Practical Strategies for Long-term VTE Management in Unique Patient Populations

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Jori May: Thank you for joining us for our fourth podcast in our series on the management of venous thromboembolism in the primary care setting. So today, we're going to be digging into some special populations when we're talking about long-term VTE management. And I'll start by saying we have a great panel of folks here to talk today. We will be using our first names as we have our discussion today. And I'll introduce myself first. My name's Jori May. I am a hematologist and an Assistant Professor at the University of Alabama at Birmingham.

We'll say specifically, because we're talking about specific anticoagulants in this session, that I have no relevant conflicts of interest related to those medications. And I'll ask our two experts to introduce themselves as well. And Bill, we'll start with you.

William Braun: Yeah, I'm Bill Braun. I'm a Pharmacy Clinical Coordinator at BayCare Health Systems, also Assistant Professor for the University of Florida. And I also have nothing to disclose for this educational program.

Jori May: Right, and Stephan?

Stephan Moll: Thanks, Jori. Yes, I'm Stephan Moll. I'm an adult hematologist. I deal mostly with coagulation issues, and specifically thrombosis, anti-coagulation thrombophilia. I'm a Professor of Medicine in the Division of Hematology at the University of North Carolina in Chapel Hill.

Learning Objectives

- Outline considerations for treating VTE in special populations, including elderly patients, obese patients and post-bariatric surgery patients
- Summarize strategies for anticoagulation in woman with heavy menstrual bleeding and women with childbearing potential
- Evaluate the risk of developing COVID-related thrombosis in patients following infection with, or vaccination for, COVID
- Identify strategies for determining if a patient with a recurrent clot has experienced anticoagulation failure

Jori May: Great, well, excited to talk to you both today and we're going to just dive right in. I'll outline some learning objectives, things that we're intending to cover, and it's going to be a lot. So, we're going to try and kind of fly through those relevant topics you might encounter in your primary care clinic.

So, first we're going to talk about some unique populations that require special considerations for long-term VTE management. We're going to talk about patients of older age, elderly patients. We're going to talk about people with chronic renal dysfunction. We're going to talk about people requiring anticoagulation in the setting of obesity and potentially if they have had some sort of bariatric surgery. And then specific considerations for people with childbearing potential, women that menstruate, and how that might affect their care.

We're also going to do what we're going to call some rapid-fire topics, those other areas that you might encounter in your practice related to long-term VTE management; so, COVID-related thrombosis, what we'll call anticoagulation failure or someone who has a recurrent VTE while on anticoagulation, and then questions you might get from people who have family members that have had VTE. So, a lot of interesting things to discuss today.

Case 1: The Elderly Patient

- 70-year-old woman with history of unprovoked VTE
  - Currently on apixaban 5 mg twice daily
  - Lighter weight (55 kg)
  - Multiple co-morbidities
  - Indication for long-term anticoagulation

Jori May: So, let's dive right in and start with our first case. Let's say we have a 70-year-old woman who has a history of an unprovoked VTE. We've talked about this in our previous podcast, a lot of discussion about the duration of anticoagulation, so we won't dig into that too much more, but we're going to assume that this patient is going to require long-term anticoagulation.

She's currently taking five milligrams twice daily. And as an older person, we'll note she is on the lower side of weight. We'll say she's 55 kilograms, and she's got multiple comorbidities and is on multiple different medications. And so, I want us to talk a little bit about what are some unique considerations we need to think about in a patient of older age.

And maybe Bill, if you can start that conversation for us. Is there something in this patient that you might be thinking about more than a patient of younger age or in a different situation?

Polypharmacy in the Elderly

- Increased risk for ADEs due to reduced drug clearance
- Drug-drug interactions: effects CYP, P-gp and anticoagulants
- Risk of falls with CNS agents: benzodiazepines, medications with high anticholinergic effects such antihistamines, antidepressants (TCAs)
- Medication adherence

William Braun: One thing to consider is definitely polypharmacy, increased risk of adverse events, drug-drug interactions, as we talked about at the last session, with the effects of the hepatic through the CYP enzymes and P-gp absorption to the GI, risk of falls with CNS agents, benzodiazepines, agents that have anticholinergic effects, cause dizziness in those patients and could be at risk.

And then of course, medication adherence, that's a big one. The more medications these patients are on, the less chance, potentially, they'll be compliant with their medication. So, that's also a big one.

Low Body Weight

- Patient may be at increased risk of bleeding
  - Very little published data with low weight patients
  - Einstein trial: 75 patients < 50 kg
  - 1.3% < 50 kg vs 1% 50-100 kg
- Do not withhold based on low bodyweight
- Consider DOAC with shorter initiation phase like apixaban 7 days

Weitz JI, Lensing AWA, Prins MH, et al. Rivaroxaban or Aspirin for Extended Treatment of Venous Thromboembolism. *N Engl J Med.* 2017;376:1211-1222.

William Braun: Low body weight is another one to be cognizant of, basically potentially increased bleed risk. In the Einstein trial with rivaroxaban, they did show more severe bleeds, 1.3 percent in the patients less than 50 kilos compared to the patients that were 50 to 100 kilos, but I would not hold therapy in elderly patients, but just consider and monitor those patients more closely.

And then consider maybe a DOAC with a shorter initiation phase, like maybe apixaban seven days versus the rivaroxaban 21 days, based on low body weight patients.

Faculty Discussion

Jori May: Stephan, hearing that information from Bill, for you as the prescriber, are there things that you would consider in this patient's treatment plan that you might do differently? So, when we're thinking in the long term, are there ways to optimize anticoagulation safety for this patient?

Stephan Moll: Not really; what Bill outlined matches my practice. But before I even go into that, I just wanted to highlight, and we've discussed it before, the first question I have in any patient, and particularly in the elderly at higher risk for bleeding, is not particularly, but just as well in this patient, does she need to be on long-term anticoagulation? And you highlighted that the patient had an unprovoked VTE, and we know that women with unprovoked VTE, if it's a proximal DVT or PE, if we stop anticoagulation after three or six months or at whatever time, they have a relatively high risk of recurrence of about 20% over five years. So, my first answer is, I would like to see this patient on anticoagulation, and then the things that Bill addresses apply. To highlight and summarize what you said, Bill, is the people who bleed, have the highest risk for bleeding are women who are elderly, who are of low body weight. And this patient fits all of them. She's not really the extremely low body weight, but she is pretty light. So, I'm somewhat concerned about bleeding, plus then add to the multiple morbidities that she has. So, I kind of dislike seeing a long-term anticoagulation, but I want to see her on anticoagulation. So, that's where it comes in that after six months, I would lower her anticoagulant dose to the apixaban 2.5 milligram twice daily. Or if she was on rivaroxaban, which I think is a good option as well, I would lower her to the 10 milligram once daily. We've discussed this before, is

Stephan Moll: one of these two DOACs has a lower risk for bleeding than the other, and maybe the apixaban has lower risk, so I think my choice in her would be the 5-milligram BID until month 6 and then lower her to 2.5 BID. However, occasionally I lower patients to the 2.5 twice a day even earlier, at three months, even though that was not studied in the, you mentioned the Amplify Extension trial and Einstein Choice trial as the ones who looked at the lower dose. They looked at six months, after six months to lower the dose, but the acute treatment phase is really over by three months. So, sometimes I lower the dose at three months if the patient is at specifically high risk of bleeding.

Jori May: I think those are all great points. And I'll highlight again what I think both of you pointed out, nobody recommended making dosing changes outside of what is evidence-based and recommended. I think we do have data to suggest sometimes in these older people or more frail people that clinicians might make the assessment or make changes based on kind of a gut feeling, that this patient is going to develop bleeding or have bleeding problems. And particularly data in atrial fibrillation suggests that actually has worse outcome for patients. So, I think, Dr. Moll, you're kind of working with the data in order to support what you think is right from a clinical perspective and kind of using those time points to guide you in order to dose reduce, you know, when the data suggests that might be a safe thing to do.

Case 2: The Patient with Renal Dysfunction

- 65-year-old man
  - Baseline SCr 1.9
  - Hypertension
  - Diabetes mellitus 2

Jori May: Let's go ahead to another one. So, let's say we have a 65-year-old man who comes in and has a creatinine of 1.9. Let's say he has some chronic kidney disease related to hypertension and diabetes. And so, this is a question we get frequently. And Bill, maybe you can speak to this a little bit. What do we know about the direct oral anticoagulants in people with renal dysfunction? What are our options here? Are there some agents that are more preferred than others? If you can kind of go through some of those details for us.

