AMY KATHERINE GUZIK, MD: So no financial disclosures to talk about, but we will be talking about some off-label use of some different medications. I really just wanted to go through some advances that have occurred in the past couple years, both in terms of studies that have recently completed, and some new information we have about the care of acute stroke patients, and also some things that are kind of on the horizon, not necessarily available right now, but opportunities that we may have in the future to expand our treatment of acute stroke patients and also help in secondary prevention.

So the first I want to talk about is the acute ischemic stroke patients. And we'll go through a couple different categories of trials that have been out there. The first is kind of tPA "Plus." So we often give tPA, but want to do something more. We know that it doesn't help all the people all the way.

So are there other opportunities after we give tPA to further their improvement? We also know that there's a lot of tPA exclusions. So patients that come in, even if they're in the window, can't get tPA. Are there other opportunities for them? And then what's the role of endovascular therapies?

And we're going to hear more about this later from Dr. Wolfe in neurosurgery. But I just wanted to touch on a couple of the recent trials that have given us some more information about what patients really benefit the most from these endovascular therapies.

In terms of secondary prevention, the antiplatelet discussion is always ongoing. What's the best antiplatelet to use at what time? And then also there's some new oral anticoagulants on the market. I'm sure everybody's seen the commercial. So we'll talk a little bit about which ones those are, and what they're best for, and maybe some other prevention options as well.

So starting with this tPA "Plus" group-- first just talking about the basic guidelines. So we know all know the FDA approved tPA for treatment of ischemic stroke within three hours of onset in 1996. And the AHA guidelines expanded this to four and 1/2 hours in selected patients in 2009 in response to the ECASS 3 trial. In 2013, they also reinforced that early treatment is better. We all know time is brain. And they even recommended this door to needle time within 60 minutes.

But we all know that there's limitations to stroke care. The time window is short. There's an incomplete resolution of symptoms in a lot of people. We want to see them get better right away.

And we know that IV tPA, the benefit is proven for outcomes over three months. But how do we know if they're getting better right when they're in the emergency room? What else can we do for those patients? And then the patient population doesn't always fit our inclusion criteria and our rules. So these tPA kind of plus trials have been done to see what else we can do there.

Sorry.

So CLEAR-ER was a trial that was done to look at tPA plus eptifibatide. So eptifibatide is also known as Integrilin. It's a medication commonly used in cardiac care. So it's a glycoprotein IIb/IIIa inhibitor. It's been shown to improve recanalization and cardiac function in MI, interestingly not mortality, necessarily. But investigators through that there may be a role for this in acute ischemic stroke.

So the thought being that tPA is great at initially busting up that clot, but a lot of times, even though we monitor patients for 24 hours afterwards, the tPA medicine itself really only stays in your system for about 15 to 20 minutes. So once that's out of your system, what can we do to keep that vessel open? And eptifibatide is a medication that's given in a drip over two hours.

So what they looked at-- first, they did an initial dose escalation safety study. And it looked like things were OK. So they proceeded onto this phase two study, looking at the safety of the combination therapy. And they looked at full dose tPA, 0.9 milligrams per kilogram, versus a 2/3 dose of tPA, plus giving the Integrilin at this does here.

And you see, it's a drip over two hours. So this is a multicenter, randomized, double-blind trial. So people didn't know what they were getting. The docs didn't know what they were giving. And even the pharmacists didn't know what they were filling.

And these were patients that were given tPA within three hours. They had a stroke scale over five. So they're not those mild stroke patients. And they're between 18 and 85.

And so this is just kind of a diagram-- it's probably hard to see on these smaller monitors-- but of how they did it. And basically what they did was they had a bag of 2/3 dose tPA. And then after that, they either got a placebo dose or the rest of the tPA. And then in the other bag, was the eptifibatide or a placebo. So the patients were getting one of those two treatment modalities.

And because this was a phase two safety trial, the primary endpoint was the safety endpoint. And they were looking at symptomatic ICH within 36 hours. And you can see here in the combination group, only two out of the 101 patients that were in that group had symptomatic ICH.

In the tPA alone group, it was a smaller group because you remember there was that five to one randomization. And three of the 25 patients had bleeds in that group. It's a really small group, so it's hard to say if that's atypical or typical. But basically the bottom line is that there wasn't a difference. And, in fact, there may be less bleeding in this patient population with that 2/3 dose of tPA plus Integrilin.

