[MUSIC PLAYING]

SPEAKER 1: In the next hour, I want to touch on a number of topics. You know anticoagulation is such a huge area we could really do an entire week long course on this, but I want to touch on some topics that I think are fairly high yield, and things that have been coming up more recently in the literature, and in discussion. So I want to talk about peri-procedural management and what do we do when we have procedures and surgeries.

We'll talk a lot about the new drugs, the direct Oral Anticoagulants, or DOACs as I'll call them, versus warfarin, and how do we think about those. A lot about anticoagulant related bleeding, and what should we be thinking about when patients do bleed. How do we think about managing them. Some of the new reversal agents that are out there. And then I do want to touch on, just briefly, some venous thromboembolism because some new guidelines have come out. So I'm just going to highlight a couple of those spaces for you.

So let's get started with atrial fibrillation, and touch on some epidemiology. You know this is really a public health concern because, millions of Americans have atrial fibrillation. Back in 1995, about two million Americans had atrial fibrillation, by 2010, we're up to 5 million. And estimates are looking that we're probably going to increase not linearly, but start to increase exponentially, up to maybe 12 million Americans with atrial fibrillation by 2030. And there's a whole host of reasons for that, not the least of which have to do with the obesity epidemic, and untreated obstructive sleep apnea.

But this really highlights a reason why we need to think about anticoagulants, and that's because, as our patients are older and their risk of atrial fibrillation increases, so does their risk of complications from atrial fibrillation. And I'm speaking specifically here of ischemic stroke, as well as systemic embolism. And we know that the number one predictor of stroke risk or systemic embolism risk in patients with atrial fibrillation is age. Sure there's a whole bunch of other things that we like to talk about and use, but age is sort of our biggest predictor. And so we need to be thinking about that particularly in our elderly population.

Now we've had a really good drug for helping to prevent stroke in atrial fibrillation for over half a century, and that's warfarin. And a number of studies have shown us that, in general, you can get about a 2/3 relative risk reduction when you get a decently controlled warfarin to patients with atrial fibrillation. So we can do a pretty good job. The question is, what does that actually translate for individual patients into their absolute stroke risks? Well, we can use a newer scoring system, something called the CHADS-VASC scoring system, this updated the older CHADS score that I think most of us learned when we were in our training.

So as we all know, history of congestive heart failure puts you at risk, a history of hypertension puts you at risk, but this newer scoring system says we recognize this sort of exponential risk with age, so patients who are 75 and older were going to give two risk points, not just one, and then we're going to bring in those 65 to 74 year olds, and also give them a risk point. We know that diabetes is a risk, and we know that anyone whose previously had a stroke, or transient ischemic attack is also at high risk.

The new elements here, are this thing called vascular disease, so anyone with a history of myocardial infarction, peripheral artery disease, or aortic plaques, so atherosclerosis somewhere in their aorta. Where I tend to find it is people who have a triple A, an abdominal aortic aneurysm. That's where we tend to give this point a lot for in addition to our MI patients.

And then the sex category. This is sort of an interesting one. A lot of data has shown that women, as compared to men, seem to be at a higher risk of stroke when they have atrial fibrillation. And so you can go through and you can do some simple math, and add up all of your points, but where it really plays out is, what are you going to do about it? So what's the recommendation over here?

Well, if you're at low risk, if you have none of these risk elements, so you're a young man, with no other disease, you're at low risk and everyone agrees, you should not be treated. And what I mean by that is, not only should you not get any anticoagulant, meaning not using warfarin, not using dabigatran, not using rivaroxaban, but you also should not be getting aspirin. You just shouldn't get anything, because your risk of a complication outweighs whatever your stroke risk is.

If on the other hand, you have two or more points, then everyone both on the European side and the Americans side, agree you are at high risk for stroke, and therefore you should get treated. And that treatment really should be anticoagulant therapy, because that's going to be much more effective than aspirin. It's this intermediate group here, these people with a score of one, and not just if you're a woman, because that's not quite as big a risk factor, but maybe if you just have age, or you just have hypertension, this is where there's a little bit of debate.

So the Europeans would say, go ahead and anticoagulate them because we really want to prevent stroke whenever we can. Here in the North American side of the ocean, we say, well you can anticoagulate, you could give aspirin, you could do nothing, we don't know, it's a little wishy-washy. And the reason for that is because of the absolute stroke risk. So, when you have no points, your absolute stroke risk is pretty close to zero. When you only have one point your absolute stroke risk is probably only about 1% per year. So when you think about reducing that either with aspirin, or any anticoagulant, your absolute risk reduction is not very big. Yet we know that these medicines do put people at risk for bleeding.

Where you start to see big differences is in higher risk stroke patients. So CHADS of two, three, four, even up here to six. Look at that, we've got a stroke risk, a yearly stroke risk of almost 10% without therapy. Now if you give somebody aspirin, sure you can reduce that, but that's not a very big delta. However if you give warfarin, or another anticoagulant, you can significantly reduce that risk, so their absolute risk reduction is much bigger, certainly outweighing any of the risks of bleeding that are associated with this. So, I think this is important to understand, not only how the continuum of stroke risk plays out in patients, but also the difference between giving aspirin therapy versus giving a true anticoagulant.

So if you know this, you might ask yourself, well why aren't all atrial fibrillation patients treated? Well, we are doing a good job, we're reducing the incidents of stroke amongst patients with atrial fibrillation, but we seem to have leveled off and since about the mid 2000's, we haven't made quite as much progress. And it probably is reflected in the fact that we've gotten to the point where about 60% of our afib patients are being treated with an anticoagulant, but we can't seem to get over that hump, over that hurdle.

And there's a whole bunch of reasons why that may be the case, but I think it's really important that we constantly remind ourselves of this. Every time we see a patient with atrial fibrillation, we need to think to ourselves, are they at risk for stroke, and am I treating them with an anticoagulant. Because you really can save lives and reduce a lot of morbidity if you do so.

