

Behnood Bikdeli:

Hi, everyone, and welcome to this podcast sponsored by the American Heart Association on safe and effective use of anticoagulation for management of venous thromboembolism, also known as VTE. I'm Behnood Bikdeli. I'm a cardiologist from the section of vascular medicine at Brigham and Women's Hospital and Harvard Medical School, most affiliated with Yale Center for Outcomes Research and Evaluation. I'm very excited to be with you today to discuss things that we consider when we want to select safe and effective management strategies with respect to anticoagulation for our patients. We hope to get a better understanding of the general treatment paradigms of safe and effective anticoagulation, but also we'll be touching upon some specific patient populations such as those with kidney disease, antiphospholipid syndrome, or those who have obesity, particularly class III obesity. And I'm so excited, thrilled, and honored to be joined with my great colleague, Dr. Tara Lech. Tara, would you mind going ahead and introducing yourself please?

Tara K. Lech:

Well, thank you so much, and I'm excited to be here, Behnood. So as you said, I'm Tara Lech, and I'm a pharmacist who specializes in anticoagulation management. I'm currently the director of anticoagulation services for the Beth Israel Lahey Health System, and before that I was managing an anticoagulation clinic at the Lahey Hospital with about 2,500 warfarin patients and 500 DOAC patients. So I'm very familiar with these medications, and I'm looking forward to being here with you today to discuss their safe and effective use. And I think it's important to know that neither Behnood or myself have any potential conflicts to disclose.

Behnood Bikdeli:

I have no relevant disclosures for this talk either. As we were discussing, anticoagulation is really the cornerstone for treatment of venous thromboembolism or VTE, which includes patients who develop deep vein thrombosis, you might have heard of it as DVT, or pulmonary embolism, also known as PE. That being said, there are a lot of nuances and challenges to go over when we want to decide the type of anticoagulant, intensity, duration, et cetera. In my mind, these may include the acuity of presentation and illness severity, comorbid conditions, other medications that the patients receive, organ function, risk of bleeding, invasive procedures, adherence, and of course clinical judgment. Last but not least, there is also shared decision-making factors to consider, what are the patient preferences. This is a lot, but let's start with a case vignette and see where we are going with it.

Let's assume we have a 49-year-old woman who develops pleuritic chest pain two days after having an otherwise uneventful cholecystectomy for acute cholecystitis. Upon presentation with this chest discomfort, blood pressure is okay but systolic is in one teens, heart rate is 76 speeds per minute, saturating fine on room air, and there is only a history of mild asthma, diabetes, and an elevated body mass index for which patient is receiving metformin and an SGLT2 inhibitor. A CT pulmonary angiogram is obtained, which shows filling defects in lobar as well as segmental vessels.

So assuming that the patient is stable, it's reasonable to consider oral treatment, and this could be considered with a DOAC or other regimens. And I think this is a nice time to quickly talk about the choice for initial anticoagulation. Recent guidelines actually prefer DOACs as a first line agent, and when we say DOACs, we are referring to direct oral anticoagulants. These regimens are preferred over our older regimens of heparin followed by warfarin in large part because individual randomized trials and pulled analyses off of them have shown that the effectiveness is actually very similar to vitamin K antagonists with the difference being their more convenient and probably safer, but lower risk of intracranial

hemorrhage. This was demonstrated in a meta-analysis of randomized trials that were published in PLOS One five years ago. Tara, what do you think about this?

Tara K. Lech:

As a pharmacist, I'm often asked quite a bit about initial drug selection during that initiation phase, and this is when we have to really step back and think about things like are we going to start a parenteral agent like a low-molecular-weight heparin or are we going to start right up upfront with the DOAC using those loading doses or starter packs? So historically, whenever we talked about low-molecular-weight heparin outside of cancer-associated VTE treatment, we were using it as a bridging agent until the patient was therapeutic on warfarin, for example. So this meant that we would have to overlap the low-molecular-weight heparin with warfarin for at least five days or until we have two consecutive INRs in the therapeutic range. This is really cumbersome from patients and providers, so it's typically not a strategy that we use whenever possible.

We try to go with that DOAC approach, especially given all of the strong guideline recommendations supporting the use of DOACs as first line in many situations. So we try to reserve this really now for only those patients who cannot afford DOACs or those that are deemed to be unacceptable for DOAC therapy. And those are typically your patients with a new thrombosis and a history of a mechanical mitral valve, a mechanical circulatory support device, patients with high-risk APLS or antiphospholipid antibody syndrome, pregnant patients, patients that are lactating, and also those patients that might have a drug-drug interaction that precludes the use of a DOAC. We also have to use caution in severe renal or hepatic dysfunction, and in these cases warfarin may still be the drug of choice. We should mention that in pregnancy, really neither DOAC or warfarin is the drug of choice, and in most cases, those patients would be treated with a low-molecular-weight heparin has monotherapy.

I think another important point for providers to remember is that if you do have to start your patient on warfarin with this Lovenox bridge, it is not just a five-day bridge. I think that day of timeframe gets stuck in people's heads. And a lot of times in the clinics, we'll see patients get sent out with a five-day supply of Lovenox and then we're struggling on the outpatient end to get them a new prescription. I think it's important to know that warfarin has a very slow onset of action and it can typically take patients five to 10 days to actually achieve that therapeutic INR. So it's important to give them refills or send them out with at least a one to two week supply of medication at a time.

