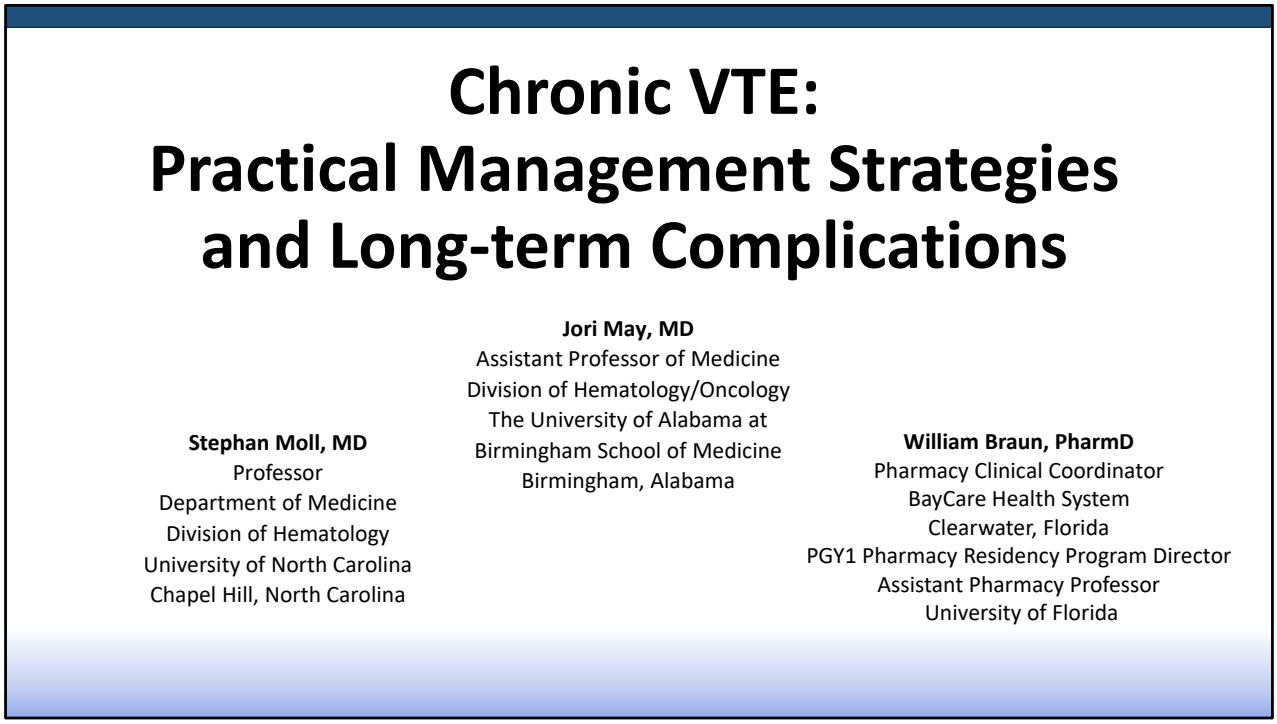


Jori May: Hi everybody, thank you for tuning in for our third podcast recording today. We are going to be discussing chronic venous thromboembolism, really focusing on those management issues and potential long-term complications. My name is Jori May. I am an Assistant Professor of Medicine in the Division of Hematology and Oncology at the University of Alabama at Birmingham. And I'm joined by two guests today. I'll mention that we have all decided we're going to be using our first names throughout the podcast and I'm going to ask them to introduce themselves.

So Bill, could you tell us a little bit about yourself?

William Braun: Hi, I'm Bill Braun. I'm the Pharmacy Coordinator within BayCare Health Systems and I'm also an Assistant Professor at the University of Florida, as well.

Jori May: Wonderful. Great to have you and great to have a pharmacist perspective here.

William Braun: Thanks.

Jori May: And Stephan, a little bit about you as well.

Stephan Moll: Yeah, thank you, Jori. Stefan Moll, I'm a hematologist, adult hematologist, and coagulationist. I'm at the University of North Carolina in Chapel Hill. I deal mostly with thrombosis, anticoagulation, thrombophilia, but to some degree also with other bleeding disorders and benign hematology. Thanks very much for having me here.

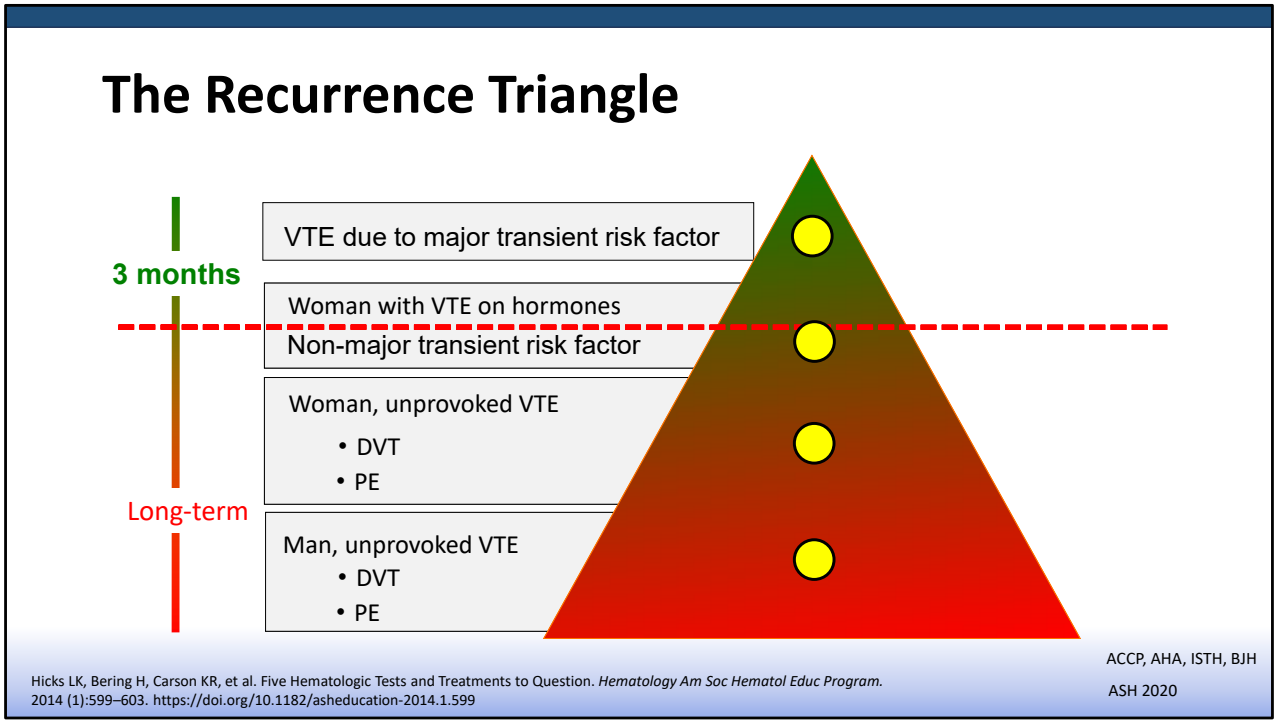
Learning Objectives

- Outline factors that must be considered when determining duration of anticoagulation in patients with VTE
- Accurately determine the appropriate dosage and duration of anticoagulant therapy based on the specific treatment and patient characteristics and preferences
- Identify potential long-term sequelae of DVT and PE and outline management considerations for each

Jori May: Great, well we have a lot to talk about, so we'll dive right in. Our objectives today are, I'm going to briefly recap what we talked about in podcast one and two. We're going to talk about some important considerations for when you're managing or treating VTE with anticoagulation in the long term. Things like drug-drug interactions, over-the-counter medications and supplements, pain medications, heavy menstrual bleeding. We're going to talk about perioperative interruption of anticoagulants as well, contraceptive management. So, trying to touch on as many themes as possible that come up in that long-term management piece. And then we're also going to talk about the potential long-term sequelae of DVT and PE, things like post-thrombotic syndrome, post-PE syndrome, and how we manage those and diagnose them.

Faculty Discussion

Jori May: Very briefly, I do encourage you to tune in and take a listen to podcast one and two, if you haven't already. In podcast one, we talk about the acute management of VTE. And then in podcast two, we talk about the duration of anticoagulation.



Jori May: Stephan introduced us to this concept of the recurrence triangle, an idea that helps us distinguish who needs to be treated for the long-term versus who is treated for a limited duration.

Faculty Discussion

Jori May: Kind of the general theme that I want you to remember is that in patients that have a clear major transient risk factor, there is a clear reason why their clot develops, like being in the hospital and having surgery, those things are reversible, that patient can come off anticoagulation after three months. In people without risk factors or with more minor risk factors, that decision can be more nuanced, but usually we're talking about long-term anticoagulation. So, those are the patients that we're going to be talking about today. And again, there's lots of rich discussion around this topic in podcasts one and two, so I encourage you to tune in.

Stephan Moll: And Jori, if I could just reinforce, I think that is one of the key first questions people should ask when they see a patient on anticoagulant for DVT-PE. Do they really still need to be on it and not just continue doing what has been done in the last year or two or five years?

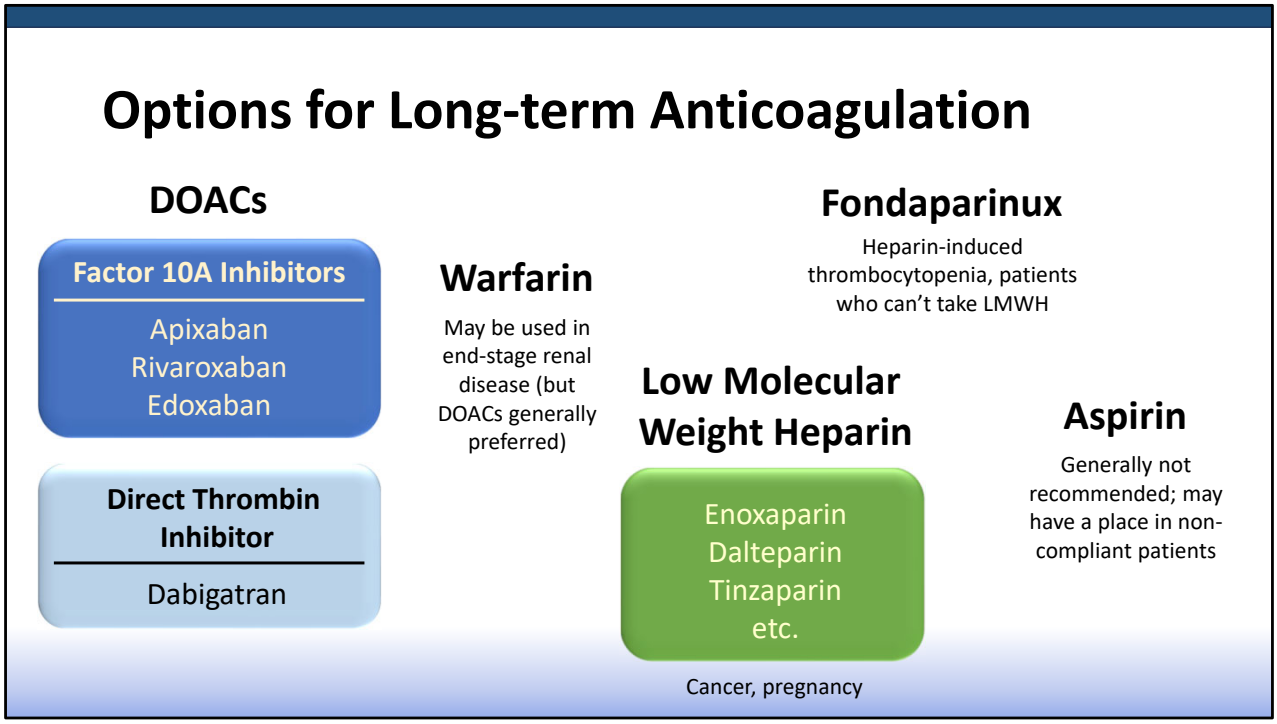
Jori May: I think that's a really important point. We're jumping to long-term, assuming that consideration is made in the encounter. And so, as a primary care provider, you're going to see a lot of people already on anticoagulation, making sure that's absolutely necessary. Great point.

Management of Long-term Anticoagulation in VTE: Case

- 62-year-old male with an unprovoked proximal leg DVT
- No major transient risk factors, no clear explanation for the clot
- Patient requires long-term anticoagulation
- How can we ensure safety and efficacy of long-term anticoagulation in this patient?

Jori May: So, let's dive into a case, a patient that's probably walked into many primary care offices, a 62-year-old male that has what we call an unprovoked proximal leg DVT. So, this patient had no major transient risk factors, no clear explanation for what caused his blood clot. And so, based on podcast two and what we learned there, we would say that this patient required long-term anticoagulation. But at this point, we want to discuss strategies to ensure the safety and efficacy of long-term anticoagulation in this patient. How can we make sure that he's optimally cared for?

So, Bill, I want to come to you first as a pharmacist. You have a lot of options for anticoagulation at this point, some newer and some older. Can you kind of touch on what our options are for anticoagulation in an outpatient?