So we started looking at a little bit more recent data, we used a national data set called the National Drug and Therapeutic index. And this is a data set that actually looks at office visits, so instead of looking at individual patients, we look to see who was coming into the office, and what kinds of anticoagulant they're using. And as you can see here, this blue line represents all anticoagulant use. And things have pretty stable through 2012, and what you see is with the introduction of dabigatran here in 2010, you start to see some rise in the direct oral anticoagulant use, and you see associated fall in warfarin use, just a replacement.

The overall number of patients with anticoagulants office visits has stayed relatively stable. But then that changed in 2013, and all of a sudden we saw this big climb, and we saw a lot more office visits where anticoagulants were being used. And when you look here, sure there's a little bit more warfarin in 2014, but we really see a big jump in the direct oral anticoagulants. We start seeing a lot more use of these drugs. And so, when we looked at this data, we said to ourselves, I wonder whether that 60% threshold of patients who were actually being treated, have we been able to make any movement, have we've actually been able to raise that bar a little bit?

So we looked at that this is just listing the top three meds that were being used by 2014 most of it being rivaroxaban, followed by apixaban, and then dabigatran. And so you take those three together and you say, are we making any progress? And this was the slide here, again going back to 2009, somewhere between 50% and 60% of all afib visits were actually being treated within an anticoagulant. And then you hit 2013, and we start to see this climb, and now we're up over 60%, and looks like we're potentially climbing even higher. So I think this starts to give us a sense that maybe we're making some progress, we're getting more patients with atrial fibrillation who are at risk for stroke treated with necessary anticoagulants.

I'm going to be very curious to see what happens in 2015, now that we have a reversal agent for dabigatran, and into 2016, 2017, when we start having reversal agents for all the drugs. Is this going to continue to rise, where is going to be the next ceiling effect, and how is that going to affect our incidents of stroke?

So, let's switch gears now and talk some about peri-procedural anticoagulation. This is a topic that I think touches lots of different specialties whether you're inpatient, outpatient, cardiologist, primary care, or other areas. There's been this balance that we all think about, when a patient has atrial fibrillation, when they've had a prior thromboembolism something like that, we want to prevent them from having another thrombus form, or another thromboembolism.

And so we think about giving anticoagulants to reduce that risk. Yet, at the same time, we know that when a patient's on an anticoagulant and they're going to have some kind of a procedure performed, they're going to be at an increased risk of bleeding, and how do we balance those to make sure the patient is most safely treated. And that's really been the approach. Sometimes we think about giving bridging anticoagulants for our warfarin patients. And so we'll give them either unfractionated heparin or low molecular weight heparin to try and increase the number of days where they're getting anticoagulant protection, but yet allow them to be off the anticoagulant right around the procedure.

However, we think that that might also increase the risk of bleeding, while decreasing the risk of thromboembolism. So on the flip side, you could choose to not get the bridging anticoagulant, yet are you putting them at risk for having a stroke or thromboembolism. So that's sort of been the question. Now, the guidelines from 2012 helped us a little bit by saying we can categorize people into three different groups.

You can either be at high risk of thromboembolism, meaning your risk was greater than 10% per year, and they broke it down by your indication. If you had a mechanical valve, specifically if it was in the mitral position, or if it was one of the older styles, the cage and ball, the tilting disk, or maybe recently had a stroke, those people are certainly a very high risk. For our afib patients, we're talking about those CHADS of five to six. Again, those ones who have lots of those risk elements, or maybe people who've recently had a stroke within the last few months. And for the venous thromboembolism patients, we're talking about those who most recently had their venous thromboembolism within the last three months.

On the flip side, you can also look at this low risk group. These are the people who their risk of a thromboembolism is less than 5% per year. These are going to be most of our aortic valve replacement patients, because they tend to have these newer bi-leaflet disks, and they don't have any risk factors. These are going to be our CHADS of 0 to two afib patients without a prior stroke. And these are going to be the people whose venous thromboembolism was more than a year ago.

And so we had this lay out, and we said, well if you're high risk maybe you should bridge, if you're low risk maybe you shouldn't, and if you fall in the middle here, you could kind of go either way. But some observational data started to question that practice, and one of the first things we looked at was a meta analysis of a number of observational studies which said, looking at all comers, we really don't see any evidence that shows benefit to bridging versus not bridging, for the purpose of reducing a thromboembolism, so I wonder whether this is actually a beneficial practice, and at the same time, we clearly see that giving bridging heparin, increases your risk of major bleeding.

Now again, this is observational study, there's a lot of selection bias, a lot of other issues. But it sort of raised this question, how should we be approaching these patients? Well, we know that the most common reason people get anticoagulated is afib, and those patients are frequently going for procedures, so the NIH and NHLBI actually sponsored a large trial to help us answer this in a randomized fashion.

So this was the Bridge trial, and what happened here is patients who were screened came in, and five days before their surgery, they stopped warfarin. And at that time they were randomized to one of two groups. They were either going to be given a bridging agent, in this case, dalteparin, one of the low molecular weight heparin's, or they were going to be given placebo. And those were given between days three and one pre-op, and so it covered for a couple days while their INR was coming down, and warfarin was washing out of their system. They then go ahead and have the procedure, and the night of their procedure, or the next day, warfarin gets restarted.

Again, because we know that it's going to take a while for warfarin to come back to be fully effective. What I think was really smart about what they did here, is they didn't make everyone restart their low molecular weight heparin right away. And they said, you know, if you had a pretty straightforward low risk procedure, maybe you had a colonoscopy without biopsy, maybe you had a laparoscopic surgery, go ahead and restart the low molecular weight heparin 24 hours after your procedure.

But, if on the other hand, you had a more invasive or higher bleeding risk surgery, you can wait between 48 and 72 hours before you restart the anticoagulant. Let's make sure that we let whatever that surgical or procedure site heal up so it's not going to have bleeding complications. And then you continue either the study drug or placebo, until the INR is therapeutic.