When you're starting warfarin, the typical starting dose is five milligrams unless the patient has risk factors for warfarin sensitivity. We're really trying to get away from those 10 milligram loading doses because patients tend to have their INRs jump very quickly in this scenario, and that can be very challenging, especially with a low-molecular-weight heparin in the background. If patients are deemed to potentially be sensitive to warfarin, meaning your patients with advanced age over 65, patients that are malnourished, patients that have significant drug-drug interactions, we tend to use a lower dose and initiate 2.5 milligrams dosing.

I think it's important to note that a couple of decades ago, pharmacogenetic testing was a hot topic, but we don't routinely use this in clinical practice because the information is very rarely available in a timely manner. But if you were to have that information, it can help you make those decisions upfront as to what dosing might be best for your patient as that initial starting dose. It's also important to know that if you don't have an anticoagulation clinic to refer to, there are nomograms out there that take into account gender, BMI, concomitant medications, and help you come up with a streamlined way to initiate warfarin dosing. One of those websites is [www.warfarindosing.org](http://www.warfarindosing.org), and they have been shown to lead to a more rapid therapeutic dosing of warfarin and give you less of a tendency to overshoot that initial anticoagulant effect.

And then I think the other important thing to note is that now with the advent of DOACs, there is another type of bridge that involves starting a parenteral therapy, a monotherapy of a low-molecular-weight heparin upfront, if you are planning to initiate dabigatran or edoxaban as your drug of choice for DOAC management. In this case we are not overlapping drugs. Instead, you have to start a five to 10-day monotherapy, low-molecular-weight heparin treatment plan, and then switch over to either your oral direct thrombin inhibitor dabigatran or your oral factor Xa inhibitor edoxaban. And this is only done in the management of acute VTE. If your patient has AFib and you're using these agents, you should just start by initiating the DOAC.

Behnood Bikdeli:

These are such important points. Thank you so much, Tara. So if I got it right, it seems like there are still certain patient populations, and we will talk about them in a few minutes more, for whom we may need to consider vitamin K antagonists and that requires bridging anticoagulation for management of venous thrombosis. Alternatively, we have direct oral anticoagulants such as edoxaban and dabigatran, which do not need a bridge, but need an initial phase of treatment with heparin-based regimens.

Now let's switch gears a little bit. There might be another alternative option, which is probably a little more straightforward for patients and clinicians alike, and that is the other direct oral anticoagulants such as apixaban and rivaroxaban. In those cases, I think they are helpful in the sense that you don't have to switch cross agents. It's just that you need a loading dose with them. In the case of the apixaban, typically it's going to happen with a week worth of 10 milligrams twice daily, and then we will follow with the standard regimen of five milligrams twice daily. And as far as rivaroxaban is concerned, we do 15 milligrams twice daily for 21 days and then we transition over to 20 milligrams once daily. And I think these are very interesting and exciting regimens. To make it even easier for clinicians and patients, there are starter packs that are available for the first month of therapy just to make it more streamlined.

Tara K. Lech:

Yes, and I think even though we have those starter packs in streamlined dosing, one thing that we commonly see people in practice get wrong from time to time is your dose suggesting of DOACs. We're so used to doing it with our AFib population, but it's just so important to remember that when we're treating venous thromboembolism, we do not dose adjust for renal dysfunction. So we're not looking at that creatinine clearance cutoff of 50 for rivaroxaban, or using those two out of three criteria like we do for apixaban of age greater than 80, creatinine greater than 1.5, or body weight less than 60.

Instead, if you deem your patient to be a candidate for DOAC, they're getting those starter pack doses so that 10 BID for seven days that you talked about for apixaban, or rivaroxaban 15 milligrams twice daily, followed by 20 milligrams daily after 21 days. We're not using the doses of 2.5 milligrams BID of apixaban or 15 milligrams daily for rivaroxaban. Because there's no dose reduction, that just means that you really have to use your clinical judgment when choosing appropriate agents in determining if either of these medications is appropriate for your patient.

And you know, Behnood, I think it's important to know that the prospective clinical trials for rivaroxaban excluded anyone with creatinine clearance of less than 30 ml per minute. However, the package insert will tell you to avoid use if the creatinine clearance is less than 15 mls per minute. This can be a little bit confusing to providers or patients that may not be familiar with that data. And I really think it's just important to acknowledge that this recommendation is based primarily off of pharmacokinetic and pharmacodynamic data and recommendations.

Similarly, the same is true for the randomized control trials for apixaban. In their VTE trials, they excluded patients with a creatinine clearance of less than 25 mls per minute or assume creatinine greater than 2.5 milligrams per deciliter. But again, their package insert has the same language for use unless creatinine clearance is less than 15 mls per minute. So this is just something to be familiar with, that if your patient does have an elevated serum creatinine or does have a creatinine clearance that hovers somewhere between this 15 and 30 mls per minute, there really is not a lot of prospective data to help guide your decision making.

It's also good to point out that the apixaban package insert has language surrounding use in dialysis, and it is recommended that no dose adjustments are necessary. But again, this is largely based on how the drug behaved in small pharmacokinetic and pharmacodynamic studies, and we do not have any data to support an appropriate dosing strategy in the management of VTE. Similarly, patients with advanced chronic kidney disease or end stage renal disease are a subgroup of populations that are extremely tricky to manage. They have both an increased risk for thrombotic events and hemorrhagic events, so treatment really has to be tailored and shared decision-making is key.