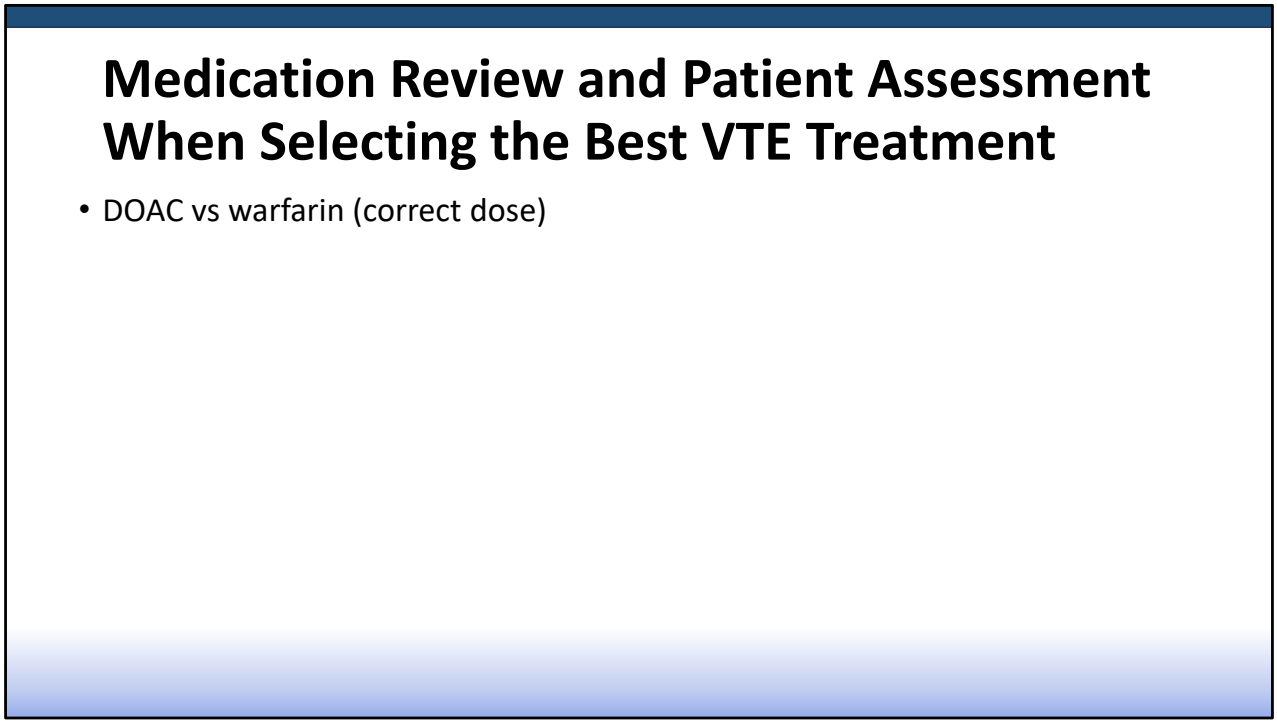
William Braun: Yeah, so the DOAC class comprises of apixaban, rivaroxaban, edoxaban, and dabigatran. They're factor 10A inhibitors with the exception of dabigatran, which is a direct thrombin inhibitor, but they're all tied in this DOAC class. So, these are all potential options.

Warfarin, of course, is our old school agent that we've used forever and potentially could have a place maybe in patients with end-stage renal disease or other factors, but DOACs typically are preferred in most cases.

Then the low molecular weight heparins still play a role in cancer patients and in pregnancy.

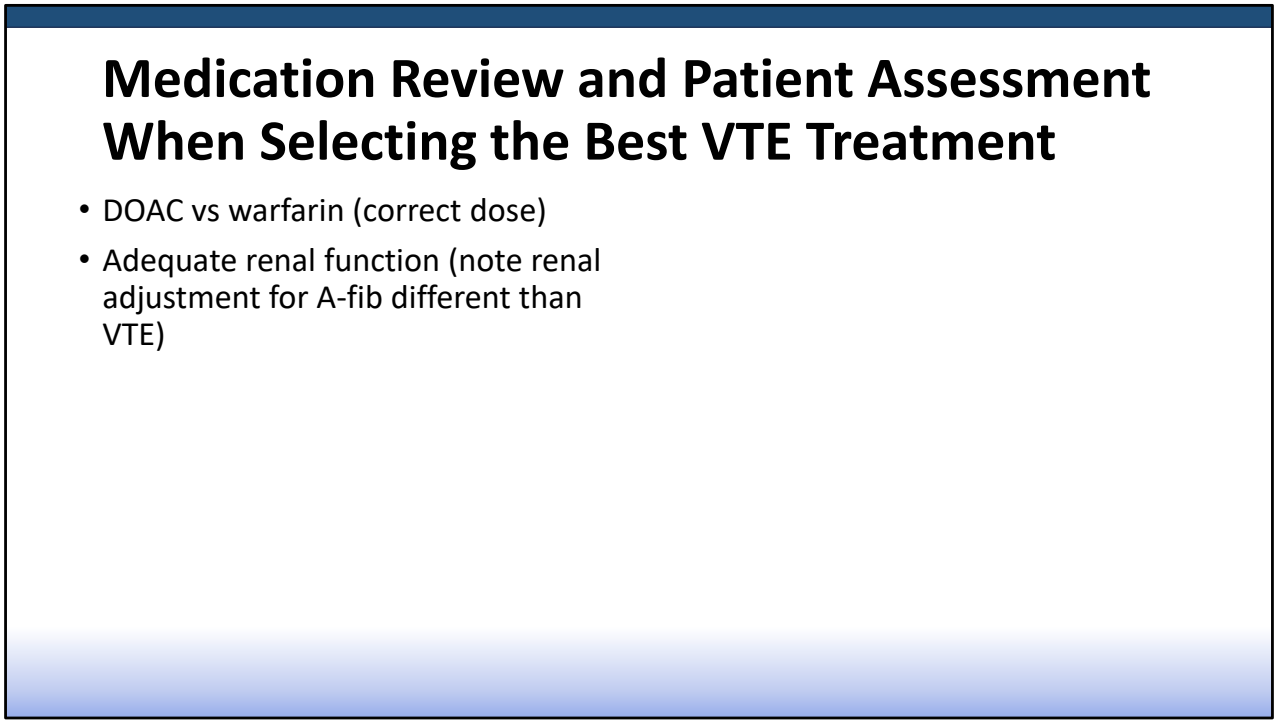
And then you have fondaparinux; typically we use it for heparin-induced thrombocytopenia patients and for patients who can't take low molecular weight heparins or heparin for the most part.

And then of course there's aspirin and that's usually not recommended in the guidelines, but as a last resort if patients are non-compliant could be maybe an option down the road for those patients.



Jori May: And so, when you're making these initial decisions on anticoagulation selection, so you have a patient with a history of VTE, they need to be on long-term anticoagulation, what are the things that a provider should be thinking about or considering, to help make the decision between which agent to use?

William Braun: Yeah, for the most part DOACs are probably the safest compared to warfarin in most of the clinical trials that are out there.



William Braun: But again, the dose specifically and making sure that we're, you know, most of the DOACs have an AFib indication as well. And they have renal adjustments for AFib, which is different for VTE. So that's something to definitely consider.

But even edoxaban, for instance, if you have really good creatinine clearance over 95 and the AFib trials, they don't recommend using edoxaban. So, and most of the VTE, we just don't have good data on it, So it's probably not a good choice to use in those particular patients.

Faculty Discussion

Stephan Moll: You mentioned edoxaban, but edoxaban in the US has not been marketed well, if at all. I've only used it twice in the last several years. You know, the clinical trials look good and it's been FDA approved for DVT-PE treatment. Does that look different in Florida? Are people using edoxaban?

William Braun: We're not really seeing edoxaban at all. It's pretty much, apixaban and rivaroxaban.

Stephan Moll: Yeah, I didn't think so either. So we shouldn’t really put it out there. That's the point I'm making that people are wondering over, should I be using this or not? People can use it, but it's not much marketed--it's really mostly apixaban and rivaroxaban. And then dabigatran as the one that's been around the longest, but with some side effects with GI upset and renal clearance that's so significant that it's being used less and less and less. Thanks for letting me put that in there.

William Braun: Yes, that's a good point. Yeah, we don't, I haven't really used edoxaban at all too much, but I just wanted to throw that out there.

Medication Review and Patient Assessment When Selecting the Best VTE Treatment

- DOAC vs warfarin (correct dose)
- Adequate renal function (note renal adjustment for A-fib different than VTE)
- Adequate liver function (severe hepatic impairment: DOACs not recommended)
- Interactions (concomitant CYP3A4 and/or P-gp inhibitors/inducers)
- Patients' financial burden (can they afford long term?); availability of copay cards
- Compliance (affordability/lab monitoring)
- Patients with weight ≥ 120 kg and/or BMI ≥ 40
- Age
- Any Hx of bleeding (GI bleeding)
- Patients with feeding tubes (dabigatran capsules cannot be opened or chewed)

William Braun:
And then liver function, severe hepatic impairment, DOACs typically are not recommended.

Then of course we have the drug-drug interactions with the strong CYP3A4 and P-gp inducers not recommended with DOAC therapy.

And then the financial burden on these patients as well. And can they afford long-term therapy and the availability of copay cards with those patients.

And of course you got the compliance, warfarin requires monitoring. That's always an issue with warfarin where the DOACs definitely have an advantage more specifically.

And then patients with elevated BMI, overweight patients. There's data with apixaban and rivaroxaban. The guidelines kind of recommend those two agents. So that's, and warfarin of course.

And then age is also a factor. Most of the patients in the studies do better on the DOACs compared to coumadin in the elderly patients and would be a better recommendation.

And then history of GI bleed as well. Apixaban has good data with regards to use in patients that have high risk for GI bleeding.

And then, tube feedings, dabigatran you can't open--the capsules are chewed, so that's also an issue with that particular agent.

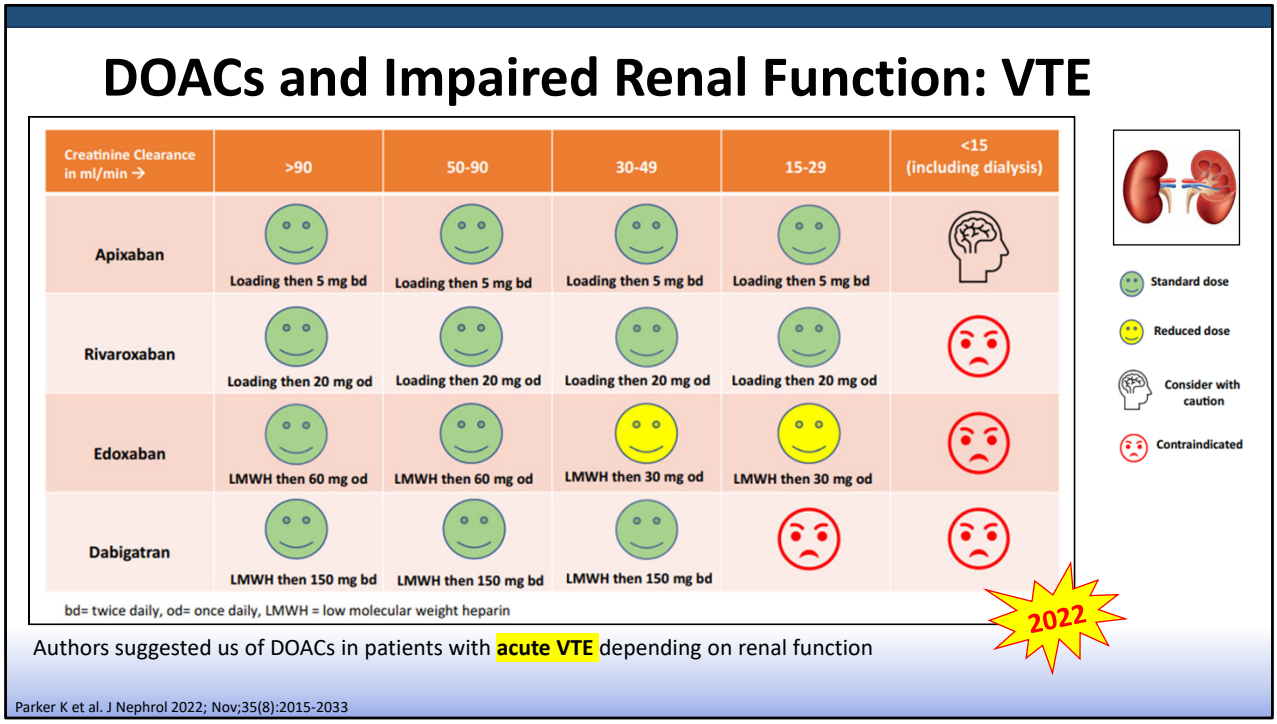
Stephan Moll: If I may just because it came up – your liver, adequate liver function, and yeah, it's true that the DOACs are cleared partially in the liver and in severe liver dysfunction, they're not a great choice. But in severe liver disease, none of the anticoagulants are good choices. In liver cirrhosis, the baseline INR is elevated. Patients often have thrombocytopenia from big spleen and thrombocytopenia, bleeding, varices. And low molecular weight heparin is also difficult to manage because those patients are at high risk for bleeding. So, none of these anticoagulants are really easy options in severe liver disease.

Jori May: That's a great point. You know, I think Bill, you provided a rapid fire of so many nuances and really highlight how difficult this is. I think, you know, oftentimes we thought with the DOACs, everything would be more straightforward. We just put people on those anticoagulants and that's what everybody does. But there's a lot more nuance to it. There's a lot of considerations based on other comorbidities, other medications. And we are going to dive into kind of specific issues that you mentioned. You provided a nice overview, but we're going to kind of go into those in more detail, some in this podcast and some in future podcasts as well.