Faculty Discussion

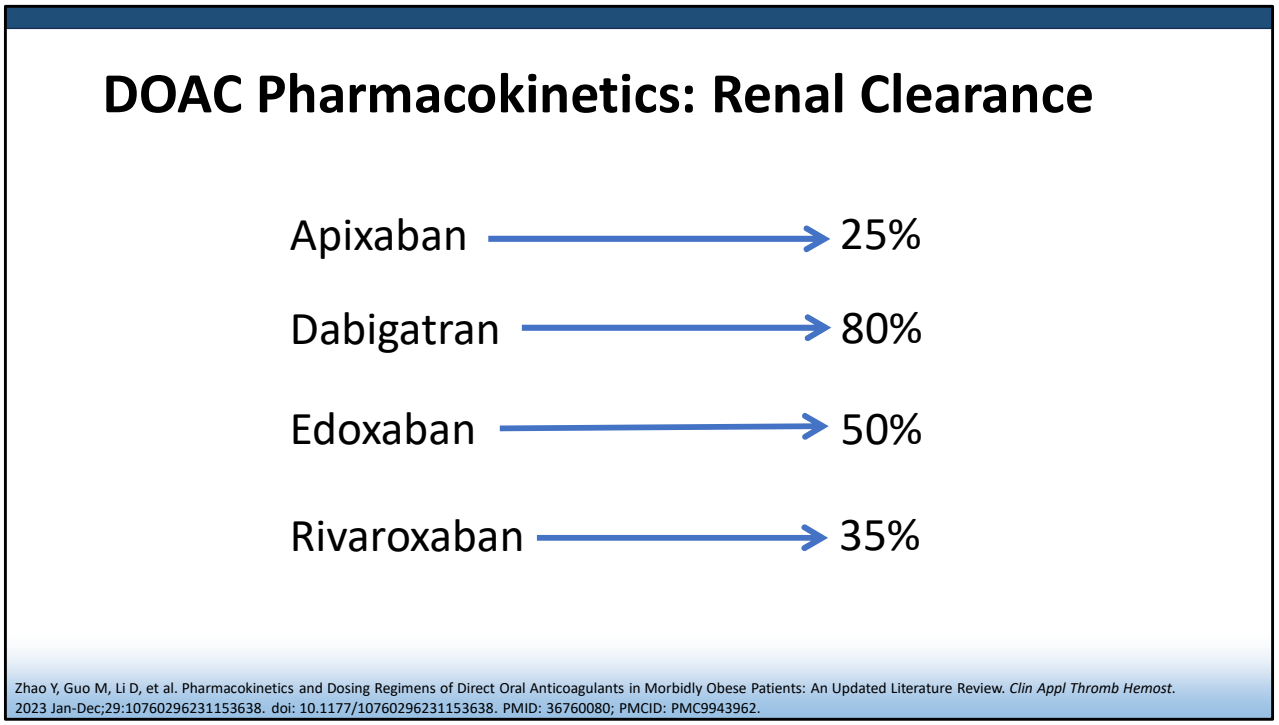
William Braun: Yeah, so basically, most of the data we have in dialysis patients with DOACs, specifically with apixaban is the only one we really have good data with, is in AFib. And so, we have some retrospective trials in VTE, and they did show basically reduced VTE and decreased bleed rate compared to warfarin, but we don't have any controlled randomized trials with VTE. With that said, though, apixaban does show potentially, 2.5 milligrams BID and 5 milligrams BID have been studied in these retrospective studies and could be an option in patients on dialysis.

Stephan Moll: So, Bill, you're referring to patients with dialysis already. What about the more slightly decreased GFR, less than 30, but not dialysis-dependent? What's your thinking about use of either rivaroxaban or apixaban or for that matter, dabigatran?

William Braun: Yeah, I would say apixaban. There's more data for sure. And 5 mg BID, probably in that particular patient population with less than 30 would be an option. And of course, warfarin always would be an option. 20% reduction in those patients usually is recommended as another option.

Faculty Discussion

Stephan Moll: So, that matches my approach that in patients with a GFR less than 30, my preference clearly is to go to apixaban. And I would also use apixaban in the patient with renal failure on either hemodialysis or peritoneal dialysis. And I typically would use, or think in my mind, about the five milligram twice daily, even with renal dialysis, if the patient are more on the well-to-do body weight, higher body weight side, lower risk for bleeding and somewhat younger, and for other reasons, lower risk for bleeding. But I would use a lower dose, a 2.5 BID, in general, in the more elderly, the more fragile, the higher risk for bleeding, and the females that we mentioned earlier. I would not use rivaroxaban, or dabigatran, clearly, in end-stage renal disease.



Stephan Moll: And maybe we should point out at this point, the reason being that dabigatran is 80% cleared in the kidney, the rivaroxaban maybe a third, 33%, and the apixaban is the least at about 25%. So, apixaban is the preferred go-to drug in this situation.

Faculty Discussion

Jori May: You know, I think there's been a lot of debate about what to do in VTE, particularly in really lower renal function and even ESRD. And a lot of the data is extrapolation from AFib. I think it's worth highlighting that we don't have randomized data to guide us in the VTE space. So, we're often guessing. And I think I see discussion of, you know, like Stephan said, do we use the two and a half milligrams twice daily? Do we do the five milligrams twice daily? And I like that you guys presented an approach that's somewhat in between really kind of catering to the patient, but recognizing that this is a really challenging patient population to treat. And regardless of what we do, if this patient is on warfarin or a direct oral anticoagulant, we see a very high risk of bleeding. So, I think that's important to acknowledge. And again, to the point that was made earlier by Stephan is that we really need to make sure that this patient actually needs anticoagulation because anticoagulating patients, particularly that are ESRD is a dangerous business and puts these people at high risk for bleeding issues.

Case 3: The Obese Patient

- 65-year-old man with unprovoked VTE requiring anticoagulation
  - 145 kg
  - BMI 45

Jori May: So, we're moving on, another special population, one that we encounter frequently is our patients that are of larger body size. So, let's say we now have a 65-year-old male with an unprovoked VTE that needs long-term anticoagulation. We'll say he's 145 kilograms with a BMI of 45. Stephan, can you talk to us a little bit about what we know about the direct oral anticoagulants in obese patients and really how that literature has evolved over recent years?

Faculty Discussion

Stephan Moll: Yes, and I'll start off with saying in 2024, what's appropriate to do? It's appropriate and okay and safe to use apixaban or rivaroxaban, even in the severely obese patients, period. Dabigatran doesn't have data, so I would not use it in the severely obese patients. Historically, and it's still, it's not that long ago, I think that was in 2015 or 2016, there were very limited data on the use of the direct oral anticoagulants in the severely obese patients, i.e. a body weight above 120 kilos or body mass index above 40. And there was a guidance document, and I was a co-author on that one. After review of the literature with the International Society on Thrombosis and Hemostasis, ISTH, that stated, above a body weight of 120 and above a BMI of 40 to not use the DOACs because we didn't have sufficient data to say this is appropriate and safe, but the preference was to use warfarin. But triggered by that publication, I like to say that it was triggered by that, additional studies came out.

And the ISTH, and again, I was involved in that, came out with an updated guidance document on the same topic, which is now about from two years ago, I think, 2021, which then stated, how I started off that sufficient data on apixaban and rivaroxaban to use it in the severely obese patients, insufficient data for dabigatran and for Savaysa . Then, what about if a patient had a BMI that's really extreme, the BMI above 55 or 60? And I've been involved in what was called, not by us, an expert panel discussion and it led to a publication. And there were different opinions. It was a group of hematologists, some pharmacists, somewhat different opinions in the severely obese patients where the one should do a drug level blood level testing. I'm somebody who tends to get a trough level in these very severely obese patients above a BMI of maybe 55 or 60. And it's a trough level because that's always reliable..

Stephan Moll: …just before the next dose. Peak level is not meaningful because the absorption can be at peak at three hours, four hours, or five hours. So, what I'm looking for is, at trough, is the patient's apixaban or rivaroxaban level roughly in the expected published range that I feel more comfortable?. Yes, this patient is absorbing well and is appropriately anticoagulated, but not everybody does that. Half of, I think about half of the experts do that. Others feel comfortable just using it independent of any trough level.

Jori May: So, a couple questions on that. So if, say, I am a primary care provider and I wanted to check a trough level in a patient, what is the lab order that you use? Is there a specific send out lab that you use? And how do you know what range is appropriate?

Stephan Moll: Good point. For most institutions in private practice and not academic hospital-based, it's a send-out test to whatever lab they use, the LabCorp or the Mayo referral app, etc. And then the lab does, typically, an anti-Xa assay. And they provide you with a result, such as 30 nanogram per mL – or, nanogram per deciliter, I think. And they list in their common field from a published, from published studies the expected trough range would be in this and that range so that you can compare it to that one.

Jori May: It's really helpful. And so in your…

Stephan Moll: It's nanogram per deciliter. That's embarrassing to, on a podcast, you have to think twice about that. But anyway….

Jori May: Well, we don't think in units very often. I will say in my institution, sometimes too, that we can send out for mass spec. And I think I'm not sure exactly how that's quantified either, even though I send for it. So, I understand.

Stephan Moll: Well, it's reported, that one I can answer, Jori, it's reported in the same nanogram per deciliter, and it's a more accurate level for the really low values. So, it's clearly not the wrong thing to do. Typically, you don't get it back as quickly because they only run it once per week. The anti-Xa assay is much more widely available. Classically, the labs do the anti-Xa level that is fairly reliable down to a value of 15 or 20 or so. And that's sufficient.

Jori May: And so, I guess to clarify very clearly in your practice, do you have a threshold? So, what BMI is when you decide to send a trough level?

Stephan Moll: Roughly 55. Nothing is written in stone, but BMI above 55, and I typically look at the BMI rather than the body weight, which you could argue has some downsides, too. But since this is not all that scientific, it's more, that's what I do, and others don't even do that, or take a BMI of 60. Anyway, 55 is for me the kind of value.