In this patient population, there's going to be a concern for drug accumulation leading to an increased risk of bleed with long-term exposure. We really need to pay attention to drug-drug interactions. Drugs that inhibit the metabolism of the DOAC and or use of antiplatelet medications in the background are going to potentially increase your patient's risk of bleeding. And again, most of the data in this space comes from our AFib patient population. And as we mentioned, VTE dosing is different and there are no dose adjustments for renal insufficiency. So it's really tricky to know if this dosing regimen is appropriate and applicable for this patient population.

But again, I think regardless of which agent is selected, all patients will require clinical monitoring even if your patient is on a DOAC. And it's really important for providers to make that clear when they're talking to their patients. This monitoring is typically going to involve a baseline and ongoing complete blood count. We really want to pay attention to baseline hemoglobin, hematocrit and platelets, a complete metabolic profile, looking at serum creatinine, liver function tests, albumin, total bilirubin and INR, and being aware that of signs and symptoms of bleeding, and make sure that's clear to your patient.

Warfarin patients are going to need more frequent labs. Their INRs have to be checked often in order to ensure they're in the therapeutic range. And again, please make it clear that your DOAC patients should have their labs checked at least annually to make sure the drug is still appropriate to be continued at that same dosing regimen, and that there may be the potential for more frequent monitoring if there is any concern for new drug interactions or new renal or hepatic dysfunction. So let's move on to something else. Okay, Behnood, with no head-to-head DOAC trials, how do you choose the right agent for your patient?

Behnood Bikdeli:

Thank you, Tara. That's such an important point. And you're right, we would love to see randomized trials that incorporate different agents and different arms such that we would be able to inform our recommendations to our patients, but such data do not exist. That being said, I think it's reasonable to explore the options a little more. And we talked about warfarin and vitamin K antagonists, and occasionally some of the scenarios where there might be reasonable, and we will get back to a couple of them later on during our conversation. But for the most part, because of the data that we shared, because direct oral anticoagulants have at least non-inferior efficacy in reducing recurrent venous thrombosis and also some potential safety advantages including reduction in intracranial hemorrhage, not to mention the convenience of using them for patients and clinicians, a lot of clinicians and also guidelines including those by chest endorse DOACs over vitamin K antagonists in these cases.

And when it comes to the choice of DOACs, it's a practical choice, the insurance coverage, et cetera, patient preferences. But one of the other factors is, is the patient stable enough not to require parenteral treatment or not? And many of our patients are quite stable, so there is really not much of necessity to initiate parenteral anticoagulation. In that case, I think the DOACs that require an initial heparin-based regimen might be a little less convenient to clinicians and patients. So those are the broad things that I keep in mind, but also love to hear what your take is.

Tara K. Lech:

Thanks, and that's a great question. So as a pharmacist, some of the things I think about are patient adherence. Is my patient more likely going to take a once daily medication or a twice daily medication long-term? I think about their drug interactions. Would one drug be preferred over another? Another thing I think about is affordability of their medications. Because if they can't afford the medication routinely, then that leads to a lower chance that they're going to actually pick it up. So with the DOACs, we do have some strategies that we can use when we work with our patients in the clinic. We'll try to put through a prior authorization to get the drugs covered at a lower cost whenever possible. Both at apixaban and rivaroxaban have drug assistance programs. Unfortunately, not all patients will qualify. We do help whenever we can with copay cards. They do exist primarily for our commercial insurance patients. And with our Medicare patients, it's important to know that they do not qualify for these manufacturer cards. So we do have to look for potential other options for these patients.

One of the things that we do struggle with is that sometimes patients do leave the ED or a clinic or office with one of those free starter pack cards. So this gives every patient that initial 30-day supply with those loading doses of DOAC and a couple of weeks of the maintenance dose. But it's always important to assure insurance coverage once that card runs out because if the patient cannot afford the drug, now they're home with an acute clot, still within that three-month window, and they may not be able to afford their next month of DOAC therapy, and that can leave us scrambling, trying to get them onto warfarin with an appropriate bridge, initiating low-molecular-weight heparin. And unfortunately, if we can't find an acceptable plan in the outpatient setting, these are the type of patients that end up back in the emergency department. So we want to try to avoid that whenever possible. What are some other factors that you consider when you're starting your patients on anticoagulant therapy?

Behnood Bikdeli:

Yeah. Thank you, Tara. I think that was an excellent summary of important points to consider. Some of my research is related to venous and arterial thrombosis in older adults, and I get to think about the medication burden and how often they have to take medication. So I think that's one factor, no one-size-fits-all answer there. But do we want to give a once daily medication such as rivaroxaban, especially if they need assistance from somebody else to take their medications? Or are they comfortable to take a twice daily medication such as apixaban? So I think that's one thing that we should individualize. The other one is rivaroxaban, especially at the doses that we give, 15 or 20 milligrams once daily, should be taken with the largest meal of the day. Is this something that the patient or family members remember to adhere to versus a apixaban which doesn't have this mandate?

And last but not least, I'm going to step into your field of expertise a little bit. There are drug-drug interactions to consider, and the ones that I remember, please correct me if there is other issues to consider, the common ones would be strong CYP3A4 or P-glycoprotein inhibitors. A common example in the days of COVID was Paxlovid, which has ritonavir, leads into excess dosage of plasma dosages of direct oral anticoagulants. For rivaroxaban, many experts recommend for the drug to be stopped. For apixaban, more of the same, even though less strongly. And quite the opposite, also very potent

inducers of CYP3A4 and P-glycoprotein. Common examples are anti-seizure medications such as carbamazepine.