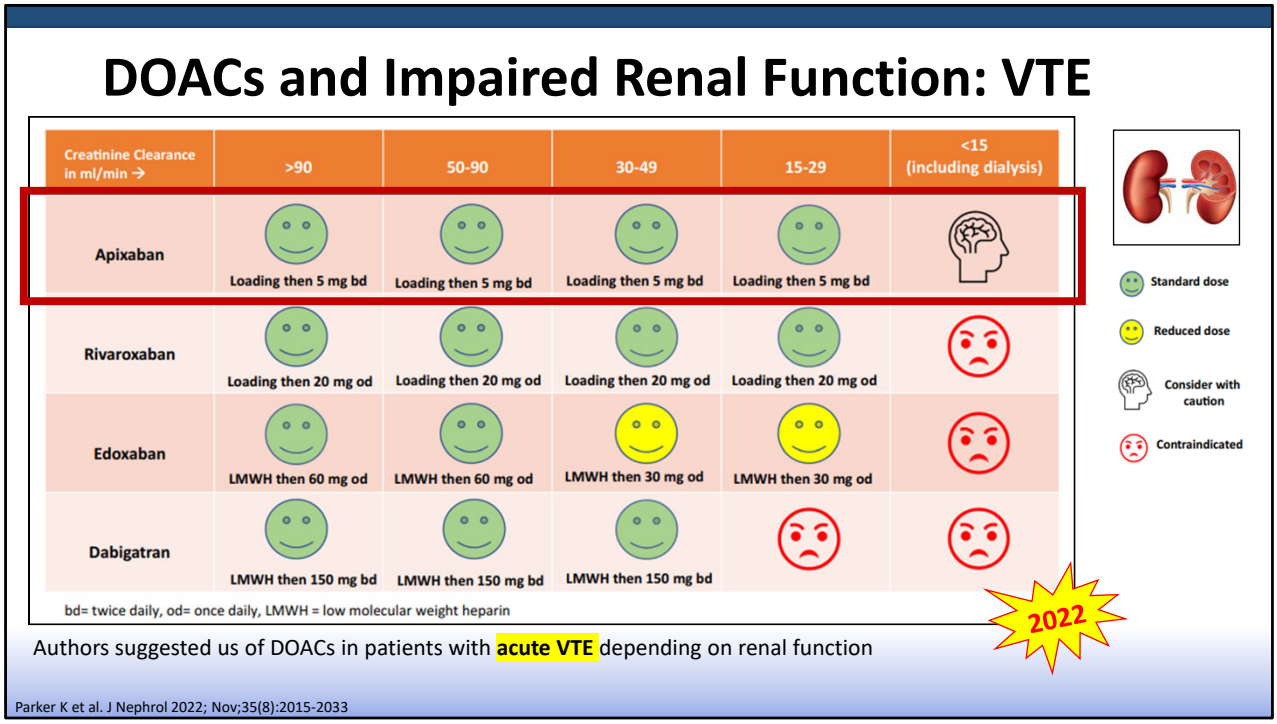
Jori May: You know, one of the things that you mentioned is renal function. We're going to talk specifically about that in the future because this is a challenging area of what to do with certain direct oral anticoagulants in the world of VTE. Can you kind of give us a quick rundown? Is there one direct oral anticoagulant that you tend to favor in someone with renal dysfunction or is there any sort of specific threshold where you don't feel comfortable using them?

William Braun: Yeah, I mean, apixaban probably has the most data from the standpoint for renal. There's a lot of data in Afib actually, not so much in VTE, but basically, you could go down to about 15 creatinine clearance, but you wouldn't want to go below that typically with the data that we have so far.

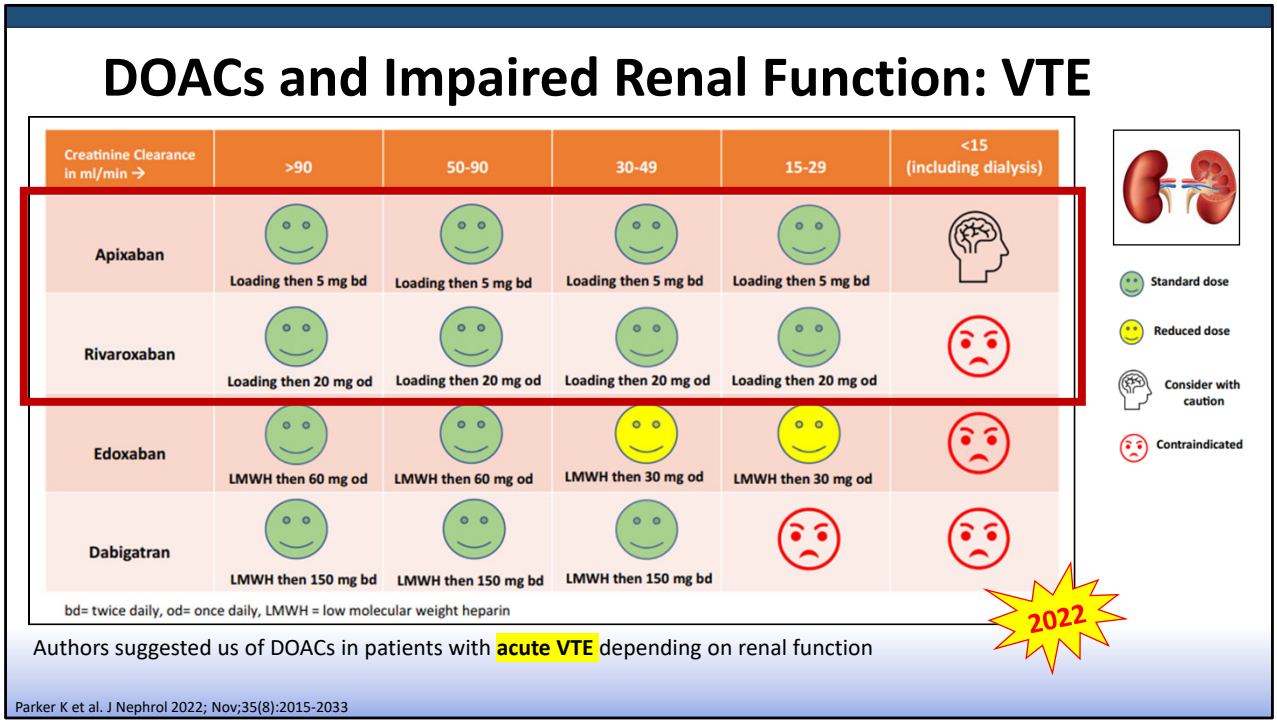
Stephan Moll: Even though it sounds a little complex, I want to say all these things to consider, but underneath the line, it's still pretty straightforward. And the ACCP guidelines and other guidelines also clearly state the go-to anticoagulant in the majority of patients with DVT-PE are the DOACs.



Stephan Moll: And the ones that we marketed or that we use mostly and most widely are apixaban and rivaroxaban. And with the renal function that you just mentioned, it's true.

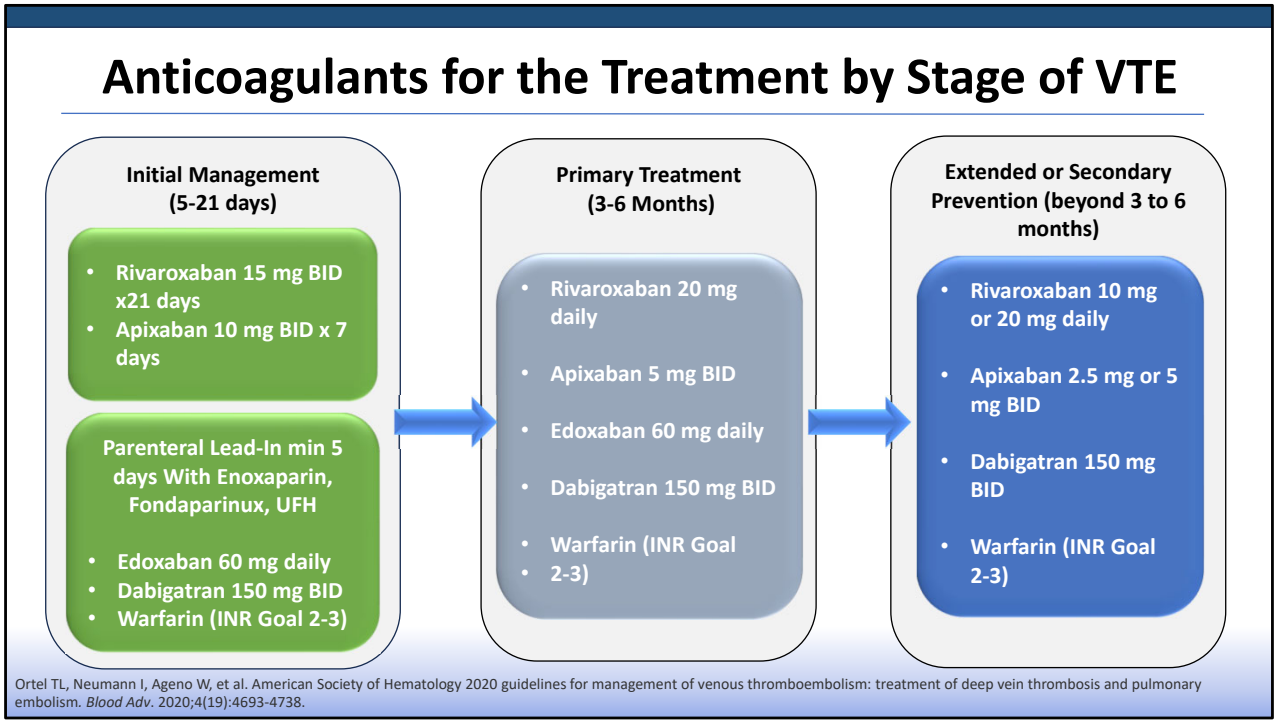


Stephan Moll: Apixaban is the least cleared in the kidney, so it's the go-to drug in end-stage renal disease, including hemodialysis, and in the patient with some impairment. Yes, there are nuances with all the other liver disease and such, and we'll get to that. But in the majority of patients, decision-making is not that difficult.



Stephan Moll: Apixaban or rivaroxaban mostly. And often the driver is, and we'll talk about that, is the cost. What is most affordable for the patient? Where is the copay the least?

Jori May: And so that's a great point, Stefan.



Jori May: And I guess it would be helpful, and Bill mentioned this, some of the differences in selecting doses for those two most common agents that we use, for apixaban and rivaroxaban. Can you highlight briefly the dosing for venous thromboembolism of apixaban and rivaroxaban, the difference of that initial management and long-term management, how doses might differ, and how that might differ from patients that are on the same medications for atrial fibrillation?

William Braun: Yeah, so you know, typically for initial management with rivaroxaban, you don't have to, you know, use parenteral lead-in with those particular agents apixaban or rivaroxaban. So you can start right when you diagnose the VTE. You start at 15 milligrams BID for 21 days and then of course after that you stepped into 20 milligrams daily. And then apixaban, you know, 10 milligrams BID for seven days and then transition to apixaban 5 milligrams BID.

With the other agents, you got to have the lead in, with parenteral anticoagulation for a minimum of five days before you can switch. Edoxaban would then go to 60 milligrams daily and the dabigatran 150 BID.

And then of course warfarin, you would base that off INR of two to three for the most part.

Stephan Moll: And an interesting concept here to observe is people thought in the clinical trial design that maybe for the first few days or weeks you need a higher dose because the patient is very clottable, but there is no agreement. Is there really an acute time where people need a higher dose? And if there is, is it a week long, like the apixaban trials were designed, or is it three weeks long, like the rivaroxaban trial was designed? Or the dabigatran trial did not use any higher dose, they just kept the same dose. It's a lack of scientific knowledge. Do you really need a higher dose? But by clinical trials and the FDA approval, this is how the drugs should be used.

Jori May: That's a great point and different from AFib, right? That we don't have that lead-in dose. So that is a difference that sometimes people don't catch.

Stephan Moll: And we see that, all of us, right, people get started on, for example, the higher dose with apixaban and rivaroxaban. The patient for some reason doesn't get taken down to the lower dose and continue and you see them at three months and they're still on the rivaroxaban 15 BID or apixaban, the 10 BID. That's something really to keep in mind. If we see a patient with an acute DVT, that is clear indication to lower the dose to the maintenance dose.

Jori May: Absolutely, and I think the alternative in that people who meet criteria for dose reduction atrial fibrillation based on renal function, based on age, that same criteria does not apply to the VTE space. So being very deliberate about understanding the indication that you're prescribing the anticoagulant for, to ensure that you're following the appropriate dose.

Stephan Moll: Jori, should we also talk about the dose reduction that is possible at six months? We have patients with DVT-PE, if they're on rivaroxaban or apixaban. For each of them, there has been a trial that at six months, there's a further dose reduction to a prophylactic dosing. For rivaroxaban, it would mean the 10-milligram once daily, and for apixaban, it would be the 2.5-milligram twice daily. And that would be then long-term.

And those two studies referred to as Amplify Extension and Einstein Choice Trial, New England Journal quality publications, show that the lower dose is as effective as the full dose. From a safety point of view, it's similar, maybe there's a tad bit of an advantage. So certainly at six months, it could be considered to lower patients.

Do I do that in everybody? No. There are different practices. I lower the dose if I'm not quite sure does this patient really need to be on long-term blood thinners or not, which by this recurrence triangle that we discussed earlier in the last podcast is that people with this intermediate risk of recurrence. And I lower the dose, so I use the full dose in patients with clearly unprovoked clot, the more heavy ones, the ones who tolerate it well, and the younger ones. But I lower the dose in the people where I have equipoise and I don’t quite know, do they really need to be in long-term blood thinners? The elderly, the fragile, and the low body weight patients.

Jori May: It's nice to know about that data and have that flexibility, but I think it's important that you highlight it's not something you have to do. And if you talk to a lot of hematologists, there's a lot of variation in practice there. It's not that everybody gets reduced. It's with consideration of how severe their VTE was, what their risk of bleeding was, things along those lines.

And so we've mentioned cost. We actually mentioned this in a previous podcast too, but I think it's important to highlight again that particularly when we're talking about apixaban and rivaroxaban being our, tends to be first line options, that we have to make sure that it's affordable for our patients. So Bill, do you have kind of some tips and tricks on if a primary care doctor has a patient on this medication, how can they help make sure that their patient can access it if they need it?

Cost of Anticoagulants

	Apixaban Cost/Month	Rivaroxaban Cost/Month	Edoxaban Cost/Month	Dabigatran Cost/Month	Warfarin Cost/Month
Average cost with Insurance and co-pay card	$10-$38	$10-$47 (Gap Ins. coverage max out of pocket $89)	$ 4/30 days $12/90 days; max benefit $270/30 days	$0-$10 depending on generic Tier pricing	$0-$10 depending on generic Tier pricing
Cash price (WAC)	$544	$521	$377	$70 (generic)	$10
Copay Card	Yes	Yes	Yes	No	No
Patient Assistance Program	Yes	Yes	No	No	No
Free 30 day Coupon	Yes	Yes	No	No	No

DVT/PE Pricing Information for Rx ELIQUIS® (apixaban) | Safety Info (bmscustomerconnect.com); Savings & Support | XARELTO® (rivaroxaban) (xarelto-us.com); Support+™ Program & Resources | SAVAYSA® (edoxaban)

William Braun: Yeah, knowing the type of insurance they have and each insurance has tier levels, of course, and they may have one preferred versus the agent or versus other agents. And so that's something to look at.