And so the patients that they were able to enroll, they had about 1800 patients. And these are average age about 71, 72, they're CHAD scores are about 2 and 1/2, and this is pretty typical. This is the most common CHAD score is between two and three. This is what we tend to see in our clinical practice. I will point out, though, that they were not able to get a whole lot of those highest risk group. Remember how I grouped the low risk, the intermiediate risk, and the high risk.

We've really only got about 3% of the entire study population fitting that high stroke risk group . Now, when you look at other factors, I think this is an important one, because I often get asked this question, they actually had about 16% to 20% of their population who had previously had a stroke, and so a lot of their patients had had strokes, just not within the prior three months. So this did include a number of patients with a history of stroke, it just had to be a little bit more remote.

What kind of procedures did they undergo? Well, they underwent the procedures that we see all our patients undergoing. Cardiothoracic procedures, people who are getting heart cath's, people who are getting pacemakers, and defibrillators, things like that. Gastrointestinal procedures, this was the most common, we're looking at colonoscopies, and EGD's, those types of procedures. In the major group, the ones who are at higher risk for bleeding, it's the orthopedic procedures, the hips, the knees, things like that. We're also looking at urologic procedures, people who are having prostate surgery, and the like. And then, of course, general surgery. People who are having their gall bladder taken out, and appendix taken out, and other things like that.

So the question is, how were they treated? And what you can see here is before the surgery, they did a pretty good job, they stopped warfarin five days ahead of time. After surgery, and again, I think this is an important point that we need to bring up, for patients who are at high bleeding risk, they waited on average 2 and 1/2 days before they restarted the heparin agent, the dalteparin. For the patients who were low bleeding risk, they waited almost a day before restarting it, so they want to give those patients enough time to heal up so that we're not having significant post-op bleeding. And the number of doses, we're looking at about 16 doses. So eight days of the dalteparin before there warfarin was fully therapeutic. So this is a lot of exposure to an injection drug.

So, the outcomes are presented here, and I think this is important, the risk of thromboembolism was no different whether you were given bridging, or you weren't. Now the absolute numbers were really small, and I think that's also important to take away, but this first p-value is a non-inferiority p-value saying that the study met the non-inferiority criteria. The second one, they were trying to show that bridging actually was superior to not bridging, and they couldn't show that here. So, this really tells us that we're probably not getting benefit. The question is, what are the harms associated? And I think these are quite striking. Major bleeding, things that require transfusions, things that require procedures, surgeries hospital admissions, we're looking at an absolute difference of about 2% where a number needed to harm of 53.

If you instead look at the minor bleeding, all the nuisance things, maybe you go to the ER, or maybe you're having nose bleeds, maybe you're having bruises, things like that, now we're looking at an 8% to 9% absolute risk of harm, a number needed to harm of 11. So when you're giving bridging anticoagulants to your afib patients, we're probably causing 1 in 10 to have bleeding complications, yet we're probably not preventing any sort of stroke or thromboembolism. And that's really the take home from this randomized trial.

So, when I look at the balance between preventing stroke, and causing bleeding, that bleeding is starting to weigh a lot more on me, and I wonder whether we should be backing off how much anticoagulant we're giving people. So, coming out of this you may ask yourself, well, what about some of the other indications, what about our VTE patients, what about our mechanical valve patients? Well, thankfully, there's a study that's ongoing, and it's looking at that. It's called the PERIOP2 study. They're going to actually include some mechanical heart valve patients, it will be 20% to 30% of the population, so we'll get some good data. They're also trying to enrich for a higher stroke risk afib group. So, we may get some more data on those high stroke risk patients, so we have a little bit more data to help us understand what we should be doing there.

So, when I think about how to practice, how do I bring all this information into my clinical decision making. The first question I need to ask myself when somebody is having an upcoming procedure is, do I even need to discontinue the anticoagulant? We know that a number of procedures can be done safely on anticoagulants. Most dental procedures, most dermalogic procedures, some endoscopic procedures even can be done without stopping the anticoagulant.

So, that may be the best bet. If on the other hand, you need to stop it, then you really need to ask yourself, do I need a short acting agent or not? And if they're being treated with warfarin. And some experts have sort of put together a call saying, we think that there really should be limited use of bridging anticoagulation. Specifically, they think that fewer than 10% of all patients really need to be bridged with an anticoagulant. And they're highlighting that, our afib patients who had a recent stroke, those weren't included in the bridge trial, we know that they're high risk, go ahead and bridge them.

Patients who had a recent venous thromboembolism, whether it's within the last three months, maybe within the last year, who should be thinking about bridging them. And then the mechanical valve patients, and I highlight especially if it's a mitral valve, because those are our highest risk group. We're going to learn more about those with the PERIOP2 study, but certainly that's a group where bridging could be very reasonable.

So if you have a patient warfarin what are you to do? Well, seven days before the procedure, if you need to stop an antiplatelet like plavix or ticagrelor, that would be an appropriate time to stop those, make sure you check some basic labs. Five days beforehand, that's when we want to stop warfarin, just like they did in the bridge trial. And then on day three before the surgery, that's when you think about starting your low molecular weight heparin. But again, only for highest thromboembolism risk patients.

And it's usually preferable to use the BID dosing. You get a little bit better coverage, you reduce the risk of bleeding when you do that. I know it's an inconvenience for patients, and so you have to balance those two together. Day one before the surgery, that's when you stop your molecular weight heparin. Again check your INR, make sure it's come down, it's to the point where the procedure list feels comfortable, and then let them go and have their surgery.

That night, or the next day, is when you want to be thinking about restarting the anti platelets, and warfarin. And then on days one to three, depending on their bleeding risk, is when you restart low molecular weight heparin. Again, it's only for high risk patients, and it depends on the bleeding risk of the surgery. Low bleeding risk surgery, start it about a day after, high bleeding risk, wait about two to three days before you restart it. And then, starting on day four or five, after the surgery is when you want to check the INR to figure out when they're therapeutic, and you can stop the bridging. But, again, this is probably going to be the minority of patients that you need to do this for.