I think in those cases it's important to consider them because probably those are the kind of patients we want to choose options other than direct oral anticoagulants. And I would love to hear your take about it in a minute. Warfarin might be tricky there as well. If we go with low-molecular-weight heparins as an exception, that's something to consider. And cancer is a whole separate issue, but I know that it's being covered in other podcasts in this series. So let me take a pause, I'd love to hear more from you, Tara.

Tara K. Lech:

Thank you. Yes, this is something that I always struggle with. And one of the things I often tell providers is, just because I can use warfarin in these situations, doesn't mean it's safer or better because these same drug interactions still exist. Now I just can get a visual cue of how much or how little warfarin I have on board. So it gets very tricky. Another thing with strong inhibitors, we also have those interaction warnings for those moderate inhibitors of PGP and CYP3A4 drugs like diltiazem, verapamil that are also in the background.

Something that I always try to keep in mind with drug-drug interactions is, yes, I may know how to manage one interaction. There may be some papers of PKPD that look at drug accumulation or say like, "Yes, levels are higher, but it didn't have clinically significant outcomes." But again, anytime you start to have multiple interactions on board, that's when we start to get more concerned. And if you have multiple interactions like a couple of moderate inhibitors on board and declining renal function in an elderly patient, that's when we have to be more concerned and start talking and having these conversations with our patients.

And then another thing that we really try to focus on, especially in our clinics, are those pharmacodynamic interactions that we may actually be able to do something about by having close discussions with providers like yourself and bringing to attention patients that might be on an antiplatelet medication like aspirin or clopidogrel or ticagrelor in the background because these can amplify bleeding risks. And oftentimes, unfortunately, we don't catch them until the patient comes in with a bleeding event and then we say, "Oh, we could have switched the clopidogrel to aspirin, or potentially we could have stopped the aspirin completely. So let's do that now so the patient doesn't have another bleed." But let's start being more proactive.

Anytime you're starting an anticoagulant, screen that medication list. And if you see an antiplatelet assess for appropriateness, and if you don't think that you are the right person to assess for appropriateness, then bring it to the attention of their cardiologist or their vascular medicine physician or their neurologist, because many times you can stop and that can provide a safer background or profile for the patient while they're on anticoagulant therapy. What is your approach to managing these patients on combined anticoag and not antiplatelet therapy?

Behnood Bikdeli:

Thank you, Tara. These are such challenging situations, but so important to think about. And without following a cliché, I really think these are the kind of cases in which a multidisciplinary approach in seeking wisdom of different experts, pharmacists, then thinking of pharmacokinetic and pharmacodynamic interactions, clinicians who might be involved with the risk of bleeding, including a neurologist, neurosurgeon, or a gastroenterologist who would think of the risks of antithrombotic therapy. And the other side of it, clinicians including cardiovascular medicine specialist, vascular medicine specialist, neurologist or hematologist, even critical care medicine specialists who think of

whether or not there is benefit, there is gaining more of intensified antithrombotic regimen. And really, there is no easy answer. A lot of what we discussed with patients who have venous thrombosis comes actually from the AFib world.

That being said, I can tell you triple therapy, or in other's words, triple threats is rarely the answer. So except for very critical situations, I do not use dual antiplatelet therapy plus treatment dose anticoagulation. Maybe for a week after a STEMI or something like that, but otherwise try to deescalate. And do all therapy. It's really a case-by-case basis where you want to keep treatment dose and anticoagulation for acute venous thrombosis and keep an antiplatelet agent on board, be it for a recent stent, recent myocardial infarction or other situations. And once the patients become stabilized, so-called stable ASCVD, then I think we are in a more nuanced situation without a lot of data. If we want to extrapolate from some clinical trials in the AFib space, for some of these patients, anticoagulation monotherapy might be a reasonable choice. For some others, we may opt to continue single antiplatelet therapy either with aspirin or a P2Y12 inhibitor in addition to anticoagulation.

And then interestingly, we also have the compass regimen in this day and age, which includes very low dose rivaroxaban at a dose of two and a half milligrams twice daily in addition to low dose aspirin. And interestingly enough, in a sub-analysis, it was also shown to reduce the risk of subsequent venous thrombosis. I don't know which of these regimens would be superior. So until we have high-quality data, I think we could just share the potential options and benefits and risks with patients and make a collective decision along with the multidisciplinary team that I alluded to.

Tara K. Lech:

Excellent. Yeah, I mean these are all fantastic points and this is exactly why I tell the clinicians that I work with in my clinic, in the outpatient space, every patient is worth having a conversation for. These cases are so nuanced, and I appreciate you kind of guiding us through your thought process when you approach these patients.

I think another thing that comes up quite often at my clinic is this decision point of when do you transition from maintenance dosing to extended phase dosing, and what exactly does that mean? I think even for a lot of clinicians out there, knowing at the three- to six-month mark, what should we be doing? What are we thinking about? And I was hoping maybe you could tell us a little bit more about what exactly extended phase dosing is when we evaluate for it and kind of how you go through that decision making process for your patients.

Behnood Bikdeli:

Of course. Thank you so much. I think thanks to the existing body of literature and not only those that have shown the risk of recurrence or adverse events in people who have not been treated, but also randomized trials that have shown benefit, it's now routine practice to treat patients for a minimum of three months and typically up to six months with an acute symptomatic venous thromboembolic event. The real question is, where do we go from there? And in my mind, I can think of three groups of patients in terms of the baseline event. One that we want to mention and set aside fairly quickly is cancer-associated VTE, which our other colleagues will get to in separate podcasts. But of the other patients, the two big categories that I tend to think about are provoked venous thromboembolic events, those that are coming off of a major provoking factor, be it hormonal changes or exogenous hormonal use or major surgery, major trauma, things like that versus unprovoked venous thromboembolic events, the ones that do not come with a trigger.