Cost of Anticoagulants

	Apixaban Cost/Month	Rivaroxaban Cost/Month	Edoxaban Cost/Month	Dabigatran Cost/Month	Warfarin Cost/Month
Average cost with Insurance and co-pay card	$10-$38	$10-$47 (Gap Ins. coverage max out of pocket $89)	$ 4/30 days $12/90 days; max benefit $270/30 days	$0-$10 depending on generic Tier pricing	$0-$10 depending on generic Tier pricing
Cash price (WAC)	$544	$521	$377	$70 (generic)	$10
Copay Card	Yes	Yes	Yes	No	No
Patient Assistance Program	Yes	Yes	No	No	No
Free 30 day Coupon	Yes	Yes	No	No	No

DVT/PE Pricing Information for Rx ELIQUIS® (apixaban) | Safety Info (bmscustomerconnect.com); Savings & Support | XARELTO® (rivaroxaban) (xarelto-us.com); Support+™ Program & Resources | SAVAYSA® (edoxaban)

William Braun: And the copay cards, making sure that they have the copay cards so that way, when they get the script and they go to the pharmacy…

Cost of Anticoagulants

	Apixaban Cost/Month	Rivaroxaban Cost/Month	Edoxaban Cost/Month	Dabigatran Cost/Month	Warfarin Cost/Month
Average cost with Insurance and co-pay card	$10-$38	$10-$47 (Gap Ins. coverage max out of pocket $89)	$ 4/30 days $12/90 days; max benefit $270/30 days	$0-$10 depending on generic Tier pricing	$0-$10 depending on generic Tier pricing
Cash price (WAC)	$544	$521	$377	$70 (generic)	$10
Copay Card	Yes	Yes	Yes	No	No
Patient Assistance Program	Yes	Yes	No	No	No
Free 30 day Coupon	Yes	Yes	No	No	No

DVT/PE Pricing Information for Rx ELIQUIS® (apixaban) | Safety Info (bmscustomerconnect.com); Savings & Support | XARELTO® (rivaroxaban) (xarelto-us.com); Support+™ Program & Resources | SAVAYSA® (edoxaban)

William Braun: …it'll be reduced potentially based on what their coverage is and their gap basically. So typically, it could be between $10 to $40 typically for a script, which is very reasonable.

Cost of Anticoagulants

	Apixaban Cost/Month	Rivaroxaban Cost/Month	Edoxaban Cost/Month	Dabigatran Cost/Month	Warfarin Cost/Month
Average cost with Insurance and co-pay card	$10-$38	$10-$47 (Gap Ins. coverage max out of pocket $89)	$ 4/30 days $12/90 days; max benefit $270/30 days	$0-$10 depending on generic Tier pricing	$0-$10 depending on generic Tier pricing
Cash price (WAC)	$544	$521	$377	$70 (generic)	$10
Copay Card	Yes	Yes	Yes	No	No
Patient Assistance Program	Yes	Yes	No	No	No
Free 30 day Coupon	Yes	Yes	No	No	No

DVT/PE Pricing Information for Rx ELIQUIS® (apixaban) | Safety Info (bmscustomerconnect.com); Savings & Support | XARELTO® (rivaroxaban) (xarelto-us.com); Support+™ Program & Resources | SAVAYSA® (edoxaban)

William Braun: And of course there is patient assistance programs for apixaban or rivaroxaban to help those patients long-term if they don't have insurance.

Cost of Anticoagulants

	Apixaban Cost/Month	Rivaroxaban Cost/Month	Edoxaban Cost/Month	Dabigatran Cost/Month	Warfarin Cost/Month
Average cost with Insurance and co-pay card	$10-$38	$10-$47 (Gap Ins. coverage max out of pocket $89)	$ 4/30 days $12/90 days; max benefit $270/30 days	$0-$10 depending on generic Tier pricing	$0-$10 depending on generic Tier pricing
Cash price (WAC)	$544	$521	$377	$70 (generic)	$10
Copay Card	Yes	Yes	Yes	No	No
Patient Assistance Program	Yes	Yes	No	No	No
Free 30 day Coupon	Yes	Yes	No	No	No

DVT/PE Pricing Information for Rx ELIQUIS® (apixaban) | Safety Info (bmscustomerconnect.com); Savings & Support | XARELTO® (rivaroxaban) (xarelto-us.com); Support+™ Program & Resources | SAVAYSA® (edoxaban)

William Braun: And they also have the free 30-day coupon that basically, they don't pay nothing for the first 30 days. So making sure that they have those resources, I think is really important for compliance because that's something we really want to make sure that they're compliant on these medications and they don't stop abruptly.

Stephan Moll: If I may add to that, so when we see these patients at three months or six months and we see how did you tolerate it, bleeding issues, et cetera, one of the questions I always ask, number one, what is your copay? But secondly also, what is your rivaroxaban hate factor or your apixaban hate factor on a scale from zero to 10? And then you need to take it, zero means it's just a pill, no big deal, 10 I hate it incredibly. And I ask specifically about the cost and the copay, how that influences them. And then patients often spill out that the copay is so high. That's a pain for every patient and for the physicians as well. And fortunately, we have a pharmacist in our clinic who's very well versed in finding out what the copay is and why it is so high, et cetera, et cetera. But it's so time consuming to talk to patients about copay and cost. It's not a good development, but it's something that's really key to also then be sure that the patient stays on the drug. Sometimes if the copay is high on one drug, I use the other one. Or if the copay card has run out for one, for apixaban, I switch them to rivaroxaban and they have a copay card as well. So one can play around there, but it's a little cumbersome, I must say.

Faculty Discussion

Jori May: Perhaps I'll put you both on the spot a little bit. If you have a patient that has kind of, if you got to pick what anticoagulant to start in a patient, do you have a preference? Is there one that you go to more often than the other, or it's really based on kind of insurance and access? Any thoughts? Bill, do you have a favorite?

William Braun: I mean, looking at the studies, I mean, I think apixaban, I think is the, probably has good efficacy and may be the safest in my opinion. You know, there's no head-to-head trials, but there's some meta-analysis that were done that looked at rivaroxaban and apixaban, but that's my preference at least, as long as the insurance covers it and whatnot. And I think the BID dosing reflects the half-life of the drug really well, as well.

Jori May: And Stephan, what about you?

Stephan Moll: So, first of all, I'm going to say I have no conflict of interest. I'm not being supported in any way by either one of these companies.

Jori May: Yes, me either.

Stephan Moll: And then I'm going to say these drugs have never been compared head-to-head in a prospective study. So, we don't really know whether one is better or worse than the other. One prospective trial was attempted with federal funding from PCORI, I think, where they were randomizing patients with DVT-PE to get one of three arms, apixaban, rivaroxaban, or warfarin. And this study didn't fly because nobody wanted to randomize to warfarin. I didn't participate in the trial because I didn't want to use warfarin or offer patients or have a chance that they were randomized to warfarin. So, the retrospective data in general suggests that maybe apixaban is a tad bit safer from a major bleeding point of view. And maybe particularly from a vaginal menstrual bleed point of view. And yes, so apixaban is a good choice and maybe my preferred choice, but I wouldn't say that strongly. For me, they're pretty much interchangeable. Some patients really like the once daily and struggle with a twice daily. And then sometimes, and not infrequently, I pick the drug whatever is least expensive. I tell the patient we could use this or that, inquire what the copay would be for either one. And that's the one that I would support.

And I have a number of patients on rivaroxaban that I don't switch over to apixaban, even though I think maybe it's a tad bit safer, because they've done fine on rivaroxaban and they like the once daily. Yes, so that's my approach. Dabigatran I barely ever use as a first go-to drug. I have a few patients on it. Edoxaban, I've used only a couple of times, I'm using a couple of times because of cost issues for the patient.

Jori May: I think that's helpful. I'll highlight as well that rivaroxaban needs to be taken with food. I find that is often an issue for people if they are more comfortable taking their medications at bedtime or they like to take it in the morning and they don't eat breakfast. It's something that I think is underappreciated and can really affect the absorption of rivaroxaban. So important to keep in mind.

Stephan Moll: I do want to also mention there, yes, in the first three months of an acute DVT-PE treatment, I want the patient to be on full dose and take it with food and have it well-absorbed. But after three or particularly after six months, we know that the 10-milligram dose is as effective as the 20. So, if patients are on 20-milligram, I say, look, you can loosen up. I don't...it doesn't really matter whether it's absorbed 20% less, that's still 16 milligrams per day that you're getting. I'm fine with that because it's still even more than the 10 milligram with a dose reduction. So, I would not overvalue the importance of the food issues. And otherwise, which is self-understood for most people, these drugs are not interfered with by food. Patients ask that sometimes still from the warfarin times, and that is irrelevant, the vitamin K issues.

Jori May: That's a great point. Well, and Stefan, you bring up warfarin, and if you could maybe say a brief bit, I know that warfarin was a large part of your practice in the past, and certainly it still has its uses in specific populations. If you can maybe speak to a couple of pearls about using warfarin, ways to make it a little easier for patients.

Stephan Moll: Why do you say it's been a big part of my practice? Because I'm so old?

Jori May: I didn't say that.

Stephan Moll: No, Jori. So yes, I mean, many of us grew up with dealing with warfarin, and it was painful for the patients. And that's actually where this warfarin hate factor from zero to 10 came from, that I've been using for many years, and then translated to rivaroxaban and apixaban.

Stephan Moll: Take together the need for monitoring, for dietary interactions, the risk for bleeding, the cost, going to the physicians, how much do you hate it? And then they would say it's 15 or 16, which means they really hate it. And if it's then just the diet and the monitoring, then you can switch to a DOAC. But if it's just the risk for bleeding and the concern and having to take a medication, the DOAC is not a solution because it's still a blood thinner. But you also point out INR home monitoring.

I'm German and I used to practice in Germany. And INR Home Monitoring in Germany was very popular and I like it. The patient can test themselves. In Germany they get taught how to adjust their warfarin and they often do it better than providers. Here in the US, it has not really taken off, well it never really took off. There's some pockets where INR Home Monitoring is used. If I was on warfarin for some reason, I would want an INR Home Monitor. But there's been a lot of movement with legal issues, but particularly reimbursement that the pharmacist provider still gets called where the results can not bill for it or not appropriately bill for it. If the patient needs to be on warfarin, I would like to find a place for them that does INR Home Monitoring or that supports it, but those places are very few.

Jori May: Excellent teaching points from a seasoned hematologist, Stephan.

Stephan Moll: Thank you, Jori.

Jori May: So, Bill, you brought this up previously, but I think it's worth mentioning a little bit more drug-drug interactions. So as a hematologist, I hear CYP inhibitors and P-gp, and I get a little bit glossy-eyed. So, I wonder if for the clinician, you can highlight for us, what are those things that we need to be thinking about when we're looking at a patient's medication list to ensure that we're avoiding really relevant medication interactions, particularly with the direct oral anticoagulants.

Drug-Drug Interactions with DOACs

Drug-Drug Interactions Guidance for Rivaroxaban and Apixaban	
COMBINED P-gp and STRONG CYP3A4 INDUCERS **Apalutamide, Carbamazepine, Fosphenytoin, Phenytoin, Rifampin, St. John's Wort**	Avoid Use
STRONG CYP 3A4 INDUCERS (no P-gp induction) **Phenobarbitol, Primidone, Enzalutamide, Lumacaftor, Mitotane**	Consider patients thrombotic risk as limited data with this interaction
COMBINED P-gp and STRONG CYP3A4/5/7 INHIBITORS **Cobiscistat, Itraconazole, Ketoconazole, Posaconazole, Ritonavir, Tucatinib**	**Rivaroxaban: Avoid Use** **Apixaban: If taking 5 mg or 10 mg, reduce dose by 50%; If already taking 2.5 mg BID avoid use**
COMBINED P-gp and Moderate CYP3A4 INHIBITORS Dronedarone, Erythromycin, Isavuconazonium sulfate, Verapamil	**Rivaroxaban: Avoid in patients with CrCl 15-80 mL/min unless benefit justifies risk** **Apixaban: No specific dose reduction recommended**

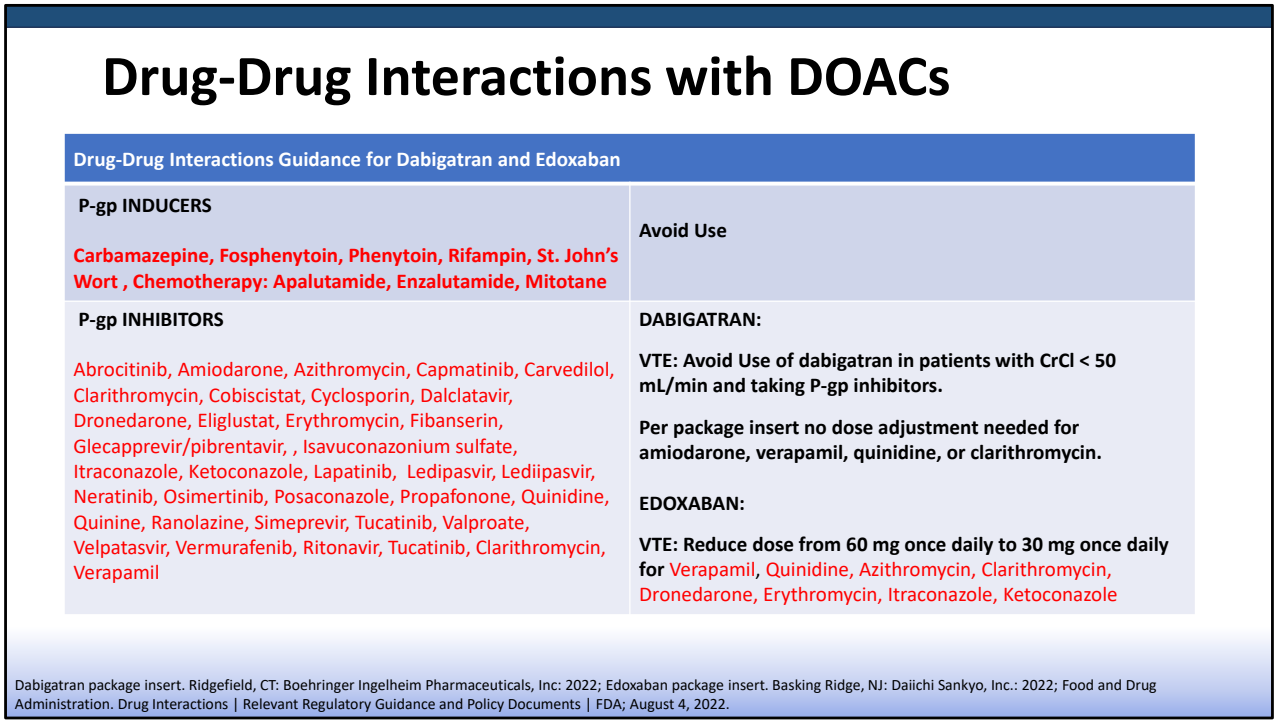
Apixaban package insert. Princeton, NJ and New York, NY: Bristol-Myers Squibb Company and Pfizer Inc: 2022; Rivaroxaban package insert. Titusville, NJ: Janssen Pharmaceuticals, Inc: 2022; Food and Drug Administration. Drug Interactions | Relevant Regulatory Guidance and Policy Documents | FDA; August 4, 2022.