Jori May: Bill, I'm interested to hear, is that similar to what you see in practice or are there different approaches that you've encountered or that you tend to use in your personal practice?

William Braun: Yeah, I mean, we do order anti-Xa's. We do order that, like, like I said, like, Stephan basically said, you know, to get a baseline on those patients. So, you know, we monitor Xa's quite a bit in the, in the institution side.

Jori May: Yeah, that's a nice reinforcement.

Stephan Moll: What about you, Jori? What do you use as a BMI?

Jori May: Yeah, so I'm kind of similar. If I get into that 55 range, I start to get a little bit more uncomfortable. I do tend to send a trough level, it makes me feel better. I can't say that I've ever encountered one that was out of a range where I felt that I had to switch a patient to warfarin based on checking that. In my experience, I haven't found that. But it does provide, I think, me and the patient some peace of mind.

And it's really a relief for patients because I think for a while, I have some patients that were put on warfarin initially, because of these concerns that the medications, the newer medications, were not appropriate for them. And that was really difficult for them. So, being able to switch them, I think it's a real relief for a lot of patients.

Stephan Moll: I think an important point to make is, if the level were to be low, that would not be the go-ahead to increase the direct oral anticoagulant to a non-traditional dose. That should not be done, and everybody's in agreement with that. For me, it really, as you say, it's peace of mind, but it's also if the level is, and I've seen a couple or three patients with low, unexpectedly low values, then I start to wonder and I really ask them, did you really take it and was it really at the time that you indicated? And really, more question the compliance, the taking it in rather than think, well, the metabolism is bizarre.

Jori May: Yeah, great point. So, to clarify that point, if you're out of range, we switch to a different agent, presumably warfarin.

Stephan Moll: After you've thought, is it really, is the compliance okay? Yep.

Jori May: Yeah, as we make sure, yes. Yeah, yeah, great. Well, another issue that we run into is, what are our options for anticoagulation in the person in the setting of some sort of gastric bypass surgery or procedure. You know, that's a range of procedures now. We have sleeves, we have bands, we have the classic Roux-en-Y. And I wonder, Stephan, I know the ISTH commented a little bit on this too, if you can speak to kind of what we know about the absorption of these medications and what we'll need to consider in a patient with some sort of a gut-modifying procedure.

Stephan Moll: Yeah, all of the anticoagulants are absorbed in the more proximal part of the intestine, including some in the distal stomach and then the duodenum and proximal jejunum, with apixaban also to some degree absorbed a little further downstream in the small intestine. But any of the bariatric procedures can potentially theoretically change the absorption. Typically, you would expect that it might decrease it. The passage time of the drugs, and of food in general, is faster. The meals are smaller. The acidity is different. So, there are a variety of different changes that may lead to changes in absorption. So, the ISTH does have a section on bariatric surgery and what is maybe not so relevant for the, well, maybe it is for the primary care physician. Right after the bariatric surgery, the recommendation is to use a parenteral anticoagulant if the patient has an indication to be on long-term blood thinners or develops a DVT-PE after the bariatric surgery. So, for the first few weeks, use a parenteral anticoagulant because you know that's absorbed. Even though there's some difficulties with a lot of adipose tissues, absorption, even low molecular weight heparin is not all that reliable with it or fluctuates quite a bit. But use a parenteral anticoagulant for a few weeks.

And once that period is over, one can try a direct oral anticoagulant, but then there's a clear recommendation to test the trough level to make sure that the patient is really absorbing and is in the expected range. So, maybe more common in clinical practice is somebody who is on long-term anticoagulation for unprovoked VTE in the past or atrial fibrillation, now undergoes bariatric surgery, you need to interrupt the anticoagulation. Then think for the first few weeks, use a parenteral anticoagulant, and then only then later on, switch over back over to the DOAC and get a trough level.

Jori May: And do you think differently about say a gastric band versus a Roux-en-Y? You do not.

Stephan Moll: No, same thought process. It also, I think, is an important point. I tend to, in anybody I see in clinic, particularly more obese patients who need an anticoagulant, I tend to ask, have you had a bariatric surgery? Because sometimes they had it eight, 10, 12 years ago. Now they get started on a DOAC, and people don't consider that they had bariatric surgery, or the patient didn't volunteer it. So, I specifically try to ask for it.

Jori May: Absolutely, I think that's helpful to consider. And then weight loss is looking differently now with new medications available to assist in weight loss. And I wonder if there's any specific considerations that you think about for people who are taking these newer medications initially approved for diabetes management, but are kind of being more widely used for weight loss and if that affects anticoagulation at all.

Stephan Moll: No, so I checked on this probably four weeks ago. There are no drug interactions that I'm aware of that I saw on Micromedex. So, that's actually good. So, they can do whatever drug they use and continue their drug. Bill, do you see that differently?

William Braun: Yeah, the same. There's no real interactions with the GLP-1s and the SGL2s. You don't really see any issues with those diabetes medications or interactions.

Case 4: Women

- 23-year-old female on anticoagulation for unprovoked VTE
- Discussion required: menstrual bleeding and anticoagulants

Jori May: That's great. I think we're seeing them more frequently, so worth highlighting that we don't need to think about anything differently. So, let's move on to yet another population. So, we're going to say we have a 23-year-old female coming in requiring anticoagulation in the long term for an unprovoked VTE. And so, we've touched on this topic a little bit before, but I think it's worth us having a conversation about how to think about menstrual bleeding in people on anticoagulation.

And I think first and foremost, thinking to even ask about it, because unfortunately it's something that may not come up in conversation. The patient may be hesitant to bring it up. And we find in our practice and in the data that it's not something that's more frequently addressed. So, Stephan, I wonder if you could talk a little bit about kind of your approach in a young person like this. What are the first things that you're thinking about? What are the questions that you're asking to a patient on anticoagulation who menstruates?

Faculty Discussion

Stephan Moll: Yeah, I think the key first point is to bring it up at all. That it's something you discuss. And then secondly, in this comes, and you are too a coagulationist, we see women with bleeding disorders, von Willebrand's disease and what have you. It's trying to get really a quantification of how much do they bleed.

Questions That Support Quantification of HMB

- How many total days do you bleed?
- How many of those total days are heavy?
- On those heavy days, how often do you change your protection?
- Do you have to double up?
- Do you bleed through?
- Do you miss school or work?
- Have you had blood transfusions?
- Have you had IV iron?
- Have you had anemia that required you to take oral iron?

Stephan Moll: And I ask how many total days do you bleed? How many of those total days are heavy? On those heavy days, how often you change your protection? Do you have to double up? Do you bleed through? Do you miss school or work? Have you had blood transfusions? Have you had IV iron? Have you had anemia that you required oral iron?

Faculty Discussion

Stephan Moll: So, get those questions answered that you get some idea, yeah, there's pretty significant bleeding. After that, you obviously get your CBC and your ferritin back and you see, is the patient anemic or not? And then one can talk about if they need, well, this patient needs anticoagulation, what kind of treatment options and how can we deal with this?

Jori May: Yeah, I think that's really important. I think oftentimes providers will ask the question, is your menstrual bleeding heavy? And we know that that's really insufficient because a person only knows how heavy their menstrual bleeding is relative to themselves. It's not something that's frequently compared. So, asking very specific questions can be really helpful.

And so, Bill, I wonder if you could take us through, we have a patient in our office who's on anticoagulation and experiencing heavy menstrual bleeding. We have some limitations to what medications we can use to control that, but we do have a lot of great options. I wonder if you could speak a little bit about what the pharmacologic options are for people with heavy menstrual bleeding on anticoagulation.

William Braun: Yeah, sure. Yeah, the progesterone class for sure. Levonorgestrel is one we can use in those patients, which basically will help with the menstrual bleeding. And then also one factor to look at is the type of anticoagulant.

Anticoagulant Risks of Menstrual Bleeding

Relative risk of heavy menstrual bleeding by choice of oral anticoagulant in women aged ≥18 years

Oral Anticoagulant	Incidence of Uterine CRNMB/MB	Relative Risk
Warfarin	4.5% - 9.6%	Reference
Apixaban	5.4%	1.18
Edoxaban	9.0%	1.26
Rivaroxaban	9.5%	2.10*
Dabigatran	4.7%	0.53*

*Statistically significant, $P < 0.01$

Godin R, Marcoux V, Tagalakis V. Abnormal uterine bleeding in women receiving direct oral anticoagulants for the treatment of venous thromboembolism. *Vascular Pharmacology.* 2017 Aug 1;93:1-5.

William Braun: There's observational studies here looking at the risk of menstrual bleeding with each agent. And dabigatran actually is one of the lower ones, of course, and then apixaban could be a good option if someone was on another agent to switch to. And so those are some of the main changes you can do, to help with that, as well.

Hormone Therapies

- Subdermal Implant 20% amenorrhea
- Depo-medroxyprogesterone acetate
  - 55% amenorrhea rate at 1 year (associated with 3.6-fold increase in VTE[1])
  - Caution as last for 3 months

1. van Hylckama Vlieg, A et al. *Arteriosclerosis, Thrombosis, and Vascular Biology.* 2010;30:2297–2300.

William Braun: Other options, you know, subdermal implants, of course, have been used. And then, of course, depo-medroxyprogesterone, or Depo-Medrol, is an option but usually that patient has a higher risk of VTE with that agent. And so, I would use caution maybe towards the end of a VTE treatment cycle, not early on because of that risk with that particular agent. So, those are a few options.