Regardless, once we complete the initial phase of treatment three to six months, after is a compelling case to continue anticoagulation, and we will talk about that I believe soon enough. The question becomes do we still continue the initial dosing? For example, for apixaban, do we continue the five milligram twice daily dosing? Or for rivaroxaban, do we still continue the 20 milligram once daily dosing? Or do we switch to so-called reduced dose, or the term that I like, low intensity direct oral anticoagulation such that you're giving apixaban two and a half milligrams twice daily or rivaroxaban 10 milligrams once daily? And I want to clarify, this is not dose adjustment. This has nothing to do with renal function. It's just because randomized trials for patients who completed the early phase of treatment tested these lower intensity regimens, and they found that they help, but they probably cause less bleeds. What are your thoughts, Tara?

Tara K. Lech:

I agree. I think there are lots to consider for these patients. It's usually a shared decision-making process. And yeah, at this six-month mark, if they've been effectively treated but they still have some risk, the risk is never zero once you've had an event, given the bleed risk is low for the patient, it can be a good time to switch to the reduced dose DOAC. A lot of the trials looking at the low dose efficacy, they were tested against placebo. So I think that's important to know that a lot of times, even a small dose of anticoagulant is going to be better than nothing. But there is actually one trial, the EINSTEIN CHOICE, which looked at rivaroxaban. This was the only DOAC to go head-to-head versus aspirin in prevention of recurrent VTE. And they compared rivaroxaban 20 milligrams and that reduced dose, again, not dose adjusted dose, but reduced dose rivaroxaban 10 milligrams to aspirin, and both doses showed a decrease in the VTE recurrence risk without a significant increase in major bleeding.

But again, it's important to know that this study was not powered to compare the safety and efficacy of the rivaroxaban 20-milligram dose to the rivaroxaban 10-milligram dose. But if affordable, that rivaroxaban 10-milligram dose could be a nice alternative for your patient given its safety profile, the fact that it did show to be better than aspirin and now it takes away that need to be taken with food. As we mentioned earlier in the podcast, those doses of rivaroxaban 15 milligrams or 20 milligrams must be taken with food or you can have a significant impact on the absorption and efficacy of the drug. But once you start taking those 10 milligram doses, it's much more bioavailable. So it can be done with or without food.

But whether or not you reduce the dose, the anticoagulation duration really should be assessed at least annually. And the most important thing that we can ask of you to do as a provider is to clearly document how long a patient needs to be on therapeutic anticoagulation for the index event because this can have a significant impact down the road should your patient develop another comorbid state like atrial fibrillation. Can you talk to us a little bit about what you do for your patients and how you make those kind of decisions and documentation?

Behnood Bikdeli:

Of course. Again, I think this is a very, very interesting point that you made. And full disclosure, I think there is a lot of unknowns that we have and a lot of decisions that we make come with imperfect data. But one thing that we've learned is, really, the decisions for either the duration or intensity of anticoagulation are not set in stone. In statistical terms, I would like to think of them as time varying covariates. And what I mean by that is, there's a dynamic nuance of the thrombotic risk might be going up or down based off of the clinical situation that our patient has, and so would the bleeding risk. So we really need to think of the trade-off.



Without getting too much into the weeds, I think one case that we might be potentially considering is somebody who's been receiving rivaroxaban full intensity, 20 milligrams once daily for a few years, or secondary prevention for venous thromboembolic events, and now imagine the patient could develop atrial fibrillation. And again, hypothetically, let's imagine creatinine clearances like 40 or 45. So the patient technically qualifies for dose reduction for the eighth of indication, right? So the question becomes, does this 15-milligram once daily regimen, which hasn't been studied in venous thromboembolism in a randomized trial fashion, the appropriate both for atrial fibrillation and for secondary prevention of venous thromboembolic events? If we go with the 10-milligram regimen, it hasn't been studied for Afib. And the 20 milligram is kind of an option but that's not what was recommended for this degree of renal dysfunction for management of atrial fibrillation. What are your thoughts, Tara?

Tara K. Lech:

This is a very tricky situation, but not uncommon, especially in my patient population in my hospital. We have quite a few patients over the age of 70 and a lot of octogenarians. So these patients often go on to develop Afib, and as they age, their creatinine clearance does drop over time. So our thought, and I'd love to hear your take on it, is that if that initial index event has been fully treated and that patient could have either been on extended prophylaxis or potentially have stopped anticoagulation, then weighing risk of bleed, risk of recurrent clot, new risk of stroke with this atrial fibrillation. We actually do flip-flop, and now atrial fibrillation becomes that primary diagnosis that we're treating, and then we use that dosing at the recommended 15 milligrams for that creatinine clearance of less than 50, and counsel the patient because their baseline risk of VTE is never zero. And if the patient were to down the road have another event, that's when we would have to discuss either going back up on the dose or switching to another agent altogether. What are your thoughts?

Behnood Bikdeli:

I'm hundred percent with you. Completely agreed.

Tara K. Lech:

Well, that's good to hear because I just think so many times we see patients that are left indefinitely on anticoagulation. I see it from inheriting a warfarin clinic with so many patients already involved. Some of them had their index event more than 10 years ago and have just been maintained on Coumadin ever since. And we've seen that now with the DOACs since they've been on the market now for a decade. We didn't have these touchpoints. We didn't know about extended prophylaxis when these drugs came on the market. So oftentimes, therapy was initiated and just renewed annually. But now that we have more information and this imperfectly perfect data, at least we know that we should be having these conversations with our patients. And I think that is the most important thing that we can do at this point in time.