Well, what about the new drugs? What about the direct oral anticoagulants? How do you think about them? Well, it's really nice, because they're so quick on, and so quick off, that we don't need to think about bridging at all. We really just need to think about, can they have their surgery done safely anticoagulated, or do we need to clear it out of their system? And to figure out when we should be stopping it we look at three questions. Well, what's the thromboembolism risk, is it standard, meaning low or intermediate, or is it high? What's the bleeding risk of the procedure, is it standard, or is it high?

And then this is the important point, and this is what's really different than your warfarin patients. What is their renal function? All of these drugs are at least, in part, cleared by the kidneys. And so the poorer of the renal function, the slower it's going to be cleared out of your system. And so there are a number of different groups, and experts, and papers that have given different days, and everyone's going to be slightly different whether it's one day or two day for each category. But you can pretty much pick whichever one is your favorite, put it up there, and follow it, and decide when you should be stopping one of the direct oral anticoagulants before the time of surgery.

Now again, just like we did with the warfarin patients, we want to wait at least 24 to 48 hours post-op before we resume, and that's because, just like when you're giving Lovenox, when you give these drugs within a couple hours, they're fully effective. So these patients are fully anticoagulated within maybe two hours of giving the drug. So it's not like warfarin where you can give it that night, you need to wait a couple of days. And we're always reminding our surgical colleagues of this, because it's something that they're often forgetting because they're so used to treating patients with warfarin.

So that's a whole bunch of knowledge that was out there, and we asked ourselves, well I wonder how much of this, colleagues who maybe don't deal with anticoagulation, or think about it all the time. What's their level of knowledge? How well has this information assimilated into practice? And we wanted to ask ourselves, who has this knowledge, and how can we improve the coordination, so that our patients are getting better care?

So, to do that, we actually put together a survey, and I am going to guess that many of you in this room may have participated, where we surveyed all cardiologists, all primary care providers, meaning both internal medicine, med ped's, and family medicine, and all of our GI doc's who do endoscopy, both at our center as well as in four other centers across the state. And we gave people four different scenarios of afib patients who were undergoing a colonoscopy, and they needed to have their anticoagulant held. And we varied the risk of stroke for each scenario, we either had a CHADS of one, low risk, three, intermediate risk, or five, high risk. And we also varied whether or not the patients had previously had a stroke.

So we ended up with four total scenarios. And what was interesting was, we see the sort of stair step in how our survey respondents chose to give bridging anticoagulation. So for our lowest risk group, almost nobody said that they would give a bridging anticoagulant. And I think that's consistent, not only with the randomized trial, but with the older guidelines. And similarly, when you look over here, your highest risk group, CHADS of five, prior stroke, nearly everyone said, yeah, that person should probably be bridged.

Where you see this discrepancy is in the middle. Notice how both of these are CHADS of three, they both have the same absolute risk of stroke. The only difference is, this guy did not have a stroke before, he just had hypertension, diabetes, and heart failure. Where as this patient here who had hypertension, also had a prior stroke. And we see a huge difference in whether people chose to give bridging anticoagulation or not. And it really seems to be influenced by that prior history of stroke, even though that wasn't necessarily shown in the randomized trial.

When you break it down by specialty, you also see some important differences. And what you'll see is that, in general, the cardiologists, these guys in the blue, they're always less likely to give bridging anticoagulation than the gastroenterologist, the proceduralist in this case, your internal medicine primary care docs, or your family med primary care doc's. Everyone stair step's up, but there seems to be a little bit of a difference there. So, clearly this is highlighting that there's some variation in practice amongst our different specialties. So we took away from this that we need to probably get some better education out there, make sure people are aware of the results of these trials, and of these studies.

But we also said, do we need some better institutional mechanisms? Could we put a system in place that helps practitioners manage this, and helps give patients evidence based care? And when we asked our primary care doc's and our proceduralist, over half of them said yes, I would like our institution to do more to help me with that. And then when we asked everyone, do you think the anticoagulation clinic could be a place where this is done, we got near universal support. So there's a lot of support for helping to operationalize a better system so it's not being left up to each individual practitioner to try and coordinate all these different aspects. So, this is a project we're going to be working on over the next couple of years

OK, so I've talked a little bit about warfarin, and talked a little bit about the direct oral anticoagulants, let's get into them a little more. Now you've heard me use this term DOAC, but you've probably all heard the term NOAC, and maybe even heard that more. Well, there's a lot of different terms that have been out there. First, these drugs, when they first came out, they were new, they were novel, so we called them the novel or new oral anticoagulants, NOAC's

Then after a number of years we said, gosh, they're not really that new anymore, but we like this acronym, so let's call them the non vitamin K antagonist oral anticoagulant . And if you can say that fast, you're better than me. Other people said let's call them the direct oral anticoagulant because they actually directly inhibit one of the steps in the coagulation cascade, so we're calling them by what they are, not by what they're not.

Some other people that fancy and said, well, maybe we should call them target specific oral anticoagulants, because again, they specifically target one step. TSOAC is a little harder to say, but it's out there. Other said we can call them ODI's, oral direct inhibitors. That doesn't roll off the tongue very well. And then, as a cardiologist, my favorite are the SODA's, the specific oral direct anticoagulants.

So you know there's a lot of different things you see, certainly when you search the literature you see all kinds of things, what should we actually be using? Well I think you're probably going to come down to one of two different acronyms. You're either going to call them NOAC's, meaning non vitamin K oral anticoagulants, and this has really been supported by a lot of the cardiology community specifically over in Europe. The problem is, there have been a couple different case reports where people will write in a chart NOAC, and then somebody else will interpret that as meaning no anticoagulant.

So, although you intended to give an anticoagulant, the patient actually didn't get it. We're not helping that 60% threshold of our afib patients. So, because of the safety concern, a multi society group, covering multiple continents got together and said, we really should be calling these DOAC's, direct oral anticoagulants. And by the way, if you read that in the same way, do anticoagulant. So, I guess it kind of works, right. So, that's why I call them DOAC's. You'll probably hear both, and only time will tell which one wins. So that's the one we're going to use.