Faculty Discussion

Stephan Moll: And maybe it's – so, I think the progestin IUD is the first typically go-to method, great for contraception, great for menstrual bleeding. What is also worthwhile to mention is the patient is on anticoagulation, so protected more or less from blood clots, and increasingly, we, in the last three, four, five years or so, we've realized it's probably okay to even give estrogen contraceptives unless the patient is very prothrombotic. Certainly, I would start with the lowest risk and that's why we talk about the progestin IUD or the rods that you can implant or then as you say, the depo progestin shots. But certainly the estrogen pills are not completely out of the picture. If the woman is done with, not this 23-year-old, well, maybe, maybe not. But if the woman is done with childbearing, to think about endometrial ablation procedure as well to deal with heavy menstrual bleeds. The gynecologists also like to use progestin as an oral drug. And then you can also argue, even though it's prothrombotic, the patient is protected with anticoagulation. But I think that is a discussion, probably when the women bleed that heavily, it may be a discussion with definitely gynecology and maybe already hematology involved at that point.

Jori May: Yeah, I think we know that there are institutions that have the ability to have these multidisciplinary clinics where OB-GYN and hematology get together. That's an ideal, but that doesn't always happen. So, you know, for a primary care provider dealing with these issues, you know, working, trying to get into contact with an OB-GYN that's also seeing the patient in order to come up with a plan that may include medications, may include procedures, I think is really important.

Jori May: And Stephan, I want to highlight what you said, about the use of estrogen while on anticoagulation because the situation that we often see is that a patient that is on an estrogen-containing OCP comes in with a VTE, and that estrogen is immediately stopped and the patient is immediately started on anticoagulation. And I unfortunately have seen many women come into my office that come in with a hemoglobin of six, that all of a sudden, we have exacerbated their menstrual bleeding with anticoagulation and we have removed something that was previously controlling it.

And so, the data does suggest that in the setting of an acute VTE, we can keep that, ideally you keep that estrogen-containing OCP while we establish the patient on therapeutic anticoagulation. And if we want to transition, that we come up with a plan to do that in an organized fashion so that we don't precipitate more heavy menstrual bleeding, more iron deficiency. There's a lot of system-level issues with that. And you know, a patient coming to the emergency department, understandably, there's a desire to get rid of that estrogen so there's no confusion, that the patient's not taking the anticoagulation. But in someone who is established in a primary care office, I think it is important to remember that we can keep that estrogen around, if we do want to transition to another agent, ultimately, to make sure that we don't run into more issues.

Stephan Moll: Good point, and Jori, maybe at this point as well, worthwhile to highlight that real good follow-up with a CBC and with a ferritin in those heavy bleeding patients is good that we discover iron deficiency early enough, and then not necessarily muck around with oral iron for a prolonged period of time, but think about intravenous iron much earlier. This is an issue that I see in clinical practice so frequently, women who then just had heavy bleeding and they went for weeks and months and people tried the IUD and then this and that and that and they were anemic and iron deficient and felt fatigue and people tried with the oral iron instead of quickly thinking about intravenous iron which is so easily available these days.

Jori May: Yeah, I think that's a wonderful point and important to emphasize. And remembering just as a quick iron deficiency overview that ferritin is going to be your best measure of iron deficiency and that our normal ranges for ferritin in our hospital labs are often unreliable. But if you see a ferritin less than 50 in an iron deficient patient, even if your normal range says it's normal, it's not. A ferritin less than 50 is iron deficiency. So, really being aggressive about treating iron deficiency I think is a real service to the people who are experiencing this, just because there's real risk that comes with them being that anemic. Fortunately, we see these people getting transfused, and transfusion, particularly in people of childbearing age, comes with risks. So clearly, this is an issue that gets me talking. So, I just want to emphasize that aggressive treatment of iron is really a great opportunity to improve care for these patients.

Jori May: I want to highlight too tranexamic acid as an option. And Bill, maybe you could speak a little bit. I think people get a little bit uncomfortable with tranexamic acid because of thrombotic risk. But that being said, this is something that certain providers in hematology were a lot more comfortable using even in people with thrombotic history. Can you speak a little bit to the back and forth that we run into with this medication?

William Braun: Yeah, so the orthopedic surgeons use it all the time for anemia management and then in trauma, we use it in the ED. And so, there was always that risk of VTE, but we really have not seen the VTE and the studies really haven't shown increased risk of VTE in those scenarios. However, we don't have a lot of data in treatment of VTE and using it in women that, you know, have menstrual bleeding. So, there's not a lot of data for that, but the overall VTE risk seems to be lower than what we initially thought.

In this particular situation, you'd probably reserve it for like a last resort if patients weren't responding to hormonal therapy, because it can potentially have a risk of VTE. But typically, I don't see it too often in the inpatient setting here.

Stephan Moll: Can I add a word on that? So, I would even lessen the concern about thrombosis. I mean, as you say, it's been used in orthopedic patients who had high risk for DVT-PE after knee and hip replacement or fracture surgery. And there have been good trials in orthopedics that the tranexamic acid did not increase risk for VTE. The problem arises, it's still listed on the black box warning with tranexamic acid. So, I've had times when I...there was a woman with heavy menstrual bleeding on anticoagulation, I prescribed the tranexamic acid. They tried to get it and then the pharmacist told them, oh no, we can't give that to you. It is contraindicated to you, you've had a blood clot before. In the hematology world, there is no real concern about DVT-PE, so I would really lessen that concern very much and I wish it was taken off the black box warning.

Jori May: Absolutely. It is something that I use in my practice and people on anticoagulation with a VTE history because I do feel comfortable in the safety data regarding that. But it's a lot of medication to take. It's taken frequently, so that can be really difficult, particularly for young people. So, certain limitations for sure, but worth recognizing as a great option.

Case 4: Women

- 23-year-old female on anticoagulation for unprovoked VTE
- Discussion required: menstrual bleeding and anticoagulants
- Patient returns to the office, is now pregnant

Jori May: Let's say now this same 23-year-old patient who has a history of VTE is on anticoagulation, calls your office to let you know that she's pregnant. So, Stephan, can you speak a little bit about kind of counseling about pregnancy? Even at the time of VTE, do you bring it up? Or if you do, what are the things that you highlight to a patient even before they become pregnant if they are on anticoagulation and have a history of VTE?

Faculty Discussion

Stephan Moll: So, I do bring it up because it's a significant concern for women, for the younger women who wonder, I would like to have a family. Now I've had a clot, what does that really mean? I'm on blood thinner. And in my assessment, which is very structured where I talk about first, in this case, venous thromboembolism, there is a, and whatever else problems they have, there is a paragraph, women's health issues, where I talk about contraceptive choices. And I do mention, as we said, the progestin IUD.

I do mention that you should not get pregnant on the DOAC because DOACs may cross over to the baby given the size of the molecules and that you should be on in the future pregnancy if you want to get pregnant. We need to switch you over to low-molecular weight heparin when you try to get pregnant and then you would be on low-molecular weight heparin throughout pregnancy and then after delivery you would…if you breastfeed, you would remain on low-molecular weight heparin because the direct oral anticoagulant crosses over in the breast milk. But if you don't breastfeed, then we can switch you back to a DOAC after delivery. The dosing of the anticoagulant in pregnancy, we can talk a little bit more in detail, but it's this overall approach. Yes, don't get pregnant on the DOAC. Have good contraception. If you get pregnant, this can be done, can be safely done. But we would want to switch to low-molecular weight heparin beforehand, get it through a pregnancy, and afterwards, let's talk about breastfeeding. You can do that if you remain on the low-molecular weight heparin.

Jori May: I think it's nice to highlight too another reason to be very cautious about what we do with contraception around this time because pregnancy is more complicated in these patients and so if we immediately withdraw that birth control we could run into even more issues. And so, Stephan, you highlighted kind of the nuances of anticoagulation management during pregnancy and after, but I wonder, Bill, if you could dig in a little bit deeper from a pharmacy perspective of you know, what do we know about what are our anticoagulation options in pregnancy, the safety associated with those, and how that changes kind of over the course of pregnancy and after delivery.

Anticoagulation Pregnancy/Postpartum

- Heparins: recommended as they do not cross the placenta and will not cause fetal anticoagulation
- LMWH preferred over heparin except if CrCL <30 mL/min and if near delivery (surgery, neuraxial anesthesia)
- Heparin-induced thrombocytopenia (HIT): Fondaparinux
- DOACS should be avoided with increased reproductive risks in animal studies (insufficient human safety data)
- Warfarin should be avoided; crosses placenta, is teratogenic

William Braun: Yeah, Stephan kind of highlighted, the heparins are pretty much the go-to agents during pregnancy because they don't cross the placenta and will affect the fetus basically. And so yes, that's pretty much the recommendation.

Low molecular weight heparin is preferred, obviously, in pregnancy unless you run into situations where you have a low creatinine clearance, less than 30, and then potentially you need to be switched to heparin. And HIT situations, fondaparinux is an option as well.

And again, once the patient's not breastfeeding and is past pregnancy, then you could eventually go to the DOACs like he summarized earlier would be an option.

And then a warfarin actually could be an option as well, once the patient has delivered. You would not want to use that during pregnancy because it can be teratogenic as well.