So now let's get onto specific patient populations. First off, I think it's one that's always on people's minds of what to do in extremes of body weight. So obesity has gotten a lot of attention recently. Over the last couple of years we've seen a shift in the management of patients with obesity, and by that we mean patients with BMI greater than 40 kilograms per meter squared and or a weight greater than 120 kilograms with acute VTE. Back a few years ago, ISTH, just due to lack of data, had put out some pretty strict guidance to say that you should not use any DOAC in patient with a BMI greater than 40 or a weight greater than 120 kilos. But back in 2021, they actually updated our guidance statement based on newer literature that's come out. And now they've just taken away that clarification and said that there

is no weight or BMI cut-off for the use of DOACs in patients with obesity. So this kind of had a lot of rippling effects throughout the vascular community. Is it full speed ahead? Are there any patients that we should still have concern for?

And I think it was reassuring that this recommendation was further endorsed in a recently published expert consensus panel where experts like Rachel Rosovsky, Geoffrey Barnes and colleagues addressed the use of direct oral anticoagulants in obese patients with thromboembolism. I know that you've seen this paper and I was hoping maybe you could speak to a few of the key takeaway points for us.

Behnood Bikdeli:

Yeah, I agree with you, and I think it was a very interesting contribution. One of the biggest takeaways that I can have to summarize a lot of thoughtful discussions from that paper is that overall, clinicians have become a lot more comfortable using DOACs in patients with elevated body mass index and obesity. And part of it is because off of the existing randomized trials, when subgroup analyses came out, granted subgroup analyses are always underpowered, but there was no smoking gun suggesting that there is a differential treatment effect. And several observational studies kind of supported the observations from subgroups of randomized trials. So I think at this stage, for a lot of patients with elevated body mass index, clinicians and investigators similarly feel comfortable using direct oral anticoagulants as a very valid option. You can always consider weight-based low-molecular-weight heparins or fondaparinux as other options. However, this is more so in the setting where you have concerns for diminished drug absorption.

And for full disclosure, I think people with extremes of body weight such that either the rate is greater than 150 kilograms or their BMI was greater than 45 kilogram per meter squared, those are the kind of people that we see less often. But for those patients, we barely have any data with respect to direct oral anticoagulants. So for those, vitamin K antagonists, in my humble opinion, are still a very valid option.

The other piece, which is still something we are learning about, is bariatric surgery. There was a point, I'm sure you remember everybody was saying bariatric surgery. No, no, no DOACs whatsoever. Now the recommendations have been softened to some extent such that the International Society on Thrombosis and Hemostasis recommends don't do them in the first few weeks up to four weeks. Reason being there is concern for diminished absorption. And after that, they give an option in case patients and clinicians want to consider a direct oral anticoagulant. And that's one of the few cases where checking or drug absorption might be reasonable.

Tara K. Lech:

Yeah, I think we're starting to see a lot more of these patients in my clinic as well. And I think it's actually a little bit more reassuring now that these DOAC clinics are popping up so that we actually can follow these patients long term. It's one thing to say your patient is safely tolerating if all you see them at is that time of initiation and then there's no longitudinal follow up. So I think that'll be great to see in a couple of years what people are seeing as we're tracking these patients more long-term. And then when it comes to the bariatric surgery patients as opposed to just patients with an elevated BMI or weight, there are some other considerations that you do have to take into after when you're making these treatment decisions. So maybe what are your concerns for a patient who has bariatric surgery when you're thinking about who may or may not be a good candidate for use of a DOAC?

Behnood Bikdeli:

Right. Again, I think it's a very important question, but not with an easy answer. I think the first few weeks, as ISTH was recommending, it makes a lot of sense just to hold off until the new physiology kicks in. And after that, I think we need to think about which agent we are talking about and what specific type of surgery took place because, for example, you know better than I do, rivaroxaban is primarily absorbed in the stomach. And for apixaban, it's more complicated. Some of it there, it has some absorption in the colon, and even I think ileum is involved. So depending on the type of surgery, whether or it's rivaroxaban based off of the dosing, are they able to have a decent size meal to improve the absorption? So I think those are all the nuances to consider, and that's why I think because of so many ups and downs, that would be one of the few situations in which it's not unreasonable if DOACs are chosen to consider checking some sort of levels.

Tara K. Lech:

And I was going to say that's a nice segue because I think the question everyone wants to know from you, Behnood, do you ever check drug levels in your DOAC patients?

Behnood Bikdeli:

Thank you for asking that. In my clinical practice in patient and outpatient, I don't do it routinely. It's very rare, and I limit it to situations similar to the one that we discussed. But you are a director of health system for antithrombotic therapy, so what are your takes? What are the kind of pearls that you think about, Tara?

Tara K. Lech:

So first off, we try to restrict it. I do not want just anybody ordering these levels. I think it does have to be someone that is very adapt, very skilled because interpretation is still very challenging. We don't have direct drug levels widespread at this point of time. I know my institution, and I believe your institution does not have wide access to being able to just get a rivaroxaban or apixaban level at any time. And also, time that you draw the medication is key too. Are you getting a peak? Are you getting a trough? They're studied in different ways. So a peak level might reassure you that your medication is being absorbed, but it's not really going to tell you anything about efficacy. And same thing if you're checking a trough of a drug, you're just making sure that there's still some drug present at the time that your next dose of medication is due. And that can be reassuring as well.