William Braun: Yeah, the inducers are the big ones, you know, the anti-seizure medications, carbamazepine, you know, phenytoin are big ones. You know, the herbal, you know, St. John's Wort, not too common, but rifampin, an antibiotic that's added a lot of times to therapy and endocarditis. But those are the main ones. And that's for all the DOACs actually, the inducers.

And there's also a combined P-gp inducers as well, which affects the absorption of these drugs. So those are the main ones to really look at. And it kind of gets a little cloudy when you start jumping into some of the other ones that we start getting a moderate, becomes a little more difficult.

But one thing to think about that I want to just mention is rivaroxaban; you know, 50% of the metabolism goes through the hepatic [CYP] pathway, whereas apixaban only 25%. And so that's kind of why you see a lot of times the dose reduction on rivaroxaban for these inhibitors, you know, it says avoid use potentially for rivaroxaban because of that.

And then apixaban has a dose reduction on those patients that have the strong P-gp inhibitor combination. So that's something to think about with the azol and antifungals.



Drug-Drug Interactions with DOACs

Drug-Drug Interactions Guidance for Dabigatran and Edoxaban	
P-gp INDUCERS **Carbamazepine, Fosphenytoin, Phenytoin, Rifampin, St. John's Wort , Chemotherapy: Apalutamide, Enzalutamide, Mitotane**	**Avoid Use**
P-gp INHIBITORS Abrocitinib, Amiodarone, Azithromycin, Capmatinib, Carvedilol, Clarithromycin, Cobiscistat, Cyclosporin, Dalclatavir, Dronedarone, Eliglustat, Erythromycin, Fibanserin, Glecapprevir/pibrentavir, , Isavuconazonium sulfate, Itraconazole, Ketoconazole, Lapatinib, Ledipasvir, Lediipasvir, Neratinib, Osimertinib, Posaconazole, Propafonone, Quinidine, Quinine, Ranolazine, Simeprevir, Tucatinib, Valproate, Velpatasvir, Vermurafenib, Ritonavir, Tucatinib, Clarithromycin, Verapamil	**DABIGATRAN:** **VTE: Avoid Use of dabigatran in patients with CrCl < 50 mL/min and taking P-gp inhibitors.** **Per package insert no dose adjustment needed for amiodarone, verapamil, quinidine, or clarithromycin.** **EDOXABAN:** **VTE: Reduce dose from 60 mg once daily to 30 mg once daily for** Verapamil, Quinidine, Azithromycin, Clarithromycin, Dronedarone, Erythromycin, Itraconazole, Ketoconazole

Dabigatran package insert. Ridgefield, CT: Boehringer Ingelheim Pharmaceuticals, Inc: 2022; Edoxaban package insert. Basking Ridge, NJ: Daiichi Sankyo, Inc.: 2022; Food and Drug Administration. Drug Interactions | Relevant Regulatory Guidance and Policy Documents | FDA; August 4, 2022.

William Braun: But yeah, for the most part, and then you had the dabigatran and edoxaban don't really have too much of a CYP pathway. They're pretty much on the P-gp pathway. And of course, dabigatran has warnings for creatinine clearance, not to recommend in situations.

And edoxaban has a dose reduction and they specifically on their package insert verapamil, erythromycin, clarithromycin, Multaq is used, [genitorone], which is common for antiarrhythmics, erythromycin, you don't really see too much. And of course, the azol, itraconazole and ketoconazole, you have to dose reduce in that particular situation. So it does become complicated.

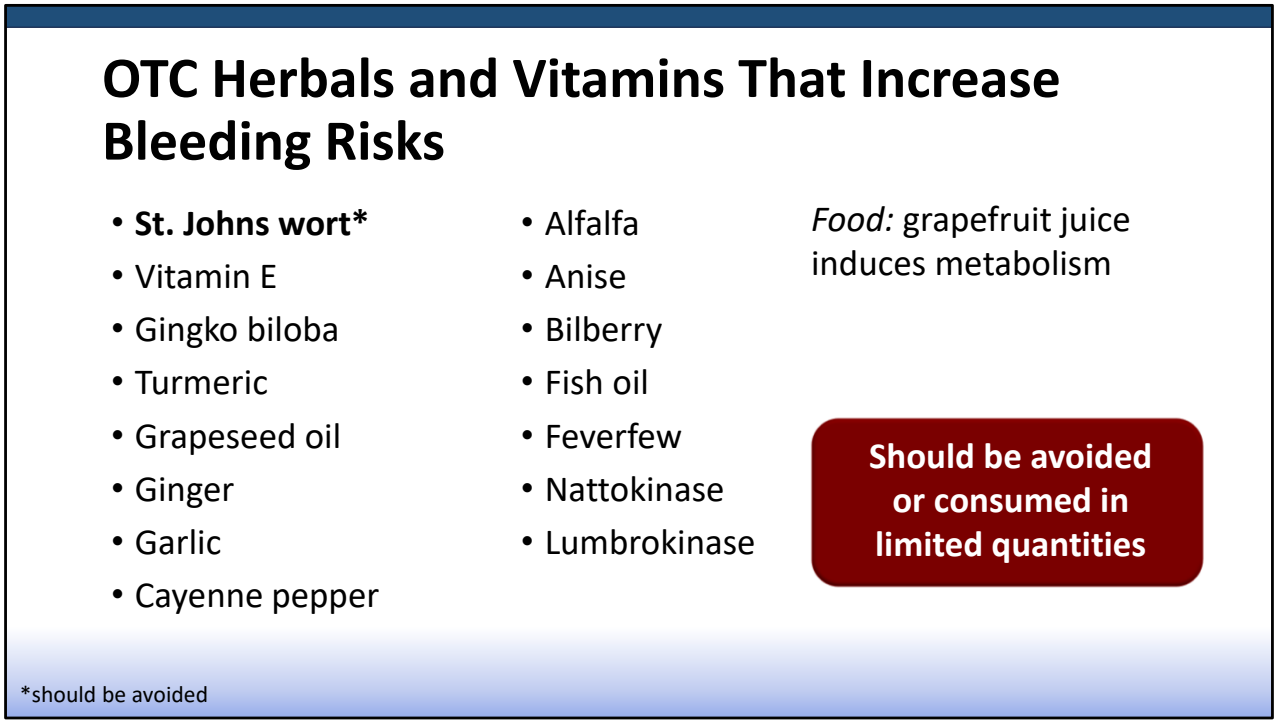
Jori May: Yes, it does.

Stephan Moll: Well, it's complicated even though, in a way, it's also simple. We have the internet-based drug interaction abilities and that's what I find myself doing at times that I just check on is there drug interaction and how severe is it. I think one of the important teaching points is there's so many new oncological drugs in use. Particularly in oncology, my teaching to the oncologist is make sure that you put whatever oncological drug you're using into the drug interaction database to see how it interacts with the DAOCs that your patient is taking.

Jori May: Yeah, I think it's, I kind of think of it, you know, certain antimicrobials, anti-seizures, anti-cancer, those are the classes of medications where I try to remind myself, like you said, Stephan, using an interaction checker in order to guide us or calling a fantastic pharmacist like Bill to guide us.

William Braun: Yeah. And COVID now is, you know, paxlovid is common and it has ritonavir in there. So that's something to consider as well. But I think we'll talk about that maybe at the next session.

Jori May: Yeah, that's a great point. So let's also mention, you know, we talked about, I think you mentioned St. John's wort, but Bill, could you go through, are there supplements that you're concerned about? These are things that often don't show up on a patient's medication list, but are there things that you're asking about or double checking for patients on DOAC?



William Braun: These are the pharmacodynamic issues. A lot of them have antiplatelet properties and can have an additive effect to patients. So I think we need to counsel and find out what they're taking. Some are definitely more an issue than others. Turmeric seems to be pretty popular now. Everyone's taking that and it can have some moderate platelet aggregation reduction. So, you know, that's possible as well. So yeah, I mean, I think it's something, St. John's wort definitely should be avoided at all costs, but I think counseling patients on moderation and not overdoing it, I think is a key component here in making sure if you had aspirin with a combination of this, then I think you're definitely increasing your risk and definitely should counsel patients on that.

Faculty Discussion

Jori May: Yeah, and you bring up aspirin. I think that's really important to talk about because it is in the unprescribed realm, but has significant blood thinning activities. And so let's say, you know, trying to bring this back to the patient that we talked about in the beginning, that patient 65 years old has an unprovoked VTE. And let's say that patient has been on aspirin, we'll say for primary prevention of coronary artery disease. I know that's a huge topic of whether we're using aspirin for that purpose, but we're certainly seeing it a lot now. So I wonder, you know, what do you think about in that patient? Or do you keep them on the aspirin? Do you stop the aspirin if you're continuing an anticoagulant? And maybe, Stephan, could you kind of take us through your thought process on that?

Stephan Moll: I can, but I'm going to turn it around, Jori. You have published on this, and it's a really nice paper, when people have an arterial indication to be on an antiplatelet agent, and have a venous indication to be on an anticoagulant, what do you do? Do you just add aspirin and anticoagulant? And then what about if they have a stent? Do you add aspirin and clopidogrel, and they have a V, then you have triple therapy, these really complex patients need a lot of thought. This one that you mentioned just now, if a patient is on aspirin for primary coronary artery disease prevention and now needs anticoagulant for VTE, you stop aspirin. That's the right thing to do. There's no role for continuing aspirin. More commonly, even before that, the question should come up, should this patient have been on aspirin in the first place? But that's not our, we see the patient when they have a VTE and they should not be on aspirin.

Beyond that, it becomes a little more complex. When did they have their heart attack or their stent placed? And where in the course of the double therapy are they? We'll discuss that somewhere down the line. I do want to say though, Jori, because it didn't fully become clear, I think a little earlier. Aspirin does not have much of a role in the prevention of venous thromboembolism. So if a patient had a DVT-PE and there is an indication to be a long-term blood thinners and they don't want to take it, and they stop at three or six months, I tell them. They ask me, can I not just take aspirin? I tell them it has minimal effects, so don't count on it. The risk of recurrence is still pretty significant. Yes, if rather than nothing, it's appropriate to take aspirin, but I really would like to see you on blood thinners. And I mentioned the low dose of apixaban and rivaroxaban.

At least we know that for the rivaroxaban, are as safe or unsafe as aspirin. Aspirin is not a completely safe drug. So with aspirin, you get the negative side effects of bleeding risk, but not the positive of preventing VTE.

Jori May: Those are really helpful points. And I think from a primary care perspective, I think what I think is most helpful is asking that question of is the aspirin needed? Like you said, particularly if you've got a patient who's now on anticoagulation, and is it that you can question the cardiologist who may be more familiar with the guidance in the cardiology space of, you know, when a patient is on anticoagulation, do you continue the aspirin based on when their stent was, or the patient with peripheral artery disease, the patient with a history of stroke?

We've talked about multiple things we're looking for in the med list, adding aspirin to your mental checklist to say, I have a patient on anticoagulation, they're on aspirin, who do I need to talk to see if that's necessary or if we can potentially deescalate?

Stephan Moll: Jori, I would like to, if you allow me to say one word to the previous topic of the fish oil and vitamin E and the non-prescription supplements that people take. My comment to the patient is a little stronger than what Bill's comment is when Bill said, take it in moderation or consider taking it in moderation. My comment is many of them have antiplatelet effects. We don't know whether it really increases the risk of bleeding if you take it together with a DOAC, but it may. And my preference is that you don't take them when you're on the anticoagulant. So I'm much stronger about that. But it's also my background that I don't believe in too many supplements that they really have beneficial effect. In that case, I am indeed, as you said earlier, more seasoned.

Jori May: So, I think along this line again we're talking about other medications that we're thinking about. So, it's often that a patient, so let's say our 65-year-old patient with an unprovoked DVT comes in and he's still having a lot of leg pain associated with his blood clot. So the pain, the question we often get is well what pain medications are safe for that patient to take? Bill, could you maybe speak to that a little bit? Over-the-counter medications, prescribed medications, what are our options for pain management in people on anticoagulation?