Jori May: All to highlight, having these conversations early at VTE diagnosis is ideal and really in anybody on anticoagulation for any reason, just because this is so complicated.

Case 5: COVID

- 65-year-old male
- Develops proximal left lower extremity DVT
  - 3 weeks after COVID infection without hospitalization

Jori May: Well, we have a couple other scenarios we're going to call a little more rapid fire. So, we've dug into some of the complex scenarios in detail, but there's some other special populations that we often run into. And so, first let's talk about COVID.

So, we've all encountered this in our practice. A 65-year-old patient with a proximal left lower extremity DVT, we'll say about three weeks after a COVID infection. During his infection, he did not end up in the hospital. He was managed at home, but that DVT developed three weeks later. And Stephan, I wonder if you could speak a little bit about how you determine, is this a COVID-related thrombosis or, and therefore you could keep this patient on anticoagulation for a limited period of time? Is this a major transient risk factor? And how do you make that distinction in a patient like this?

Faculty Discussion

Stephan Moll: Commonly people want to simplify that and just tell me, did the COVID cause a clot, then we'll stop, or is it just coincidental and then it's an unprovoked clot and we treat long-term. And it's not that simple, but it's also not difficult. There are two aspects to what you want to know as a clinician. Number one, how sick was the patient with the COVID? We know that really sick patients who are hospitalized, particularly in the ICU, they are at significant risk for blood clots with COVID. That was big three, four years ago, the inpatients with DVT and anticoagulation issues. Whereas we know that the outpatient who's not very sick with COVID can be managed at home or has minimal symptoms or is even incidentally discovered, they are at extremely low risk for VTE. So, it matters how sick with COVID they are.

So, I want to know first, how sick were you with it? And the second part that factors into it, what is the patient, the individual patient's risk for VTE independent of COVID? Are they obese? Are they on birth control pill? Have they had recent long-distance travel? Do they have a family history of clot? Have they had a previous clot? So, it's the individual VTE risk factors. And those two together make me conclude, yes, it's the COVID that caused it. For example, the patient, not this one that you just talked about, but a patient was in the hospital with, in the ICU, and had severe COVID, and then five days later has a clot. Yeah, that's COVID-associated. That's a major transient risk factor. Three months is appropriate, or maybe six months, three to six months, and we stop.

Stephan Moll: Whereas the patient that you just described, three weeks ago, they had COVID, they were not very sick. They were not even bedridden at home. They walked around, they just had a sore throat. That COVID didn't play much of a role. That's a minor contributing factor. That's much more of an unprovoked VTE. And one just needs to keep in mind, not anymore, but COVID was, maybe it's still very prevalent. I just don't get exposed to that much anymore. But COVID is common and clots are common. So, the simultaneous occurrence is fairly common too.

And that's even more important, and we'll talk about that with vaccines. But two things, how sick were they? And then what are the patient's individual risk factors? That will determine where in the, if I may bring that up, the recurrence triangle. And if somebody wasn't on the previous podcast, it's podcast number one or two. Two.

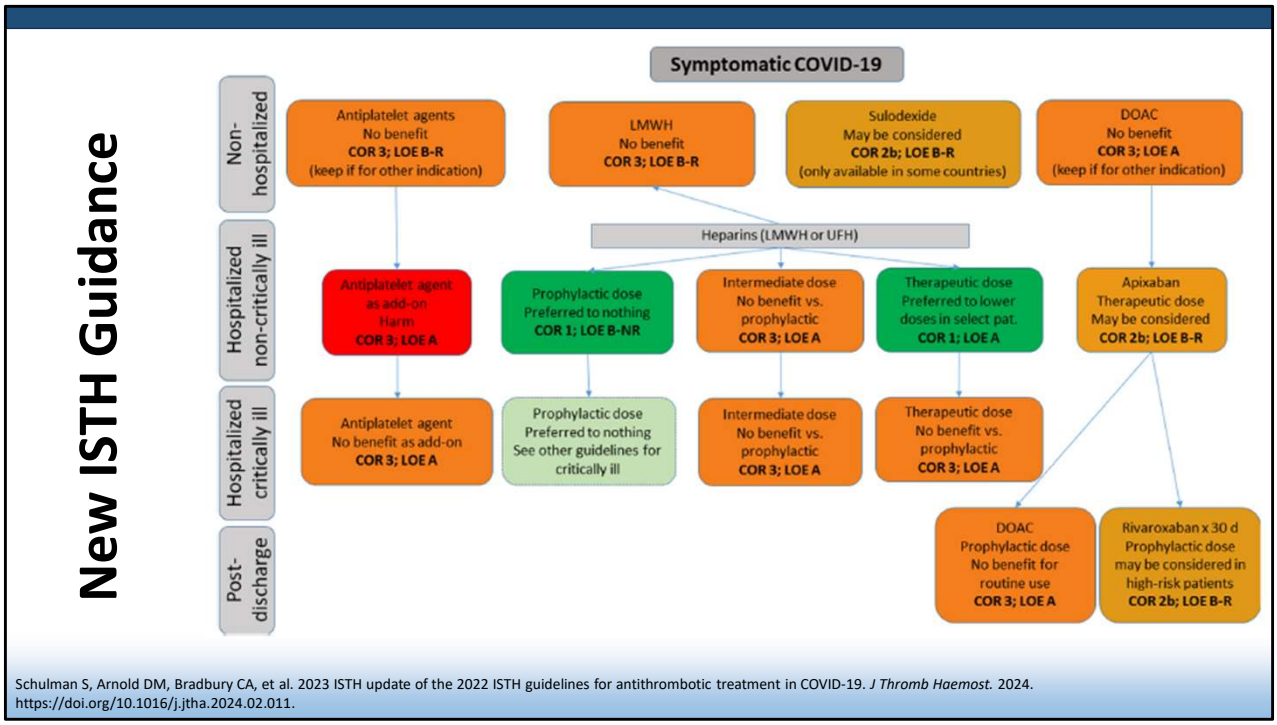
Jori May: Two. I think two.

Stephan Moll: It's a concept that I use how long to treat a patient with anticoagulation, and helps me think long-term versus short-term anticoagulation, the recurrence triangle.

Jori May: And do you consider if the patient was vaccinated or not, or maybe a COVID case now versus a COVID case, a different viral variants back in 2020, does that enter into your triangle at all, or it's really about kind of the patient's symptoms regardless?

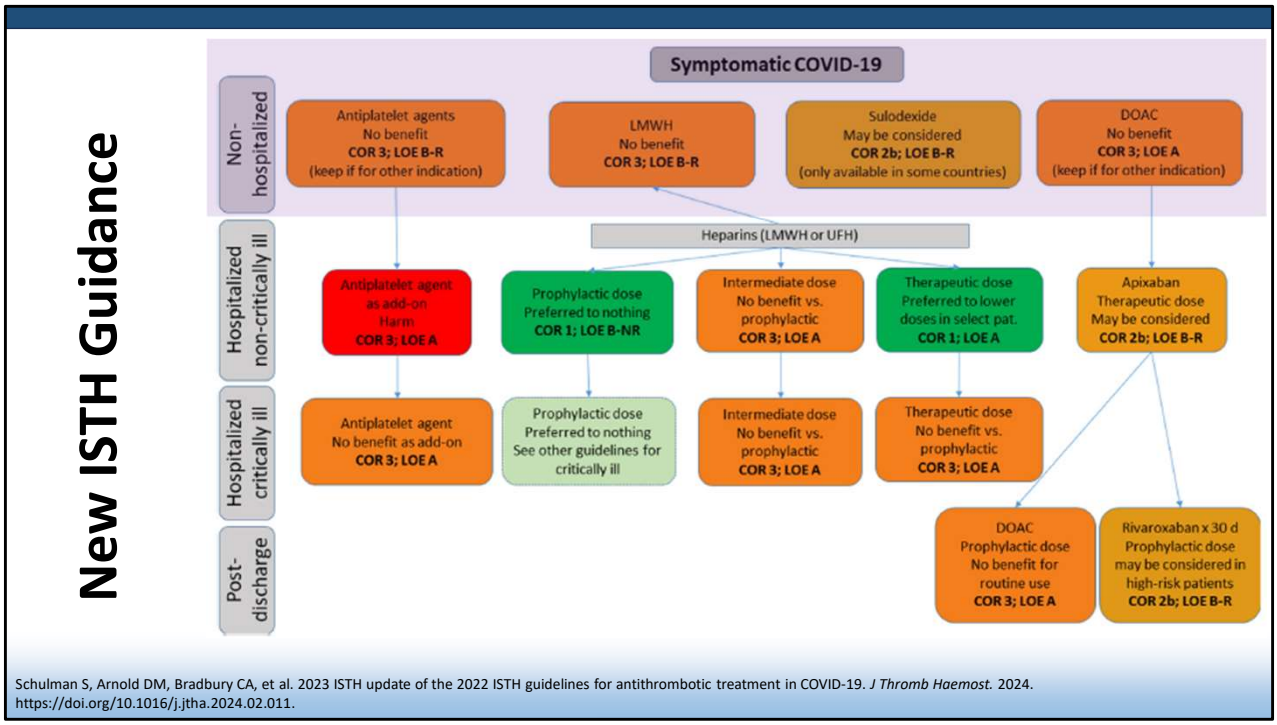
Stephan Moll: Well, it's really the symptoms, how sick were they, were they admitted. I think the question that you're also asking kind of indirectly is, are the current variants of COVID less pro-thrombotic? And I don't know. I haven't seen any data on that. But maybe I've also lost a little enthusiasm about the blood clots in COVID issue. But I don't, and sorry to say that so bluntly, I was involved for three years with the anticoagulation, prophylaxis regimens in the hospital. At some point, you just want to move on.