But again, I think the biggest take home with drug levels, especially for DOACs, is that there is no data to inform us about the clinical appropriateness of these levels and if they do have any impact on safety or efficacy. So at this time, even if you were to check a level, there's no recommendation for any type of dose adjustment. I would never go up or down on the dose of DOAC. I think the only thing I've ever really used a DOAC level for, to be honest, is either in an emergent situation to say, "Is there DOAC on board?" and I need to reverse this drug and help get my patient to stop bleeding. Or if there are these true concerns, an acute high-risk VTE patient that does have a history of bariatric surgery. Or is BMI greater than 45 or 50 or weight greater than 150 kilos? I like to see that there is some drug absorption there. If the level were to be zero, then I know I probably need to find something else for my patient.

But I think time will tell. I'm not a big advocate for DOAC levels, but the future of their utility will remain to be seen, especially as we start to use DOACs in more and more less conventional or these gray zone patients where people still don't have that great level of comfort of, is this safe? And again, are there ever times when you utilize a surrogate marker like an unfractionated heparin or low-molecular-weight heparin anti-Xa level to detect the presence or absence of drug in your practice?

Behnood Bikdeli:

I just came off service this week, and I know we're not talking about heparin-based regimens, but even for that, we've been using heparin for decades and how to correlate, let's say our APTs with anti-Xa. It's so challenging, and I think it speaks to the need for learning more about the epidemiology of how these track with clinical outcomes. And I think more importantly, as clinicians and investigators, I would love for us to join forces such that we do studies that can inform practice. Are there things that we do better with one assay versus the other? And going back to our DOAC situation, we do have tests for drug levels and we do have anti-Xa. And I want to clarify, these are very different tests. The drug levels are actually rarely checked because they need a lot of specialized facilities and they're not commonly available in many health systems in contrast to anti-Xa assays which could be calibrated to each specific DOAC.

And as we were talking about, there could be rare situations. The patient that you mentioned would concern for critical bleeding is one that we can consider do be reverse or not. For example, if they're having a head bleed. Or the other way around, if there is a clinically relevant thrombotic event, and we are highly concerned if the patient is absorbing, I think those are the situations we're doing the test and interpreting it the right way. As long as it was drawn appropriately, if we wanted the trough drying the trough, if we wanted to peak drying the peak, I think those tests could be informative, but again, it's a very challenging situation. So my strong suggestion to our audience would be, if they want to get these tests, it might be best to consult with their local expert in their own health system.

Tara K. Lech:

Agreed. When in doubt, probably don't check or ask an expert.

Behnood Bikdeli:

Agreed.

Tara K. Lech:

I think the other tricky group of patients is that low body weight population where your patients are less than 50 kilos, but adult populations. These patients were not adequately represented or studied in the clinical DOAC trials. I mean, the average weight was typically 80 kilos in these studies or BMI well into the 20s or 30s. So the safety and efficacy in this population is largely unknown. The only DOAC actually specifically addressed low body weight in their VTE clinical trials was edoxaban, where they actually dose reduced from that standard 60-milligram dose down to 30-milligram dose in patients that weighed less than 60 kilos. But again, I don't think a lot of clinicians use this DOAC. In practice, I think I have maybe one or two patients in my entire clinic on edoxaban. And there's just this general overall concern that fixed drug doses could potentially lead to an increased drug exposure in the underweight patient population. What are your thoughts on this or what's your approach?

Behnood Bikdeli:

Yeah, you're absolutely right. And I think this has been an under-recognized problem. I have less of a concern in people with low body weight about efficacy, but I have a lot of concern, as you mentioned appropriately, about safety. Part of it is, I think we might be overestimating the renal function. Part of it is, we talked about it, yes, we don't do dose adjustment in venous thrombosis because, for example, for a apixaban, this low body weight is one of the three factors that we keep in mind if we want to adjust the dose and reduce the dose, especially in older adults. And those are people who might be frail and who might be peptic and whatnot.

So I think it's a very important issue to keep in mind for older adults. Frail people have a clear estimate of renal function. And you are right, it's actually one of the few situations where I do think of edoxaban. I've used it in a few patients. And the other alternatives if need be could be potentially either low-molecular-weight heparin or warfarin. That could be one of the situations where warfarin could be a valid option because I think INR is still INR, and as long as the patients are able to take it, that could be a situation where they could be reasonable.

Tara K. Lech:

And then another tricky patient population are those with an acute VTE and a creatinine clearance less than 30 milliliters per minute. How do you approach DOAC use in this patient population?

Behnood Bikdeli:

Yeah, this is by far the most difficult of questions in my mind, Tara. And part of it is because I really love to follow some sort of evidence to give share recommendations with my patients. And this is where, in my humble opinion, there's just a data desert. Even in the AFib space, the randomized trials that were conducted for people with very severe CKD or end-stage renal disease were neither powered nor having glowing results, let alone VTE space where we don't have anything. So just to compound the situation, dabigatran is mostly renally cleared, so I think that's a no-no. But even for apixaban and rivaroxaban, personally I'm hesitant, but I know that other clinicians use them and I would love to hear what your thoughts are.

Tara K. Lech:

I'm hesitant as well. I'm usually probably the last call on these patients because I am the one that will bring up the warfarin. I know that everyone wants to use DOACs. It's easier. We can get the patients out of the hospital faster. We don't have to worry about bridging. Especially when the creatinine clearance is less than 30, a bridge with a low-molecular-weight heparin becomes less ideal. We can renally dose adjust a low-molecular-weight heparin once daily dosing, but then we're starting to think more like is it appropriate for this patient to be on a heparin drip and bridge to Coumadin? So those are the conversations that are difficult to have and don't always lead to the easy choice to make. So I agree. I think warfarin is still very much on the table for this patient population until we get some more clear data.