Safe Pain Medications with Anticoagulants

- Tylenol max recommended daily dose 3000 mg for chronic > 7 days; doses above 4000 mg have been linked to liver toxicity
- APAP > 2 grams per day can cause increase in INR when on Warfarin
- NSAIDs?
- Celecoxib safe and appropriate option?
- Opioids no interactions with anticoagulants (Avoid chronic use due to concerns with dependence & addiction)
  - Oxycodone + APAP (Percocet)
  - Hydrocodone + APAP (Norco)
  - Tylenol with codeine
  - Butalbital + caffeine + APAP (Fioricet)

William Braun: Yeah, Tylenol doesn't really have any interactions at all. Slight interaction with the coumadin, but we're not dealing with that usually. But yeah, 3,000 milligrams a day is typically a safe bet if you're going to be on it chronically. Of course, we don't want to get close to 4,000 milligrams because it's linked to liver toxicity. But definitely, you know, acetaminophen definitely is a good option, I think, for pain.

Non-steroidals you want to avoid, you know, increased bleed risk.

You have the COX-2 inhibitors, the Celebrex is definitely a potential option as well, because you don't have the same issues with the typical standard COX-1 and COX-2 inhibitors with the standard non-steroidal anti-inflammatory. So definitely could be an option as well.

And of course, opioids don't have any interactions. But again, there's a fall risk with these patients as well. And that's something to think about. I didn't really discuss earlier, but that's something. You know, I work in the hospital and I see patients admitted for falls with intracranial hemorrhage. So, you know, that's something to keep in mind too, to make sure we're not overdosing on opioids that could potentially cause increased fall risk.

Stephan Moll: Let me make, please, an additional comment. I agree that the nonsteroidals obviously increase risk for bleeding. But so often, patients are being told, you absolutely cannot take ibuprofen or a non-steroidal. And then they suffer through the rheumatoid arthritis or whatever pain they have, the chronic lower back pain. And Tylenol doesn't touch it. I think about Celebrex use, and this comes from the hemophilia population and I feel okay using Celebrex. However, I also tell the patient, look, yes, the nonsteroidals do increase the risk for bleeding in the overall studies, but the overall risk for bleeding is not huge. Keep in mind that we use anticoagulants plus aspirin in a number of people with history of stents and what have you. And yes, we do increase risk of bleeding, but we also need to keep in mind the quality of life of the patients. So I tell them, nonsteroidals, ibuprofen is not unreasonable if you have significant pain, realizing that there's some increase of bleeding, but you may very well do fine. Take just not, take as little as you can. I'm not this black and white, you should not take nonsteroidals. I don't think we do a good service to patients by saying that so strongly.

Jori May: That's helpful. I think it's often helpful to think about too, you know, there's no direct data for this, but in the antiplatelet, anticoagulation world, there's data to suggest using PPIs can be helpful to decrease that risk of GI bleeding. So, if you have that patient that really needs celecoxib or really needs a concurrent medication, is there a benefit from adding a PPI? I can't say for sure. It makes me feel a little better. So sometimes I do. But, but acknowledging the nuance there, I think is really important.

Management of Long-term Anticoagulation in VTE: Case Continued

- 8 months after VTE
- Apixaban 5 mg twice daily
- Patient now requires an elective cholecystectomy for gallstones

Jori May: So, let's say this same patient now, he is, let's say eight months after his VTE, he's on his anticoagulation, he's taking his apixaban five milligrams twice daily, he's doing great, but he's having issues with gallstones and so he needs to have a cholecystectomy. This is, I'm sure, a question that our primary care providers get a lot, and Bill, I'm sure something you deal with even on the inpatient side. So, can you talk a little bit about how we hold anticoagulation for procedures? Maybe talking more about the direct oral anticoagulants, but mentioning too, warfarin, how that literature has changed recently.

DOAC Interruption for Procedures/Surgeries

PAUSE trial

DOAC	Surgical Procedure-Associated Bleeding Risk	Pre-surgery						Post-surgery			
		Day -5	Day -4	Day -3	Day -2	Day -1		Day +1	Day +2	Day +3	Day +4
Apixaban Rivaroxaban Dabigatran, GFR>50 mL/min	High	→	→	→	X	X	(No DOAC)	X	X	→	→
	Low	→	→	→	→	X		→	→	→	→

Modified from: Douketis JD, Spyropoulos AC, Anderson JM, et al. *Thromb Haemost.* 2017 Dec;117(12):2415-2424. Erratum in: *Thromb Haemost.* 2018 Sep;118(9):1679-1680.

William Braun: Yeah, so with the PAUSE trial, that was a pretty big trial in JAMA, actually it was published in 2019, they kind of changed practice a little bit. Before we would be bridging patients and it was very complex in that scenario. But yeah, the PAUSE trial basically showed it was safe that we could hold these medications before the procedure…

DOAC Interruption for Procedures/Surgeries

	Half-life
Apixaban	ca. 12 hrs
Dabigatran	12–14 hrs
Rivaroxaban	6-13 hrs

3x t½ = 36 hrs (1.5 days)

5x t½ = 60 hrs (2.5 days)

Samuelson BT, et al. *Chest*. 2017;151:127-138.

William Braun: …depending on if it's high risk or low risk, based on the half-life of the drug, three times the T half, basically you'd hold one day prior, and then if it's a severe surgery or high-risk surgery. You would go out two days based on the half life of the drug.

DOAC Interruption for Procedures/Surgeries

PAUSE trial

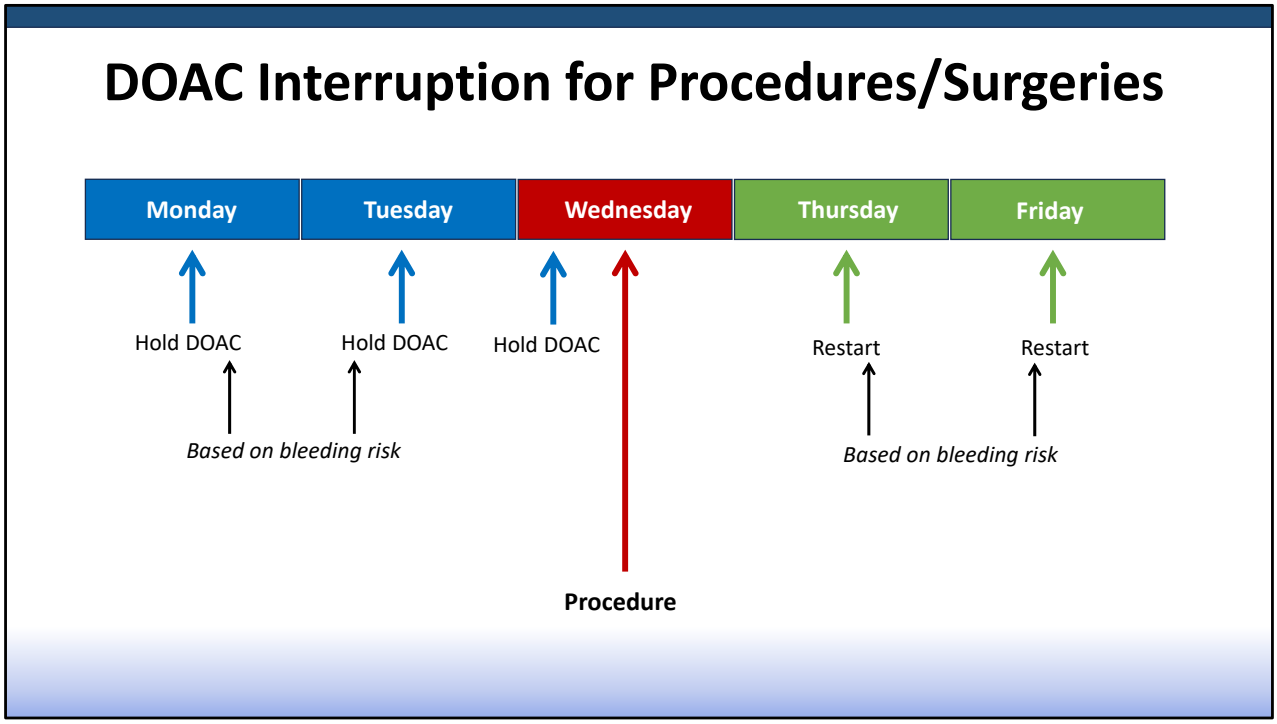
DOAC	Surgical Procedure-Associated Bleeding Risk	Pre-surgery Day -5	Day -4	Day -3	Day -2	Day -1		Post-surgery Day +1	Day +2	Day +3	Day +4
Apixaban Rivaroxaban Dabigatran, GFR>50 mL/min	High	→	→	→	X	X	(No DOAC)	X	X	→	→
	Low	→	→	→	→	X		→	→	→	→
Dabigatran etexilate (CrCl <50 mL/min)	High	→	X	X	X	X	Day of Surgery	X	X	→	→
	Low	→	→	→	X	X		→	→	→	→

Modified from: Douketis JD, Spyropoulos AC, Anderson JM, et al. *Thromb Haemost.* 2017 Dec;117(12):2415-2424. Erratum in: *Thromb Haemost.* 2018 Sep;118(9):1679-1680.

William Braun: And then of course, for dabigatran studies with the creatinine clearance less than 50, we would go out further two days for low risk and then out four days for high risk. And so that seemed to work really well in the study and was really good that we had some sort of guidance in this because there definitely was an issue in the past when these agents first came out. So definitely the PAUSE trial was a significant trial for surgery.

Stephan Moll: An important point there also is when we see a patient who had a recent DVT-PE, we typically recommend for the first three months, we should not do an elective procedure. It should be uninterrupted anticoagulation. And once they're over this acute phase, then it's reasonable to have them off for a day or two or three. That risk of recurrence during those few days is not particularly high. But for example, if a patient presents with DVT-PE, there's a question, they haven't had their screening colonoscopy. We hold off. We don't do that in the first three months. And even more so sometimes there's a more, not more so, but important in a different way. Sometimes there's a more urgent need for a surgery and the patient had a very recent DVT-PE. Then I tell the provider, if you can avoid operating in the first four weeks, then we're really beyond the very acute phase. If they cannot wait for three months, at least wait for four weeks.

Jori May: I think that's really important. And if I might summarize for DOACs, I think I still get a lot of questions about bridging them. And so the take home that Bill said is, there's no bridging in the DOAC world anymore. We basically, based on our assessment of bleeding risk, we hold it.



Jori May: So, let's say the procedure is Wednesday, hold one to two days before. So don't take it Monday, don't take it Tuesday, don't take it Wednesday. And then we usually restart either the day after, on Thursday, or the day after that, on Friday. Some wiggle room with that based on the assessment of risk but that there's no benefit to putting the patient on Lovenox at all in that period of time.

Stephan Moll: And the reason is that the half-life of the DOACs is not that different to low molecular weight heparin. Low molecular weight heparin has somewhat of a shorter half-life, but based on the dosing, low molecular weight heparin and enoxaparin once or twice daily, dalteparin often once daily. It doesn't make any intuitive sense to bridge one short half-life drug with another short half-life drug.

Jori May: Absolutely.

Stephan Moll: Now, you talked about the interruption with a major risk bleeding surgery. You stopped for two days before and nothing on the day of surgery, and I fully agree with that. And the PAUSE trial is a nice algorithm, which I have in our EPIC system as a table, and I import that into the patient's information material. And then when to restart after the surgery, well, with a high-risk bleeding procedure, you don't want to start immediately.

You also don't want the patient on nothing because they were on blood thinners for a DVT-PE history and now they have major surgery. So then I make the point that you want to start probably prophylactic anticoagulation at least. And then when it is safe from the surgeon's point of view to progress, then you can put them back on full dose anticoagulation. But we shouldn't forget about the prophylactic dosing because they had a DVT-PE and are now at high risk because of the major surgery.

Jori May: And Stephan, I think we're going to talk about this in detail in the future, but I think another question when we're talking about holding blood thinners, people may get in their practice is, what about those people that are active in sports that might increase their bleeding risk? So our patient likes to go mountain biking or he likes to play soccer. Can you give us a brief overview of how you think about that or how you approach that?

Stephan Moll: So we said the half life of the DOACS is around 10 hours. That's a relatively wide spread, but for mountain biking, for example, on the weekend. And I asked how significant is the mountain biking that you do? How often have you fallen in the last year? How likely is it that you will have some trauma? And that helps us. Do they really need to come off anticoagulant at all or not? But it's easy enough to skip if they're on BID apixaban, skip the morning dose, or if they're on QH evening dosing of rivaroxaban then don't take the drug on the evening before. Again, not in the first three months when they need uninterrupted, but after three months. And then the risk for another clot if you skip one or two doses is not significant. But the risk for bleeding depends really on what sport they do, how often during the week do they do it, and how often have they actually had trauma, make sure they do the usual with biking and skiing to wear a helmet.

I feel like, Jori, I would love to talk about this a little more, but I don't want to duplicate what we do in podcast number four, because one of my interests, as you know, is high level athletes on blood thinners. And we use an intermittent anticoagulation strategy. Maybe we'll talk a little more about that at that point.

Case: Moving from Anticoagulation Management to Long-term Sequelae of VTE

- The 62-year-old male returns to the clinic 3 months after RLE proximal DVT with persistent RLE swelling
- What do you do next?

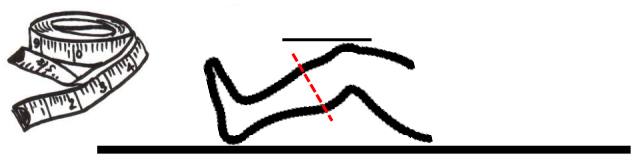
Jori May: I think that's a great idea. Let's save it because I do want us to save some time to talk about these long-term complications of venous thromboembolism. So what we often find, or occasionally will find, is that same patient that we've been talking about, our gentleman that had an unprovoked DVT, is three, six months out, and he's still having swelling in that right lower extremity where his clot was. And so I think the question to the primary care doctor is, well, what do you do next in that situation? And maybe, Stephan, can you talk a little bit about the long-term complications of DVT, what to look for and how to manage that?

Stephan Moll: Sure, and everybody's familiar with the symptoms of DVT, mostly the swelling and pain and leg heaviness and not being able to do what they want to do. And this is not uncommon after DVT-PE and it may stabilize at a certain level.