Jori May: Understandably.



Schulman S, Arnold DM, Bradbury CA, et al. 2023 ISTH update of the 2022 ISTH guidelines for antithrombotic treatment in COVID-19. *J Thromb Haemost.* 2024. https://doi.org/10.1016/j.jtha.2024.02.011.

Stephan Moll: However, it's still relevant because people do develop COVID and it's still the question who should get anticoagulation and who should not, prophylactic anticoagulation. And it's worthwhile to say that just, I think last week, and I just saw it a few days ago, the new ISTH guidance has come up, an updated version of who with COVID infection should get DVT prophylaxis. And I need to look at that. I get it just systematically and then we can quickly go through it.

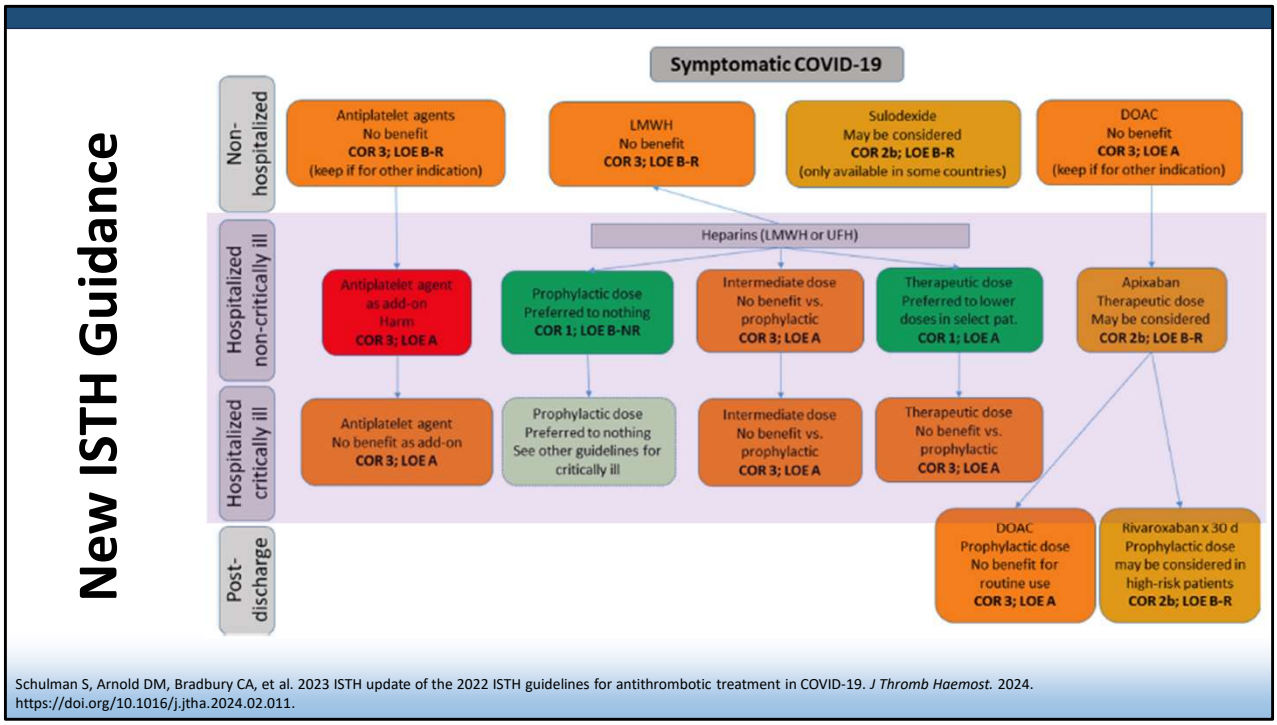


Schulman S, Arnold DM, Bradbury CA, et al. 2023 ISTH update of the 2022 ISTH guidelines for antithrombotic treatment in COVID-19. *J Thromb Haemost.* 2024. https://doi.org/10.1016/j.jtha.2024.02.011.

Stephan Moll: They talk about non-hospitalized patients who have symptomatic COVID-19, so non-hospitalized. So, they're not very sick. And as I said earlier, they're not at very high risk for VTE. So, intuitively, automatically, we're thinking, they don't need DVT prophylaxis. And that's true. And the ISTH says there's no benefit of giving them aspirin. That doesn't help.

There's no benefit of giving low-molecular weight heparin.

And they say there's no benefit of giving direct oral anticoagulants. So, outpatients, symptomatic, are not sick enough to be in the hospital. They don't need any prophylaxis.

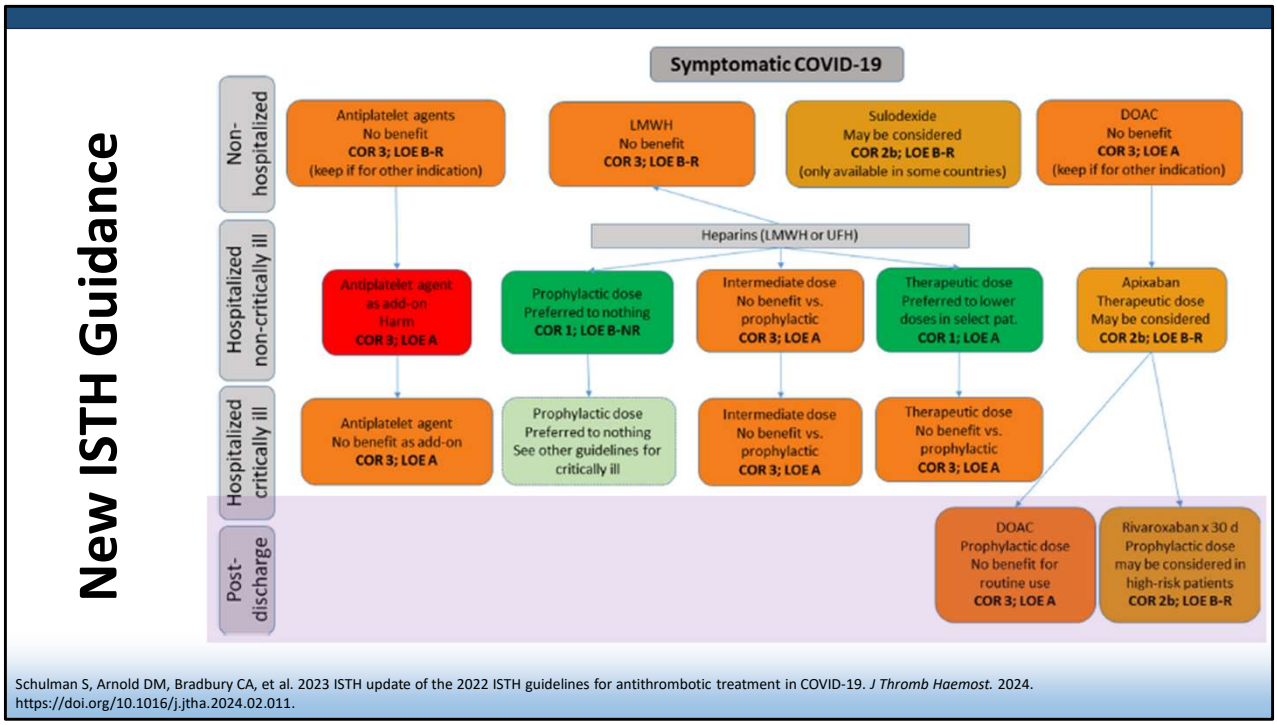


Schulman S, Arnold DM, Bradbury CA, et al. 2023 ISTH update of the 2022 ISTH guidelines for antithrombotic treatment in COVID-19. *J Thromb Haemost.* 2024. https://doi.org/10.1016/j.jtha.2024.02.011.

Stephan Moll

And when they're in the hospital, and I would think that most of our listeners are not hospitalists, but certainly this ISTH guidance document is available and that gets a little more differentiated who gets prophylactic and who gets full dose anticoagulation. But many of them need prophylactic anticoagulation.

After discharge from the hospital, people are at somewhat higher risk because they had COVID, they were hospitalized. Again, it depends on how sick were they within the unit and what individual risk factors do they have.



Schulman S, Arnold DM, Bradbury CA, et al. 2023 ISTH update of the 2022 ISTH guidelines for antithrombotic treatment in COVID-19. *J Thromb Haemost.* 2024. https://doi.org/10.1016/j.jtha.2024.02.011.

Stephan Moll: It's certainly in the more prothrombotic individuals, the higher risk people, prophylactic anticoagulant is appropriate.

And the ISTH guidance document, and I need to look at this here a little more in detail, they say rivaroxaban for 30 days may be considered in the high-risk people. And they said prophylactic dose in the normal risk, a lower risk people is not beneficial after discharge.