So how do we pick? How do you choose whether to give somebody warfarin, or whether to give somebody a DOAC? Well, some people have said, maybe we should try and guess how good somebody is going to have their warfarin managed. Are you going to be a person who's INR is always in the therapeutic range? Well sure, then you've got a really good drug, it's really inexpensive, let's go ahead and do that. Or are you somebody who's going to be bouncing all over the place, really hard to manage, maybe you should be on a new drug. So they tried to come up with the same TTR scoring system, it's really not very good, it's kind of cumbersome to use, and I don't think it actually addresses the real problem.

And the real problem is, what do the patient's care about? It's not so much what we want them to do, they're the ones who actually have to take the drug, so what are their preferences? Do they want the latest and greatest, newest, best drug that's out there? Or are they reassured by a drug that we've had on the market for 50, 60 years, that we have a lot of clinical experience with? Do they want something that we know we can reverse, or are they comfortable with the fact that although it's not reversible, it's less likely to cause bleeding.

And then, of course, how do they think about lab monitoring? We all assumed that INR's are a burden for patients, and they wouldn't want them. Many patients actually really like the fact that they know just how anticoagulated they are, and that their dose is always adjust to them, it's not this one size fits all. So different patients are going to have different preferences. And of course, I think the biggest one is the cost. Can they actually afford to be on the new medicines, or do they need to be an warfarin because it's much less costly out-of-pocket?

So, we're in the process of developing a decision aid which does something different than most other decision aids. Most other decision aids will calculate your stroke risk, calculate your bleeding risk, and say, here you go, pick a drug. And we're trying to really incorporate these values. What do the patient's care about, how can we help them make a more informed decision that really better fits what they're looking for? So, they'll get the print out, they'll get the showing of their stroke risk and they're bleeding risk, but we'll also make a recommendation on which class of drugs might be best for them. So, this will be coming, it should be live within about the next month or so. So, we hope to have that out there, and available for people to use. We're partnering with the Society for Vascular Medicine to do this, to get some broad dissemination.

OK, so now you've actually decided to treat your patient with a direct oral anticoagulant. Is that it? Do you just write a script, and off you go, nothing more, like we would treat say lisinopril in hypertension, or something else? We sort of think there may be a role for the anticoagulation clinic to help these patients. So, a couple of years ago, we actually started using the pharmacists at our anticoagulation clinic to help support patients on the direct oral anticoagulant. We have three pharmacists, and what they'll do, is they'll do an intake assessment.

They'll say, is this an appropriate indication for the specific drug that you're on, and what do your lab show. Specifically, what's your renal function, and does that match up with the right dose? Do you need to dose adjust just for a specific reason? They'll also make sure that the patient actually got the drug. Frequently, we'll write the prescription, the patient goes to the, pharmacy the pharmacist tells them they have a $150 expense, and they say, oh, I'm not going to pay for it, and they go home. If they don't call us and let us know, w don't know about this, we're not routinely doing follow up. The anticoagulation clinic can do that, and the pharmacists know how to help them navigate that system.

And then, we think there is importance to follow up. So it's not just when they start, we need to make sure that they continue to comply with taking the medicine. Are they actually taking it every day, so that they get benefit? Do we need to do any dose adjustments? If your patient has a DVT, or PE, there's going to be some dose adjustments at different times. The pharmacist can help them navigate that process. And then of course, getting back to this renal function problem, any of our patients with any degree of chronic kidney disease may have some fluctuations, and we may need to be looking at whether the dose is appropriate at any given time.

So, we looked at some of the data. The patients who were in our pharmacist clinic versus patients who were not seen by the pharmacist clinic. Their prescriber just wrote the drug, and they were managed by usual care. And what we saw is that everyone is pretty good at selecting an appropriate drug, and that's probably because all these drugs have pretty broad indications. Where we see a difference is looking at the dose, and in this case, being in the pharmacist clinic was associated with more often, having an appropriate dose prescribed. And that was the same both at baseline, and when they did follow up at three to six months. So, I think that's important. We want our patients to be on the right dose, so they get appropriate thromboembolism protection, and they're not being overly anticoagulated and bleeding.

But I think this was the other key thing that we found. We seemed to show an improved adherence for patients who were in the pharmacist clinic. 92% of all patients in the pharmacist clinic showed good adherence to their medicine, compared to only 80% of the patients in the usual care arm, so there may be a role. Of course, this is observational, it's not causation that we're showing here. But it's sort of raising this question. And we're not the only ones to show this either.

The VA system looked at this, and in all of their VA systems where they have dabigatran , prescribed the range of adherence goes from about 40%, all the way up here to near 80% or 85%. So huge variation across the systems. And when they looked at what the predictors of that are, they said, well, it's the patients who come into the anticoagulation clinic who get tailored education, who actually meet face to face, and the longer that they're being seen by that anticoagulation clinic, the better there adherence seems to be. So, again, not only are we seeing this here, but we're now seeing this in some national data, that ongoing monitoring and follow up is probably beneficial, because these are anticoagulants. People are going to have concerns, they are going to have complications, they need to have somebody that they can go to.

So, when we think about this, and we think about some of the peri-operative stuff I mentioned before, it got us thinking, what is the role of the anticoagulation clinic, and is it just about managing warfarin and INR's, or is there something more that it can be doing. So, we wrote this as a thought piece, reimagining what an anticoagulation clinic should do. And we said, they probably can assist us with not only drug selection, but dose selection. Making sure we're getting the right drug and dose.

They can help us minimize bleeding risk with long term monitoring, and peri-procedural management. And, they can help us encourage long term medication adherence, no matter which anticoagulant they're on. And there may even be a role for this beyond just anticoagulants. There may be a role in other meds that require long term monitoring, adherence issues, and the like. So, we need to be thinking, what should the anticoagulation clinic be evolving into, not should it be dying off has fewer patients are taking warfarin. So, this is something we're studying and looking into now as well.

OK, let's talk a little bit about bleeding. What do you do when your patient bleeds, how are we going to manage them? Well, let's start with warfarin, that's the one we had before. You know everyone was taught in their training that you give vitamin K and you give FFP, and you can reverse an INR. Interestingly, there was very little data to show that reversing an INR actually improved clinical outcomes until just recently.