Examination

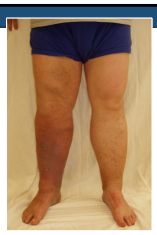
3- or 6-month examination:

- Symptoms?
  - Swelling
  - Pain
  - Leg heaviness
  - Limitations in ADLs
- Leg circumference at mid-calf



Mid-calf circumference: R > L by 2 cm

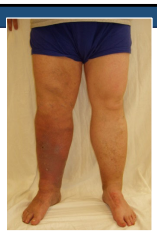
Stephan Moll: When I see the patient at three months or six months, I typically ask about those symptoms, measure the leg circumference at the mid-calf and then make an assessment; has it stabilized, or is it still improving? If it's pretty significant and it's not improving further and its quality of life impacting, then I think what can we do to help this patient?



Post Thrombotic Syndrome

1. Stockings (30/40 mm Hg)

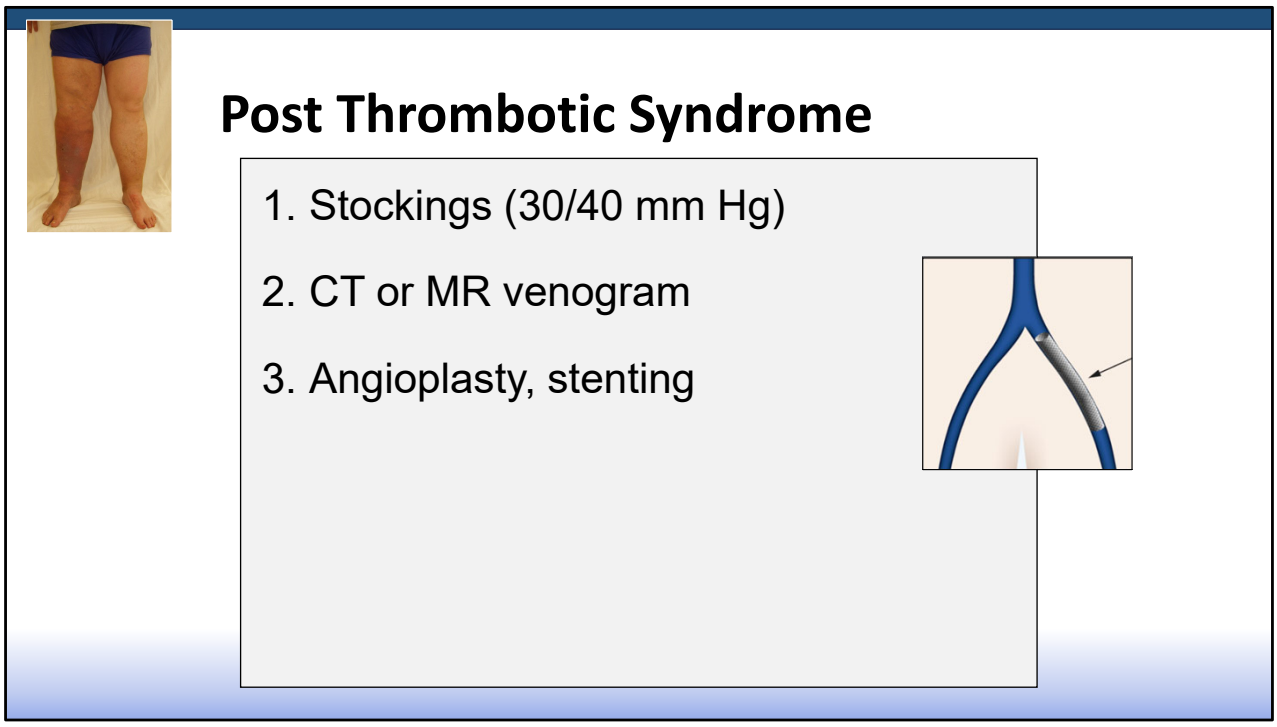
Stephan Moll: Number one, we can recommend compression stockings. And the compression stockings are not mandatory for everybody. That's really up to the patient. Some people find they're beneficial. They should then wear it and they judge themselves. Some people feel they're uncomfortable. We have learned that the stockings don't prevent the post-thrombotic syndrome, they just treat the symptoms. So as long as the patient wears them, they may have benefit. If they don't, then stop them. The post-thrombotic syndrome is there. So you don't prevent the long-term complications. So it's up to the patient whether they wear them or not. So stockings are one option.



Post Thrombotic Syndrome

1. Stockings (30/40 mm Hg)
2. CT or MR venogram

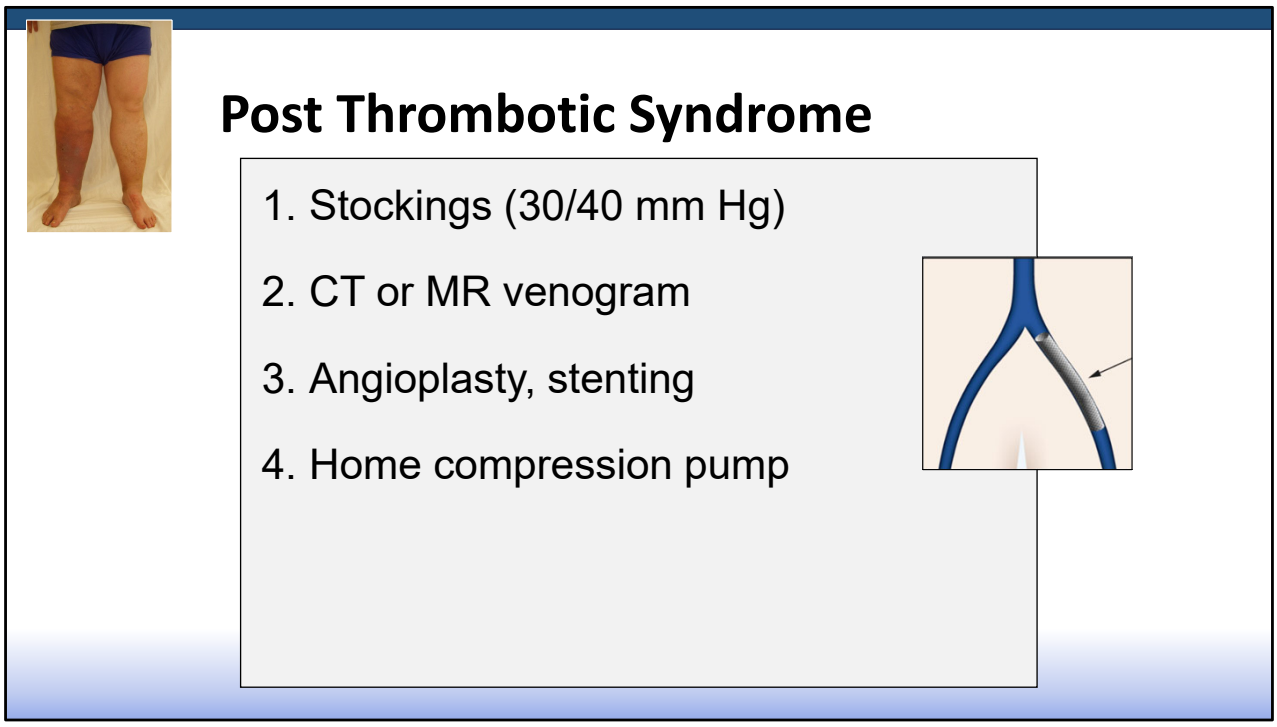
Stephan Moll: Then I tend to get a follow-up Doppler to look at residual scar tissue. And then particularly I think about, and this is maybe going a little too far, or maybe not for a primary care physician, if they have significant symptoms, I wonder if there's some pelvic vein scar tissue that's obstructing outflow. And if there is, then potentially vascular intervention or vascular surgery intervention with angioplasty and stenting might be beneficial. So I then think about a CT venogram. Some people might do an MR venogram, but CT venogram is more widely available, more experience with it.



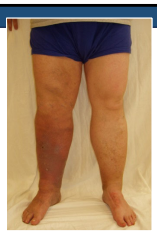
Stephan Moll: And that may well show you that there is some narrowing in the pelvic veins, and then one can send them to vascular surgery or vascular rheology for consideration of angioplasty. However, we don't really know how beneficial these interventions are. In many patients, they don't help.

Faculty Discussion

Stephan Moll: There is currently a trial ongoing called the C-TRACT trial that takes patients with chronic post-thrombotic syndrome and randomizes them into an intervention versus no intervention, because we just don't really know who benefits and is it overall beneficial. Because you could argue, the radiologist, they see a narrowing, they would like to put a stent, a stent is placed, but a stent is a foreign body, it may reocclude endothelial cell proliferation actually things may get worse by doing an intervention. So that's a little bit of an unanswered question, but, and we participate in the C-TRACT trial, so I do refer the patients for consideration and enrollment. But I think it's worthwhile to do a CT venogram, assess the status, and if it's quality of life limiting, then to send the patient to radiology and ask them for an angioplasty with potential stenting.

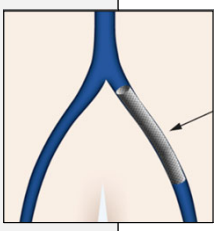


Stephan Moll: And then lastly, and I don't use that very often, I prescribe it often, maybe once or twice a year, a lymphedema pump that can be worn by the patient at home, 30 or 60 minutes in the evening. At least I get symptom relief, next morning they feel better, but once they're up on their feet it swells up again, but then in the evening they can put the pump back on.

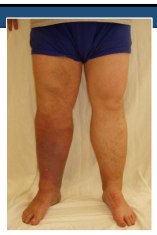


Post Thrombotic Syndrome

1. Stockings (30/40 mm Hg)
2. CT or MR venogram
3. Angioplasty, stenting
4. Home compression pump
5. Pain Clinic (gabapentin, etc.)

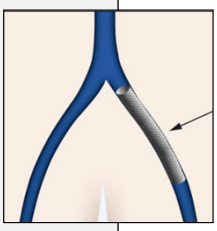


Stephan Moll: And then less commonly, I get involved in the pain management issues; more likely I refer them to the pain clinic for consideration, how do we manage this chronic leg pain?



Post Thrombotic Syndrome

1. Stockings (30/40 mm Hg)
2. CT or MR venogram
3. Angioplasty, stenting
4. Home compression pump
5. Pain Clinic (gabapentin, etc.)
6. Disability assistance



Stephan Moll: And then disability assistance may be appropriate because they cannot do what they used to be able to do.

Faculty Discussion

Jori May: That's a really helpful overview. One thing I want to highlight that I think I come across in my practice is sometimes if there is residual swelling in the leg and say a provider orders an ultrasound and we are six, 12 months out and they do an ultrasound and the ultrasound says there's clot there. Oftentimes people see that, patients see that. If they're off anticoagulation, that makes them uncomfortable that there's clot, something's wrong. Stephan, can you maybe translate that a little bit? Is that concerning to you, is that clot? Does a patient need to be anticoagulated based on that finding?

Stephan Moll: Now that's good that you bring this up, Jori. First of all, I would discourage us from calling it chronic clot because patients often think it's clot, it can still break off, and physicians, some think, oh, it's clot, it needs to be anticoagulated, but it's scar tissue. It does not break off. So the question you are scientifically asking is, does residual scar tissue or residual clot, residual scar, does scar tissue predict a higher risk of recurrence if the patient comes off blood thinners. Should it influence our management? And there are mixed scientific results on that with the clinical studies. I barely ever use the residual scar tissue or clot to determine how long to treat.

We know that 50% of people after DVT will have leftover scar tissue at three or six months. That's really common and no, I would still stop anticoagulation if this was a hip replacement associated DVT. At three months there is scar tissue, it would not influence my management. However, whenever we stop anticoagulation, it's appropriate and it's recommended by the International Society on Thrombosis and Hemostasis, ISTH. And I agree with that. I do that too. Whenever we stop anticoagulation, we should get a baseline Doppler ultrasound. And why, not to look is there scar tissue or not? And should I restart the anticoagulant? Or should I maybe not have stopped? But we do that so that if problems come up in a year or two, new leg symptoms, and there's a DVT then diagnosed, we know this is new since the patient came off blood thinners, and that's where the baseline study comes in. I don't do that for pulmonary embolism. I don't do a routine follow-up CT scan for two reasons. Number one, the lung has a huge potential to dissolve blood clots. So after a PE very frequently the lung returns to normal and the CT is radiation exposure so I like to avoid that. But people after a PE, particularly after the major PE that was not treated with thrombectomy for example or that was only partially the clot was removed people may develop the chronic PE syndrome, and we'll get to that a little more.

But the scan to do after a PE three, six months later is not a CT scan to assess, it's a lung damage but it's a VQ scan. The CT scan is not sensitive to pick up chronic perfusion defects. The VQ scan picks it up. And if there are multiple perfusion defects and there is concern for lung damage and pulmonary hypertension with right heart strain, the VQ scan shows the perfusion defects, then a referral to the pulmonary hypertension clinic or in general to the pulmonologist is appropriate for the consideration of a right heart cath, pulmonary artery pressure measurement, and then the decision should this patient be sent for a pulmonary endarterectomy.

Case: Sequelae after PE

- Original 62-year-old male had a PE instead
- Returns to your office 3-6 months later with improved, but still present, shortness of breath and fatigue

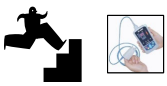
Jori May: So, you've dived into a really important topic, Stephan, and if we can maybe take a step back. So now, you know, we're venturing into long-term management of PE. And so similarly, if our patient comes in six months down the line and they're still having shortness of breath, you know, they're still feeling fatigued. You brought up this idea of post-PE syndrome and the imaging you would do for that. Can you kind of take us briefly back and then talk about, you know, again, you already talked about the imaging, VQ scan is helpful. But just an overview of what post-PE syndrome is and what a primary care doctor should be looking for in order to catch that.

Stephan Moll: Important point. So, after PE, the symptoms often improve in the next few weeks and months, and even at three months, it can still improve. But when the patient says symptoms have leveled off, that's when you start to think, is there chronic lung damage done?

And I like the term post-PE syndrome because it really, sometimes patients have this unspecific chest pain, chest discomfort. They may not be able to do what they used to be able to do. More shortness of breath. That's the post-PE syndrome, symptoms that are sometimes unspecific. It's only the more severe damage that gets done to the lung that leads to pulmonary hypertension that then is called CTEPH, or chronic thromboembolic pulmonary hypertension.