Jori May: Well, it's helpful to mention and I think to think about, you know, that in those, you know, high-risk patients that really prophylaxis is still part of the conversation. It's still a really nuanced decision. There's not a 100% right answer here, but that we do see a thrombotic risk, particularly in these hospitalized patients. And so worth highlighting that.

Case 6: COVID

- 65-year-old male
- Develops proximal left lower extremity DVT
  - 3 weeks after COVID infection vaccination
  - Patient is concerned VTE is due to the vaccine

Jori May: And maybe a very brief comment, Bill, on COVID vaccines and thrombosis. There's a lot of information out there, some of which may be somewhat misleading. So, I wonder if you could briefly summarize, you know, what do we know about the thrombotic risk with COVID vaccines? Is that something for concern and how primary care doctors might counsel their patients about it?

COVID Vaccines and Thrombotic Risk

- Vector vaccines vs mRNA COVID vaccines
- Vector vaccines have been associated with VITT thrombotic events associated with thrombocytopenia (similar to HIT with antibodies directed against platelet factor-4 [PF-4])
  - ChadOX1 nCoV-19/AZD1222 (AstraZeneca COVID-19 vaccine, not available in the US): Europe only
  - AD26.COV2.S Janssen COVID-19 Vaccine (Johnson & Johnson vaccine): was available under EUA status but currently not available in the US

William Braun: So most of the data that we saw, it was more with the vector vaccines, which are no longer available in the United States. So, they had the highest risk, the AstraZeneca vaccine in Europe. It was associated with a lot of VTE episodes, and then the Johnson & Johnson seemed to have a higher incidence as well. But the vector vaccines don't seem to really work as well with these variant strains. And so, they've kind of fallen out of favor. And basically, they had an emergency use authorization early on, but they did not get granted FDA approval.

Faculty Discussion

William Braun: We have the mRNA vaccines now, which we really don't see the risk, although still maybe a slight risk, but not like we saw with the vector vaccines. So, that's something to really educate your patients about that with regards to risk.

Jori May: And I think that's just important to highlight that we know the virus itself does come with a thrombotic risk, that is clear, and that the available vaccines really don't. And so, I think I use that kind of as information when I talk to patients, so that if they're concerned about thrombotic risk, you know, really encouraging them to consider vaccination because we think that, again, the symptom burden might correlate with the risk of thrombosis.

Case 7: The Recurrent Clot

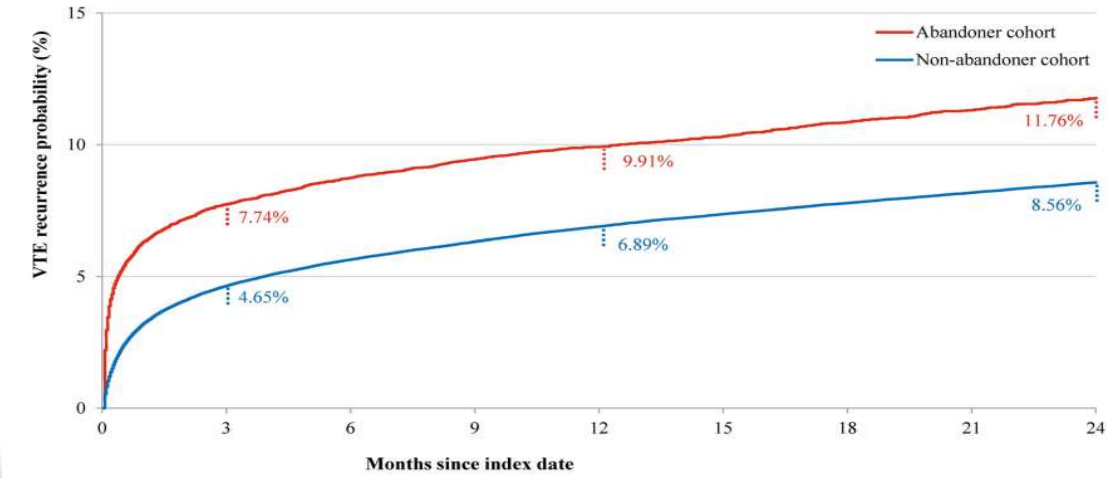
- Patient with a history of provoked DVT in the right lower extremity
- Presents with RLE pain
- Ultrasound is concerning for recurrent clot

Jori May
So, let's move to another topic in our rapid-fire review of recurrent clots. So, this is something we encounter quite frequently is a patient that's got a history of a provoked DVT in the right lower extremity, comes in with right lower extremity pain and the ultrasound is concerning for a recurrent clot. And Bill, I guess my question to you is, does anticoagulation fail? We hear about these agents, we have our patients taking them, how likely is it that a patient taking their blood thinner consistently is going to develop a recurrent blood clot?

Faculty Discussion

William Braun: Yes, it's kind of low. I mean, most of the time, the reason why there's recurrence is usually a compliance issue. And a lot of those are longitudinal studies that were retrospective studies that have looked at that as well. And compliance is a major factor.

Medication Compliance and Recurrent VTE



Venous Thromboembolism Recurrence Among Patients Who Abandon Oral Anticoagulant Therapy in the USA: A Retrospective Longitudinal Study (nih.gov)

William Braun: And the incidence could be between 90 to 73% recurrence rate when patients aren't taking their medications. And again, there's a lot of factors, cost, like I said, we talked about in some of the other sessions that need to be looked at.

But compliance, and compliance with medications is a huge factor with anticoagulation not working.

Faculty Discussion

Stephan Moll: And Bill may be correct that that's the most common reason for failure, but equally important is the question, is it really an anticoagulation failure? And that's what we see in clinical practice. A patient develops more leg symptoms, then gets a Doppler ultrasound. Not at my institution because we have a superb Doppler ultrasound lab, but then the ultrasound lab says, DVT present in the right popliteal vein.

You think, well, the patient had a right popliteal DVT two years ago, that's why he's on anticoagulation. Is it really the old scar tissue or is it a new clot? And while Doppler ultrasound, and we discussed it in a different podcast in an earlier one, the Doppler ultrasound can to some degree and relatively well differentiate between chronic scar tissue and acute clot, the certain criteria how they look. A number of labs just report DVT present and then you don't know is it acute or is it a clot.

So, my first question always is before I even wonder, why did the patient have a recurrence and compliance and all that, is it really a new clot or not? And then if it is indeed a new clot, which can be difficult to determine, we go by those three criteria, acute is dilated vein, hypoechoic clot appearance, and the sponginess on compression. And then typically it is worthwhile to get a D-dimer at the same time. A positive D-dimer argues, is one of the reasons that it could be an acute clot. It doesn't prove it. Negative is one of the arguments. It's not an acute clot. It does not disprove it. And only if then I say, well, this really seems to be a recurrent clot in spite of anticoagulation, then I start to wonder why could this be?

Causes of Anticoagulation Failure

Pseudo-failure	True Failure
Misinterpretation of Doppler ultrasound or chest computed tomography angiography	Cancer[18,19]
	Antiphospholipid syndrome[20,21]
	Established myeloproliferative neoplasm[22]
Subtherapeutic anticoagulation (due to suboptimal adherence; inappropriate dosing; drug interactions lowering efficacy of direct oral anticoagulants)[2-4]	JAK2 V617F mutation positivity without established myeloproliferative neoplasm[23]
	Heparin-induced thrombocytopenia in the patient on heparin or with recent heparin exposure
	Unexplained

Reeves BN, Moll S. Anticoagulation Failure in Venous Thromboembolism: Should We Test for JAK2 V617F or CALR Mutations? *The Hematologist.* 2017;14(3). https://doi.org/10.1182/hem.V14.3.7269

Stephan Moll: And then the things that go through our minds for anybody would be, could there be a malignancy present? Just a thorough history and physical exam and looking at the CBC and LFTs, making sure that they're up to date with the screening procedures.
And then from a hematology point of view, true recurrences without cancer or interruption of anticoagulation, you start to wonder about unusual things, well, less common things.

Antiphospholipid antibodies is high up there. Antiphospholipid antibodies have a significant recurrence rate, be it on warfarin or on the direct oral anticoagulants and then you, as hematologists we think about really less common things like essential thrombocytosis and polycythemia vera and sometimes people have an abnormal JAK-2 mutation, the mark of a myeloproliferative neoplasm without having CBC abnormalities So, it's been looked at in true anticoagulation failure, obtaining a JAK-2 mutation would be appropriate.

Causes of Anticoagulation Failure

Refer to VTE expert (such as heme)

Pseudo-failure	True Failure
Misinterpretation of Doppler ultrasound or chest computed tomography angiography	Cancer[18,19]
	Antiphospholipid syndrome[20,21]
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Stephan Moll: But I think at that point, the general internist would likely have referred to a hematologist or whoever deals with blood clots to ask, why did this patient have an anticoagulation failure? The point I'm making is I never said the patient failed anticoagulation because it blames the patient for the failure. I said the anticoagulant failed you.

Faculty Discussion

Jori May: Absolutely. And I think, you know, worth highlighting that point again, I think I get a lot of these referrals of patients where there is concern that the anticoagulation failed, that the patient had a recurrent clot. And often it is what we talked about when we do that ultrasound, it's scar tissue, it's not necessarily new clot. Or even if a patient thinks they're taking it correctly, when we call the pharmacy to verify it may be they're taking their apixaban once daily instead of twice daily. Or it may be they think they filled the prescription but their family member is putting their pills in their pill box and they didn't actually fill it and they just weren't aware. So, I think a high level of suspicion for making sure that this is truly new, that the patient is truly taking the medication. But then if there is still concern, involving a hematologist and considering some of the things that Stephan mentioned, which is great.