And this is a study that was published just last year in JAMA, which showed that for patients who bled in their brain, so an intracranial hemorrhage, when you were able to reduce the INR to less than 1.3, or when you were able to do that quickly within four hours, and if you could do that by lowering their blood pressure as well, you can significantly reduce their risk of having a hematoma expansion. And in this study, it was an observational study, they said, use whatever you need. Use a four factor prothrombin concentrate complex, 4-factor PCC. Use fresh frozen plasma, and or use vitamin K in whatever combination you need.

So we have some evidence to say that actually reversing an INR may offer some clinical benefits, at least in the intracranial hemorrhage. I think the more interesting part of this study, however, was what do you do after they bleed? And so often, we have patients who bleed in their brain, and we get very scared, or more often patients who bleed in their GI tract, and we say, you know you've bled before, no more anticoagulant for you. We don't need to worry about it. Well, unfortunately, if you do that, their risk of an ischemic event is significantly higher, than if you choose to resume their anticoagulant. And, as long as you wait an appropriate period of time, and you're sure that they're not still bleeding, there doesn't seem to be any increased risk of major hemorrhage. But, perhaps most importantly, at least for the afib patients, significant reduction in mortality, when you resume anticoagulation.

Similar observational data has also been done in the GI bleeding patient. Usually, for that group, it's waiting somewhere around 7 to 10 days, as long as you've been able to identify the source. Stop and treat the source so it stops bleeding, wait about 7 to 10 days to make sure they heal, get them on a PPI, and then you can restart anticoagulants again. Reduce their stroke risk, reduce their mortality. So, I think we need to be more aggressive about thinking, can our patients be resumed on anticoagulants. Because we still need to prevent them from having the a-fibrilated consequences, or VTE related consequences and the like.

OK, now what about the direct oral anticoagulants? Are they any better at preventing this? Well, here we're looking at major bleeding. This is all the studies of the direct oral anticoagulants versus warfarin, and when you sum it all here in the meta analysis, you see a risk ratio of 0.72. Less risk of major bleeding across this entire class of medicines as compared to warfarin. And then of course our most feared bleeding, intracranial hemorrhage. Risk ratio of 0.43.

We're talking 60% risk reduction by giving these drugs as compared to warfarin. So, we need to be thinking about the fact that even though there's not a reversal agent out yet for many of them, your chance of actually having a bleed is much lower. And when they were studied in the randomized trials, no reversal agent was available there either, yet some of these drugs were even able to show mortality benefit. So, just because a reversal agent is not available, shouldn't be the limiting factor for giving these medicines to our patients.

OK, so now let's talk about what medicines can we use to reverse? And there's three that are in various stages of development. And this is the fun part because I have to try and pronounce all these. The first one idarucizumab. I dare you to say the name, or I dare you to treat this patient, that how you pronounce it. It's a specific reversal agent for dabigatran. It's actually a monoclonal antibody, binds dabigatran, pulls it off of thrombin, so that thrombin can do its normal job in the coagulation cascade. This has been studied in bleeding patients, and patients needing emergent reversal. And the good news is, it's FDA approved, it's on the shelves, we have it here at our hospital. If your patients are so interested, you go to the manufacturer's website site, you can get a Google map of every hospital that has it on it shelf. So, if they're going to go on a trip, and they want to know where the reversal drug is, they can find that.

The next one is called andexanet alpha. And this is meant to reverse all of our Xa inhibitors. So rivaroxaban, apixaban, and edoxaban. And it's a recombinant factor Xa, so it basically acts like factor Xa, lets these Xa inhibitors bind, and then tries not to let it go, so to that your body's normal Xa can do its job, and help you form clot. Again, this has only been tested in healthy volunteers. The testing in real bleeding patients, patients needing emergency surgery, that's ongoing. Yet, because of the need, because of how many patients are being treated, it's actually under review by the FDA, and I've heard that perhaps sometime later this spring to summer, we may actually get an answer from the FDA. Potentially this drug could be on the shelves by the end of the year. I think that would be a huge help.

The last one is called ciraparantag, and again, who comes up with these names is beyond me. It's supposed to actually reverse everything. That's what they're telling us. The direct thrombin inhibitors, like dabigatran, all of the Xa inhibitors, and potentially even heparin agents. The problem is, we don't really know a lot about it. Not a lot's been published, it's being made by a private drug company, and so we're looking to learn more. There's only been one small study in some healthy volunteers. we're probably a couple of years away. If it actually comes to fulfill all of these promises, this could be a really nice one size fits all drug. We'll just have to wait and see. In the meantime, we have idarucizumab, soon we should have andexanet alpha. That will give us really good coverage for all of our available direct oral anticoagulants.

The data supporting them for idarucizumab. It's given as to boluses, each 2 and 1/2 grams given twice in 15 minutes. You get immediate reversal of your coagulation numbers, and that's persisting up to 24 hours. So, very effective suppression of the anticoagulant numbers. The andexanet, the other one, again, you give this bolus, you get a rapid reduction in you're bleeding parameters, unfortunately, it starts to come up pretty quickly, and within one to two hours it's back to normal.

So the way this is actually going to be administered is you give a bolus, and then you follow that with an infusion. And it was tested with a two hour infusion, although I can imagine that there are going to be cases where that infusion may need to last longer or shorter, depending on the clinical situation. Again this is still under review by the FDA, so we're going to learn more in the coming months.

OK so let's finish up with venous thromboembolism. So, how do we think about treating venous thromboembolism? Well, I think of it as having two main treatment periods. And the first is this acute treatment. This is the first three months. The goal here is to stop the clotting process, and make sure we don't have rapid return of thrombus formation.

Then, you get into an extended phase, that's the beyond the three months. This is really secondary prophylaxis. We're trying to prevent another thrombus from forming. And what you'll notice here, is that in this acute phase, we tend to have some high intensity treatment over the first one to three weeks. Traditionally, we've done that by bringing people into the hospital and giving them unfractionated heparin. More recently, we've been using low molecular weight heparin, but there may be some other options and I'm going to show you as well.