But if you are going to use a DOAC, the patients do need close follow-up. I think it's very important in this patient population to specify the duration of treatment. Are we doing three months, six months? Is there going to be a reevaluation period? These are not the patients that you want to just set it and forget it, and forget that we've put them on a DOAC. So I think close follow-up is going to be key. And since I have one of our experts on antiphospholipid antibody syndrome with the VTE management, I think it would be great see if you could speak to us a little bit about how you approach patients with known antiphospholipid antibody syndrome that now have either a new or recurrent VTE and your approach to therapeutic management.

Behnood Bikdeli:

Thank you, Tara. I take the compliment, but I think the only expertise that I had was to surround myself with people smarter and more experienced than myself. So kudos to all of them who really guided us and navigate us through a very complex path. And shout-out to my two brilliant fellows, Dini Khairani and Antoine Bejjani who led this study. Essentially there were four randomized trials of direct oral anticoagulants versus vitamin K antagonists in patients with thrombotic antiphospholipid syndrome.

And individually, some of them had raised concerns for some excess in thrombotic events, especially arterial thrombotic events, but neither of them were sufficiently powered to really guide practice. And there were a lot of lingering questions. Is it really the same for people with triple positive versus others? Is it similar in women versus men? How do we deal with different situations in terms of other factors that they may be having? The initial event, does it matter if the initial event was a VTE versus an arterial thrombosis?

So we pre-specified a meta-analysis of randomized trials and we pre-specified to get unpublished, if available, aggregate data from individual trials within those subgroups to answer these questions. And to make it short, what we found was that direct oral anticoagulants compared with vitamin K antagonists were associated with an excess and risk of thrombotic events driven by an excess and arterial thrombotic events, which in and of itself was driven by a nearly tenfold increase in the risk of subsequent stroke. And importantly, the results were consistent irrespective of whether or not there was triple positivity and whether or not the initial event was a VTE or an arterial thrombotic event. So in sum, I think in these patients, the concern is for a risk of subsequent arterial thrombosis, especially stroke, and it is for that reason that as of April 2023, I tend to recommend vitamin K antagonists over direct oral anticoagulants in these patients.

Tara K. Lech:

Thank you for that tremendous summary. I think when this data came out, we all took a pause because I think, again, similar to some of the above populations that we talked about, we always want to use DOACs whenever we can. So I think up until this point, there were those clarifications or kind of considerations of like, maybe if it's single positivity or double positivity, DOACs might be okay and then stay away from the triple positive. But seeing this summit of data, it just really makes you take a step back and say, in this disease space, there's really a lot that we still don't know. So taking pause and thinking about all antiphospholipid antibody syndrome patients as a whole, the best approach at this time is likely still warfarin for these patients until we know more.

And for me personally, and I know a lot of others, just seeing that uptick in arterial events was concerning and surprising. I think especially in the thrombosis clinics, we're always thinking about venous thromboembolic events and, "Oh my gosh, you're going to have a DVT, you're going to have PE." But then seeing how many of these patients were having strokes, this is not benign. So I just we're really thankful for this investigation that you guys undertook. And to be able to give these results and give us some more meaningful data to work with, I think is huge. Sorry to kind of end the special populations on a downer, but in this case, I would say warfarin is probably still a way to go.

But no, I mean this was overall such a great discussion. Very thoughtful commentary on just how to approach DOAC use in our VTE patient population. And just to kind of summarize for the audience, VTE or venous thromboembolism is a common disorder and is associated with significant morbidity and mortality. And for many populations outside of maybe our endstage renal disease and antiphospholipid antibody syndrome patients, DOACs really are the treatment of choice. They're convenient, they're predictable, we understand their pharmacokinetics and pharmacodynamics, and they have similar effectiveness in reducing VTE compared to warfarin or other VKAs with significantly less major bleeding. And that point has to be heard. When in doubt and when you can, DOACs are going to be the way to go.

But again, there are still some patient populations where warfarin or low-molecular-weight heparin are going to be preferred, and there's always going to be, at least for now, those mechanical heart valve patients, your mechanical circulatory support device patients, pregnant patients, lactating patients, rheumatic heart disease, and APLS. Do not use the dose adjustment criteria for AFib trials with VTE. In case you didn't hear us earlier, we are not really adjusting these medications. You're either keeping

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them on the full therapeutic dose or you can consider a dose reduction for extended prophylaxis. It is different than dose adjusting for renal dysfunction. And really, one of the most important things is understanding which treatment is appropriate for your patient, and knowing hopefully after this podcast, you'll be able to feel confident counseling your patients, discussing risks and benefits and giving them the tools that they need to succeed in their VTE management.

Behnood Bikdeli:

Thank you all for listening. We hope that you've found this podcast interactive and informative, surrounding how we consider safe and effective anticoagulant options for patients with venous thromboembolism. I want to thank again my friend and colleague, Dr. Tara Lech and the American Heart Association for the opportunity. In future podcasts, you're going to hear about evidence-based approaches and guidelines that exist for managing patients with VTE. And to claim credit and get additional information, please feel free to visit [learn.heart.org](http://learn.heart.org), and we hope that you'll be able to join us for future episode. Thank you so much for your time and attention today. Bye-bye.