly nothing there to suggest that. Whether or not the weight is lost, I'm not sure there's evidence to suggest that we can come off of the anticoagulant.

Rachel: I'm going to ask each of you, here's our patient, had a provoked clot by a major risk factor, but she's got to a BMI of 60. Are you going to keep her on or are you going to take her off?

Stephan: I think we all agree it's not a yes no answer. It's a discussion. She is in the greenish zone of the triangle, so you would like to stop. The obesity, pushes her down to somewhat higher risk for recurrence and then the other factors come in. The bleeding risk and particularly the patient preference, and then when one comes to a decision. Even if one continues anticoagulation, it's never forever, right? You just revisit it once a year or after six months and you talk about new studies, new dosing regimens, new drugs, new risk benefit assessment and rethink it.

Rachel: Well, Bishoy and Stephan, this has been just an incredibly rich discussion of so many different topics around obesity and VTE, and I just want to thank both of you. I want to conclude by asking each of you to talk about the most important point you want PCPs to take away from this conversation so far.

Stephan: My first three points are really non-obese, obese, or severely obese patient, the same thing. Whenever we see a patient with DVT/PE, we try to make decisions. We need to realize VTE is multifactorial, obesity is only one of the risk factors. We need to identify all risk factors so that we can eventually decide how long to treat the patient. Secondly, when we think about how long to treat, I would encourage the audience to consider the recurrence triangle and see how that works for them as a concept to think about how long to treat. Then thirdly, try the direct oral anticoagulant warfarin hate factor to assess the patient preference.

Stephan: Specifically for the very obese patient, we can use the DOACs in obese patients, even the very obese patients, but only apixaban or rivaroxaban have sufficient data. Dabigatran should not be used.

On a personal note, above a BMI of 55, I feel somewhat uncomfortable. I don't quite know whether the DOAC is appropriately reaches levels, is clinically effective, not making individualized decisions, but probably I would feel comfortable using it, but I would typically get a trough level above a BMI of 55.

Rachel: Thank you. Bishoy, what would be your take-home message for PCPs based on this conversation of obesity and VTE?

Bishoy: Yes, thanks again for having me join. I think looking broader at obesity as a whole is again considering all the risk factors and the conglomerate of risk factors that are there, VTE being one of them. Focusing on that and not giving up, just very similar to smoking cessation, it takes time, and hopefully soon, it'll stick.

Then just the other thing is, if sticking with the appropriate labeling dosing from the FDA, if levels are drawn because we are a little unsure, just remember that those levels aren't there to drive dosing decisions, but more so, again, be a part of the shared decision making on how we proceed.

Rachel: This concludes our discussion of the use of DOACs in the treatment of obese patients with risk of VTE. I'd like to thank Stephan and Bishoy for taking the time to speak with me. Your expert advice and really the experience that you've had over the many, many years is just invaluable. I've learned so much from you both, so thank you.

This was a conversation where we really looked at the epidemiology, the guidance documents around obesity, and we really had a very rich discussion on deciding who should and should not be continued on anticoagulation.

This is one of two conversations we're having and the second conversation is going to be about bariatric surgery, DVT prophylaxis, and really special populations, and so we encourage you to listen to the second one. That'll be our next video.

Please don't forget to complete your CE evaluation to claim your CE credit. I'd really like to thank the audience for your attention, and again, to thank Stephan and Bishoy for their just excellent expertise and discussion.

Stephan: See you, Rachel. Thank you.

Bishoy: Thank you.