Okay, well, if we convince ourselves that we do have a recurrent clot in a patient taking their anticoagulation correctly and consistently, what do we do with their anticoagulation? Stephan, if you have a patient on apixaban, how would you change their management plan?

Stephan Moll: So, if it was on apixaban 2.5 BID, I would increase to the 5 BID. That would be a patient who has a recurrent clot after six months after he had switched to the lower dose. Or similarly, if it's rivaroxaban 10, I would increase to 20. Or you switch to the different DOAC, or you switch to low molecular weight heparin, or you switch to fondaparinux, or you switch to warfarin. For me, the key point is, you do something different. You either increase the dose, but not beyond the FDA-approved doses from the lower to the higher dose or switch to a different anticoagulant. And I make the point to the patient, the best management is not clear, it's not data-driven, it's an empiric decision, we'll just do something different.

We do know in cancer patients, that the class when we use low molecular weight heparin that's still used at times, and there was a significant low molecular weight heparin failure rate. Then we would increase the dose by 25% typically. We'd like to have the patient on BID, low molecular weight heparin, and have the patient on a 25% high dose. There we did increase the dose, but with the DOAC, I would not do that. So, you just use a different drug.

Jori May: Okay, well I think we've covered a lot of specific populations here, a lot of information. It's time for us to wrap up, and I'm going to go each of you with some closing take-home points for our audience. So, Bill, let's start with you. Can you share some take-home points for us?

Conclusion: Pharmacy

- Monitor elderly patients with low body weight; closely consider DOAC with shorter lead-in like apixaban
- Renal adjustment for DOACs different for VTE compared to A-fib (apixaban can be used, even in ESRD and HD/PD – other DOACs should not)
- COVID vaccines: save to give; counsel patients that thrombotic risk with current COVID-19 vaccines is extremely low
- Counsel patients regarding the importance of anticoagulant compliance and risks of recurrent VTE with non-compliance
- Heavy menstrual bleeding, first line choice: progesterone therapies such as progestin IUD, which also will provide contraception while on DOAC treatment

William Braun: Yeah, we definitely want to monitor the elderly patients very closely with low body weight. You know, they're at high risk for bleeding. So, that's a key point we definitely need to look at. You know, potentially a DOAC with a shorter lead-in if you're starting versus rivaroxaban could be considered as an option.

A renal adjustment with DOACs are different compared to AFib. So, I want to just emphasize that again when we're looking at dosing with renal, apixaban can be used in end-stage renal and hemodialysis and peritoneal dialysis. Other DOACs cannot be used at this point.

And then COVID vaccines are safe, really have very low thrombolytic risk, and so should be okay to give and counsel patients regarding that point.

And then of course, counsel patients, the importance of compliance, because there's lots of data to support that leads to failure, obviously, and making sure those patients can afford their medications upfront, so that way, they have compliance through the whole treatment period.

And then heavy menstrual bleeding, first choice would be a progesterone therapy potentially, and that would provide contraception for patients that are in that age for potentially, who could get pregnant. So, those are the main points I wanted to highlight.

Conclusion: Hematology

- Apixaban is safe in end-stage renal disease and dialysis patients
- Severe obesity: apixaban and rivaroxaban are safe to use in obese patients, including the extremely obesity; use trough level testing
- Bariatric surgery:
  - Always ask: did they have it?
  - Absorption may be influenced – use trough level testing
- Weight loss meds: safe to use

Jori May: Great. Thanks so much, Bill. And Stephan, to you, what are your take home points for us?

Stephan Moll: I'm going to modify Bill's conclusion just a little bit. I would even say that the COVID vaccines have no known thrombotic risk, at least the ones that we have in the US. Weight loss medications, that's my point number four, are okay to use.

And then I'm going to echo a couple of comments from Bill. Number one, that apixaban is the choice in significant renal impairment, including end-stage renal disease and dialysis is where I tend to use it.

Then severe obesity, we've talked about that apixaban and rivaroxaban are okay to use. In extreme obesity, they can be used. I personally, and some others get trough levels if the BMI gets really extremely high.

With bariatric surgery, I always try to ask patients who need to be on anticoagulants, have you had bariatric surgery? And then I discuss with the patient, bariatric surgery may influence absorption. And therefore, if a DOAC is used, use a trough level, but the DOACs should not be used in the first few weeks after the surgery, parenteral anticoagulants needed then.

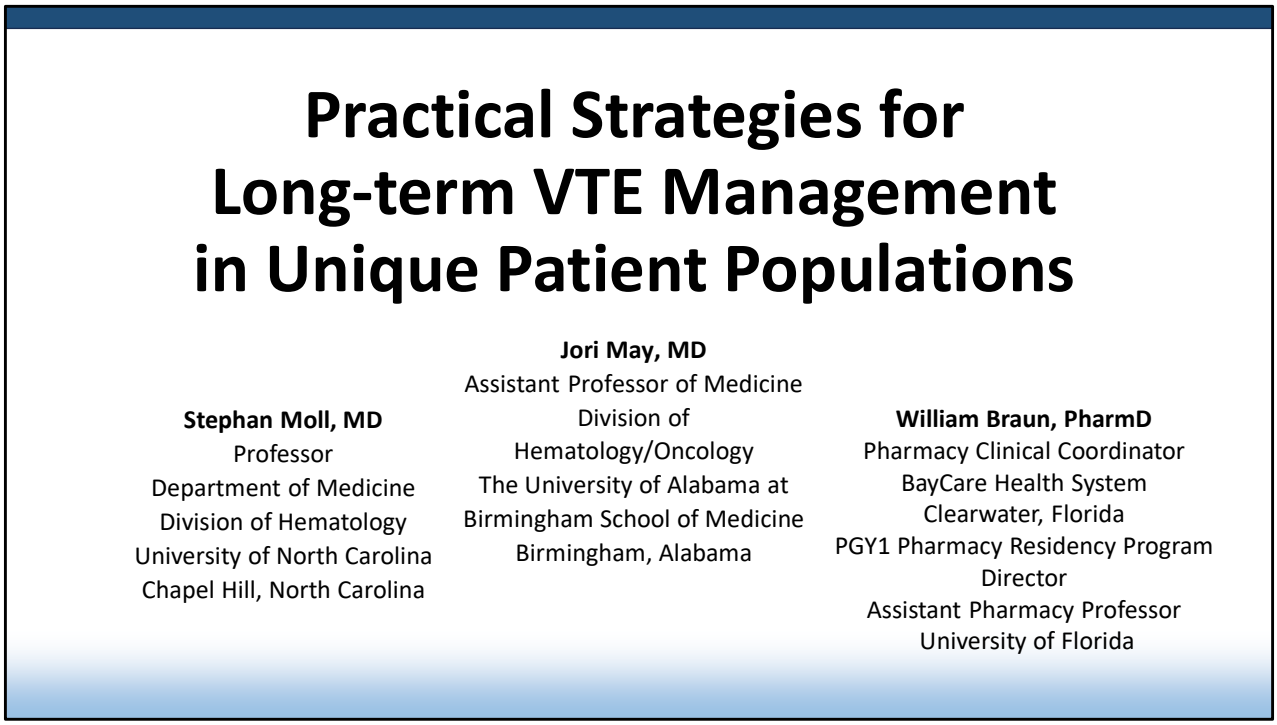
Conclusion: Hematology

- Apixaban is safe in end-stage renal disease and dialysis patients
- Severe obesity: apixaban and rivaroxaban are safe to use in obese patients, including the extremely obesity; use trough level testing
- Bariatric surgery:
  - Always ask: did they have it?
  - Absorption may be influenced – use trough level testing
- Weight loss meds: safe to use
- Progestin IUDs: good contraceptive choices and for patients with heavy menstrual bleeding
- COVID infection:
  - How sick was the patient with COVID?
  - What are the patient's individual risk factors for VTE?
  - VTE risk is multifactorial
- Anticoagulation failure:
  - Is this real failure of the anticoagulant?
  - Consider possible malignancy or APLA?
  - Referral to hematology
  - Action: "Do something different"

Stephan Moll: Number five, and we've said that several times, the progestin IUDs are good contraceptive choices and are also good for the menstrual bleeding decrease.

Then COVID infection, we've talked about that the COVID risk determines how much thrombotic risk there is with the infection, i.e. is the patient really sick with COVID, hospitalized? And then secondly, it's the patient's individual risk factors, the obesity and families, etc.

And then my eighth point is anticoagulation failure. The really important question, is it a true failure or is it just the read of the Doppler ultrasound? And if there's a true failure, I think about malignancy and antiphospholipid antibodies and referral to, for the primary care physician, probably referral to the thrombosis specialist, hematology or whoever does that in your region.



Jori May: Wonderful, well thanks for those take-home points, Stephan. I think we've had a really detailed discussion today on some complex issues, so, thank you for joining me, to Stephan and Bill. For our next podcast, we're going to be digging into some even more complex issues on the details of VTE management for the primary care provider, so we hope you'll tune in. Don't forget to complete your CE evaluation and claim CE credit. Thank you for your attention.