After a PE: Work-up

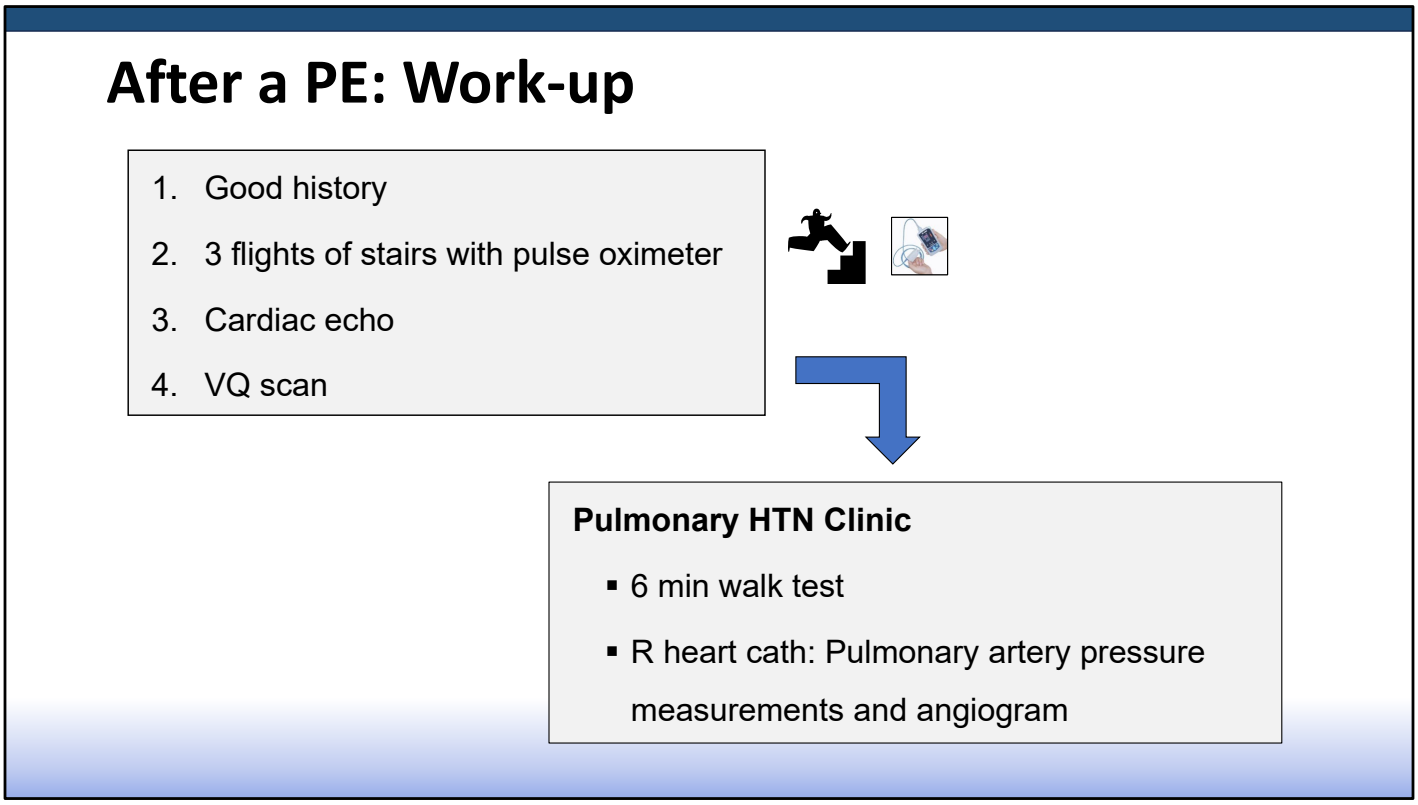
1. Good history
2. 3 flights of stairs with pulse oximeter
3. Cardiac echo
4. VQ scan



Stephan Moll: Stephan Moll: So, what I do in clinic when I see them at three months and what physicians in who see these patients, the stepwise approach is a good history. Are you back to your normal self, fatigue, et cetera, et cetera? What I actually do is in our clinic, I run three flights of stairs with a patient with a pulse oximeter and see how they do. Do they desaturate?

If the history suggests there's some residual symptoms or if they desaturate, or if they had a big PE in the past, even if they have recovered, I get a cardiac echo to look for a right heart strain. The echo is not very sensitive to pick up a right heart strain and pulmonary hypertension, but it's still a non-interventional study.

And if the patient really has significant leftover symptoms and clear desaturation, then I get a VQ scan to look for perfusion defects. And if then the perfusion defects are present, then I get the help of the pulmonologist. Now, the general practitioner, depending on how comfortable they are, they may order the VQ scan. And I wouldn't do that too early. I wouldn't clearly not do that within the first three months. And I actually don't like to do it before month six, because people really improve over the next six months or so. But if the primary care physician is comfortable and at six months, the patient still has significant symptoms, then a VQ scan can be ordered by them. If the VQ scan is normal, then the shortness of breath is not due to perfusion defects.



Stephan Moll: And then you start to wonder about bronchospastic disease or some other interstitial lung disease and what have you. The one exemption where I do get a VQ scan and cardiac echo fairly routinely at six months is a patient who had a big PE, a central PE or really in the main pulmonary arteries, even if they've recovered completely, I typically would obtain an echo and VQ scan, particularly in the young people, because the young people have a lot of ability to compensate for some lung damage, and they may still develop pulmonary hypertension where eventually pulmonary endarterectomy might be appropriate. So big PE at six months, I think about VQ scan and cardiac echo.

Conclusion: Pharmacy

- Don’t use DOACs with apalutamide, carbamazepine, fosphenytoin, phenytoin, rifampin, St. John’s wort
- Provider should have a low threshold to use a web-based drug-drug interaction database, particularly when patients are on chemotherapy drugs, seizure medications, HIV or antifungal medications
- Make sure to ask patients about herbals/vitamins they may be taking to assess added bleed risk
- Safe pain medications: Tylenol, celecoxib

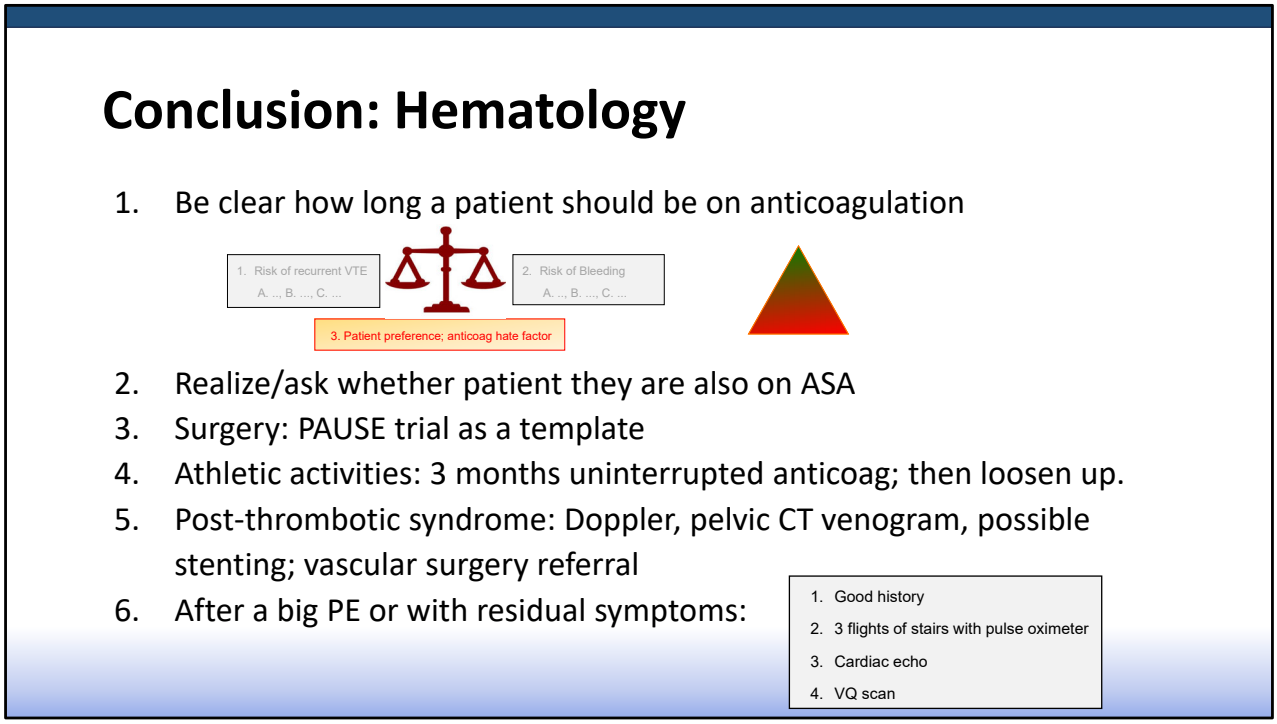
Jori May: Fantastic. Thank you for going over that. And I think we are approaching the end of our time. There's much more we could talk about, but I was hoping each of you could share a few take home points. And maybe Bill, I'll start with you from a pharmacy perspective, long-term management of VTE. What are the things you want our listeners to remember?

Yeah, so all DOACs, you need to avoid carbamazepine, fosphenytoin, phenytoin, rifampin, St. John's wort. So that's across the board. You can just get straightforward.

The other more complex situations, I think using interaction database is definitely should be utilized with chemotherapy drugs, seizure medication, HIV and antifungal medications.

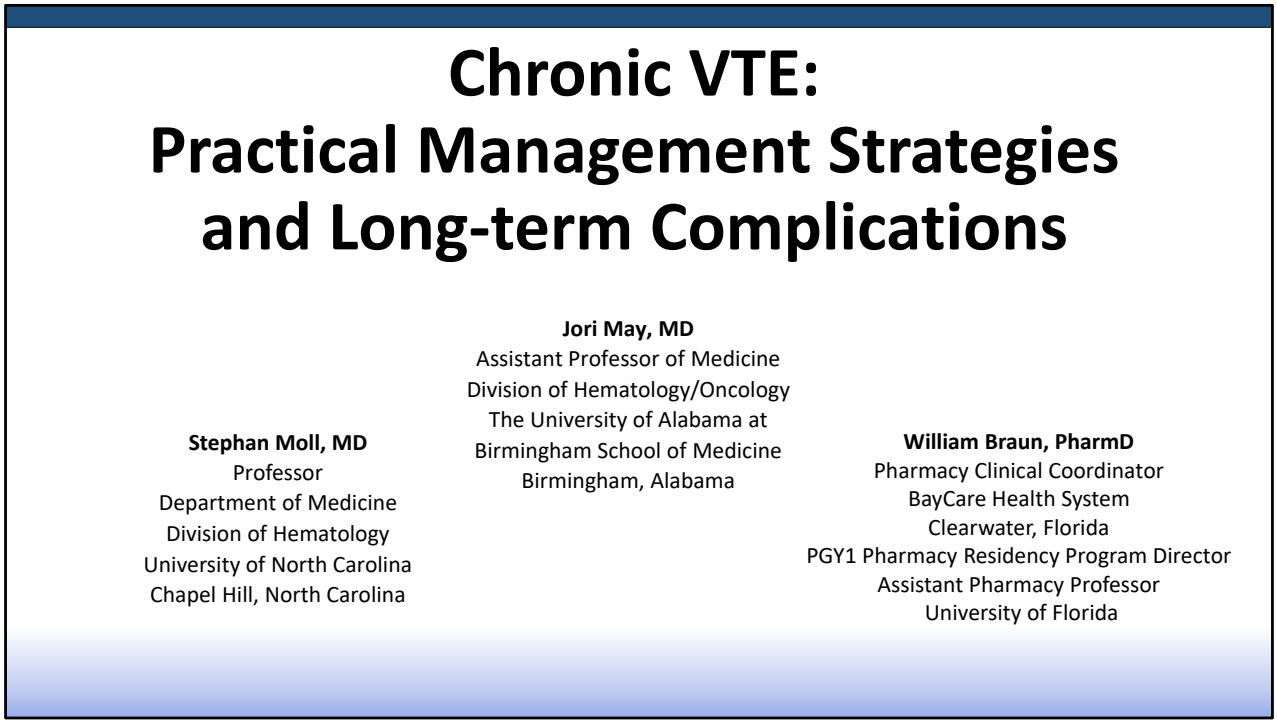
Definitely ask your patients about herbals and vitamins. It's very important, as Stephan brought up earlier.

And then safe pain medications, Tylenol, Celebrex are good options for pain to treat the VTE. So those are my take home points.



Jori May: Great, thank you. And Stephan, what about you? Some take home points for our listeners.

Stephan Moll: First of all, the simple one, be clear that the patient really needs to be on long-term anticoagulation based on the recurrence triangle that we discussed. Secondly, make sure that the patient is not on aspirin, or if they are, they really have a good indication to be on it. Thirdly, we've talked about the interruption at times of surgeries. Not in the first three months, but okay if after three months. Use the PAUSE trial as a good template for major bleeding risk, stop for two days prior and nothing on the day of. For minor bleeding risk, one day before and nothing on the day of and then restart afterwards. And then post-thrombotic syndrome, we just discussed very recently the follow-up Doppler, pelvic CT venogram and consider possible referral to vascular radiology for possible angioplasty and stenting. And finally, after a big PE or if the patient has residual pulmonary symptoms of post-PE syndrome, good history, run three flights upstairs with a pulse oximeter, cardiac echo, and VQ scan.



Jori May: Fantastic. So this concludes our discussion of the management and long-term sequelae of chronic VTE. A huge thank you to Stephan and Bill for talking with me today. I think this was a valuable discussion, very high yield for our listeners. On our next podcast, we're going to be talking about management of VTE and special populations. So some of those things that we touched on, high-performance athletes, renal failure, obesity, you're not going to want to miss it. So please tune in and don't forget to complete your CE evaluation and claim your CE credit and thank you for your attention.