And so we basically have two different strategies for treating these patients. The first is our traditional strategy. Start them with a heparin agent, transition them to warfarin. That's what we're all comfortable, what we've all done. You can do the same thing by giving low molecular weight heparin for 5 to 10 days, and then switch them either to dabigatran, or edoxaban, and then you can continue that for the remainder of the first three months, and then decide whether you want to continue beyond.

But what I think is probably an even more important and more potentially impactful strategy, is this one drug strategy. So, now with a single drug, we can cover all three stages of treatment. So we can give high intensity therapy upfront, either rivaroxaban in a twice a day dose, or apixaban twice a day but in its higher dose, and give that for the first 7 to 21 days. Then we can drop down to our maintenance doses of these two drugs and continue. Never needed to give a shot, never needing to give an injection, an infusion, never needing even to admit patients to the hospital and bring them to the ER.

So, there's potential that in your primary care practice, in your out patient practice, you can get a DVT scan, you can find that it's positive, and you can initiate treatment right away without having to send them to the ER. So there's a lot of potential health care utilization impacts of this as well. And we're working on developing some pathways and algorithms for primary care providers who are interested in doing this. Those will be out within the next couple of months as well.

So, the new guidelines came out just at the end of last year, and early this year. What did we learn, what changed from the American College [INAUDIBLE] Physicians, their last group in 2012. A number of changes happened, but these are three that I want to highlight. And the first is, how do we decide which drug we should be giving? And is that the same for our cancer associated clotting patients, and then what do we do about our subsegmental PE patients?

Well this was pretty big, so for the first time, we're now seeing a recommendation that use of a direct oral anticoagulant is preferred over warfarin, for patients with acute venous thromboembolism who do not have cancer. So, this is, granted it's not the strongest recommendation, but they're saying, the data is out there, it seems to be better, there seems to be less side effects, we really should be using this. And again, you can either use a two drug approach, or a single drug approach.

If, on the other hand, your patient has a venous thromboembolism and it's associated with cancer, they reaffirmed that yes, you still should be treating these patients with low molecular weight heparin. We now have two very large randomized controlled trials that when put together show that you definitely have a reduction in the risk of recurrent VTE when you use a low molecular weight heparin, as opposed to treating people with warfarin. So, at least for the first three months and potentially beyond that, you should be using Lovenox or another heparin agent for these patients.

Now what about subsegmental PE? So, this is an increasing common problem. You order a CT scan for something else, maybe it's a pulmonologist who is checking on a node, maybe your a cardiologist who is checking on somebody's enlarged aorta, and what do you know, you found a subsegmental PE. You weren't even thinking PE. The question then becomes, do I need to treat them? And our reflex has been, well you got a blood clot in your lung, you probably should be treated. And what the data has suggested is perhaps, we don't need to. So, the recommendation now, is that you don't need to treat subsegmental PE when the patient did not have an indication.

So there was no real reason for them to have that. Specifically, they're low risk. They're ambulatory, they're not hospitalized, they don't have active cancer, and you weren't doing the study specifically to look for PE anyway. You were looking for some other reason. Now, you want to make sure that they don't have a DVT at the same time. Pretty easy to scan that with an ultrasound, but in this case, we don't necessarily need to be treating all of our patients with anticoagulants just because we find a little something on the CT scan.

OK, so the last thing I want to leave you with is a resource. So, like I mentioned, this was a lot of information we covered, there's a whole bunch more. Where do you go when you have questions, and all of that? Well, this is a resource we have put together. So, using the experts within a six center consortium here in Michigan, sponsored by Blue Cross, known as the Michigan Anticoagulation Quality Improvement Initiative, or MAQII. We put together this compendium of expert advice on how to handle a number of clinical situations, and we have one set up specifically for providers, so it's written for physicians, nurse practitioners, physician assistants.

And we have a separate one written specifically for patients, answering their questions. Why am I on an anticoagulant? What does it do? What do I do if I miss my dose? What are the side effects I might experience, all those sorts of things. So it's a great website that you can point your patients to, and you can see the web site there. Anticoagulationtoolkit.org.

The physician side has a whole bunch of information that I think might be helpful. How do you decide whether you even need an anticoagulant? Where's the risk stratification tools? How do you decide which one to pick? What's FDA approved? What are the differences between the classes? What are some of the patient factors that influence that? How do you actually initiate, if you're going to initiate warfarin?

What are your dosing algorithms, what do you need to teach, drug-drug interactions, all those sorts of things. What about if you're going to treat them with a direct oral anticoagulant? How do you think about that? What if you're converting from one class to the next, how do you handle that? When do you this, and stop that? All these sorts of things are in there.

And then long term management. If you need to do dose adjustment of warfarin. If you need to know how to manage procedures, what kinds of follow up questions, all those things are available at the web site. We also have an iPhone app, and very shortly will have an Android app out that has some of this built right into it, and we're continuing to add more features. So, if this is something you find yourself dealing with all the time, you find this resource to be helpful for you.

So, with that, I just want to thank a lot of my mentors and collaborators. So, starting at the Michigan clinical outcomes research reporting group. People who run the MAQII registry, as well as the anticoagulation clinic who manages all the warfarin patients, and a growing number of the direct oral anticoagulant patients. And they're always looking for you to refer, so feel free to refer using that same anticoagulation clinic referral in my chart. At the cardiovascular center and then as well up in North Campus at the Institute for Healthcare Policy and innovation. People I get to work with quite a bit and who've helped me a lot.

And so with that I'll finish and take any questions.

[AUDIENCE CLAPPING]

SPEAKER 2: That was fabulous

[AUDIENCE ASKING QUESTIONS]

SPEAKER 1: So, the question had to do with diet, and the impact of diet and selecting anticoagulants, and some of the effects diet has on long term longevity and mortality. One of the biggest misconceptions that patients get is that, if they start on warfarin, they're not allowed to eat any green leafy vegetable, or anything with vitamin K. And that's actually not true, we encourage them to eat something, they just need to be consistent in it. And so it's very possible to eat a healthy diet if you're on warfarin, you just have to be consistent about it. Now how that might affect some of the absorption, is a little different question.

But I think the point you raise is really good. With the new direct oral anticoagulants, we don't have those dietary issues. There are very few dietary concerns. Usually has to do more about making sure you either take a medicine with or without food. And so it might be a lot easier and more convenient for patients who struggle to have that sort of regular diet. How that actually predicts longevity, I think is a little bit of anyone's question, but anything we can do to make our patients be healthier, eat healthier, take their medicines, I think is definitely a pro, and I'd support.

SPEAKER 2: So I have a question. The DOAC's, you didn't really comment on the differences between them. Are they all created equal, are there significant differences between them?

SPEAKER 1: Yes, so the question was, instead of looking at the DOAC's as a class, where are the differences in between each one. And I didn't comment a lot on that because we didn't have about four to five hours to go through all the nuances. What I would say is, there are a couple important distinctions, but for the most part, we can think about them as class drugs.

Distinctions that are important are things like, are they once a day versus twice a day, do you need to take them with food, do they need to stay in their blister pack, or can you add them to your pill boxes, some of those things. When you look at some of the trial data, there are some differences as far as efficacy, bleeding risk, all of that, and it's sort of been debated how much of those differences reflect the drug, and how much of them reflect the difference in trial design in the patients that were enrolled.

So, for instance, in the rivaroxaban study in afib, they were not able to show significant benefit in stroke risk reduction, but they gave a once a day drug to a higher risk population, and the quality of INR control was not quite as good. So, which of those factors, or was it something completely different, that influenced those outcomes, I'm not really sure. What I'll tell you is that, from a practical standpoint, we find that most practitioners are either using rivaroxaban, because it's once a day and it's very easy, or they're using apixaban, because across the board apixaban seems to be consistently showing the best results.

It's significant reductions in stroke risk, it's even got some mortality benefits. But I think the biggest reason is, it's the one that seems to cause the least amount of bleeding. So if you want to dive into that more, at the web site, the anticoagulationtoolkit.org, we have a really big chart, that goes into a lot of those things, and you can look at that to pick different elements.

SPEAKER 2: Yes

[AUDIENCE ASKING QUESTIONS]

SPEAKER 1: Yeah, so the question was, what does it mean to be valvular afib, and how does that influence the selection of anticoagulant. And the answer to that is, it's an evolving definition. And it's really interesting. I have a slide, I didn't include it here, but when you look at all of the trials over time, you see that the first trial that came out, the dabigatran trial RE-LY, had this very long exclusion list for any kinds of valvular disease. So any bioprosthetic valves, any rheumatic mitral stenosis, mitral regurgitation, those sorts of things. With each subsequent study, that exclusion list started to narrow, and fewer things got you excluded. Now to the point where it's really, we're just talking about rheumatic mitral stenosis. So when you really have significant mitral stenosis that's causing an enlarged left atrium, putting you at risk for a afib, those sorts of things, that's what we're thinking of as valvular.

How that actually impacts the use of the direct oral anticoagulants is a little bit of anyone's question I'll tell you that a lot of us feel comfortable, we think there's enough data to show that these are effective drugs. That we are using them whether or not you've got evidence of valve disease, and that's because some of the studies have included some valve patients. The bigger question is, what do you do when somebody has surgically had their valve either repaired or actually replaced. So, anyone who has got a mechanical prostheses in, they definitely should not be on any direct oral anticoagulant. They only should be treated with warfarin, and that's an absolute. If you have a bioprosthetic valve, so the pig valve, or the cow, or anything like that, it's a little bit questionable. We're not quite sure. We do have one study that included some of those patients. There's more studies that are ongoing. It's probably going to show that it's safe to use, but I don't have a lot of evidence to really back that up right now, and so it's a little bit of an individual decision, and it's certainly off label. They are not FDA approved for valvular afib patients at this time.

SPEAKER 2: Do TAVR's count?

SPEAKER 1: So a great question. What about TAVR's, and does that count. I think of a TAVR just like I think of a bioprosthetic valve. So, it's not going to be my go to first line, but if a patient is really insistent, they don't want to be on warfarin, it's probably an OK thing to do, as long as they're aware that they're a little bit in uncharted territory. And it may not be the right thing in the first one to two months. It may be something that you get to a little bit later on

[AUDIENCE ASKING QUESTIONS]

SPEAKER 1: So, that's a really great question. And the question was, how does the price of the DOAC'S impact, I think both the patient experience, but also us as a health care system in the utilization? A number of cost effectiveness studies, including some that we've done, have shown that yes, these are all cost effective when you use various thresholds. You know $50,000, $100,000 per quality adjusted life year.

And I think that that's important from a health system standpoint. What I find to be far more important is, what is that patient actually paying out of pocket, and how how's that going to influence their decision making. And that's really variable. I've had patients who I see who say they spend $20 a month on their co-pay, and they're able to get this drug. And for them, they love it, and that's great.

And I have other patients who tell me that it's $200 a month, even with their insurance coverage. Potentially even more without, and so that can obviously be very limiting. Now some patients are eligible for the prescription assistance programs, but any of our Medicare patients, they're not eligible. So that has a big impact as well.

I find it's really an individualized decision. Some patients say that the extra cost to them, they're willing to pay, because of the benefits that they get, and others say that they can't. And so that's why it needs to be individualized for each patient, and in our decision aid, that's a key question. If you need to spend more than $10 to $15 a month, is that going to be a significant financial burden for you.

From a systems standpoint, I think that we've shown that their cost effective, we're far more interested in preventing the stroke, which has huge costs, rather than the price of the drug. And I think that's what the drug companies have sort of banked on, and so if we're able to show increased utilization, and therefore decrease stroke rates, we'll be able to show that system wide there probably cost effective. Patient pocket is a totally different story.