They also looked at a preliminary endpoint of efficacy. So they wanted to look at the 90-day modified Rankin scale, a functional scale. And less than one basically means that there may be some symptoms, but it's nothing that's really going to affect their life. They don't have to be in a nursing home, things like that, or just returning to their baseline functional status.

And there was a bit of a difference. You can see the middle bars there, the blue bar is the combination, and the red bar is tPA alone. And even though it was non-significant, it was unpowered to really show significance in this trial, there's a hint that with the combination therapy, there may be better outcomes. So they're moving onto a phase three trial with that now.

Another option is tPA plus hypothermia. So a lot of us are familiar with hypothermia in the setting of cardiac arrest and preserving brain function after that. So there's lots of roles for hypothermia in neuroprotection.

And you can see, based on this kind of cellular model--and we're not going to go through all the details. Don't worry. But all those red bars are all the different time points where it's thought that hypothermia may help. So it's a lot.

Basically, preserving cell function and preventing apoptosis, or cell death. So-- sorry, this isn't advancing the-- so the ICTuS 2/3 trial is looking this, tPA plus hypothermia. Their initial trials were studying kind of feasibility and safety of this. And what they found from those two initial trials is that it's feasible. It's possible to do this in acute stroke patients because there's a lot going on with stroke patients. So can we add one more thing?

But there may be an increased rate of pneumonia in the patients that are getting hypothermia. Part of that is because the hypothermia arm was getting a large bolus of iced saline to help cool the body. And so they're doing this new trial, the ICTuS 2/3 trial, looking a little more closely as to those risk factors for pneumonia and making sure that that's not something that we need to worry about in these hypothermia patients.

So, again, it's patients who are receiving tPA within three hours. Their stroke scale is over seven, but less than 20. You can see the ages there. And they have to have a baseline functional status that's pretty good. And so the hypothermia arm is getting cooling for 24 hours. And that's cooling via an IVC catheter, and you set it to 33 degrees, so really just a couple degrees lower than your baseline temperature.

And these patients are awake, unlike the cardiac arrest patients where they get sedated. So you can imagine that might be a little bit uncomfortable. But there's a shivering protocol put in place to reduce that discomfort with some medications and then skin warming in the form of heating blankets and things like that.

And so their primary outcome is a 90-day functional status outcome as well. And this is currently enrolling. The other interesting thing about the study is it's a phase two trial, but they're automatically going to roll into a phase three, which if anybody kind of follows the research these days, it takes a very long time to get through all these phases and to actually be able to use these studies. So these adaptive designs where you kind of roll right into the next one are helpful in terms of getting these treatments to our patients faster.

So one study that we have going on here actually-- we're one of the sites for CLOTBUST-ER. This is a really interesting trial where the investigators found that-- they were doing transcranial ultrasounds on stroke patients. And the ones that they were continuously monitoring seemed to get better. Those clots seemed to bust up faster with or without the tPA. So they said well, maybe we're onto something here, and we need to look a little more closely.

And so the initial CLOTBUST study did show some benefit, and they wanted to do a larger phase three multicenter trial. And like I mentioned, we're one of the sites for that. And so it's, again, patients receiving IV tPA within three hours. And then they either get this transcranial ultrasound for two hours or a sham. So they have the device still put on their head. So we're all still blinded to the treatment option.

And you can see the device kind of in the bottom corner there. It's a little tight, but otherwise, not that uncomfortable. And I think, you know, if you'd rather have a stroke or a tight headband for a little while, most people would rather have that headband.

And so that's going on now, and they're enrolling patients. And it'll be really interesting to see what that shows. That would be a great type of device for especially some of our smaller hospitals, where if you don't necessarily have interventional capabilities, this is the type of thing that could be put on patients either in transport on their way to a bigger comprehensive stroke center or even just in the ambulance. It's a relatively safe device, so it'll be interesting to see what some of this shows and where this goes.

Kind of along the same lines, there's other institutions using transcranial laser therapy. So other things that you're shooting laser beams into the brain, but basically what this does is it's thought to increase Cytochrome C oxidase activity. And that's just kind of maintaining the energy metabolism in the cells after stroke.

And there's been a couple trials looking at this, as well. And they're the NEST trials. NEST-3 is currently enrolling. NEST-1 and 2 showed some early evidence of improvement in baseline functional status at 90 days. So you see, we're kind of talking about the same types of outcomes in all of these patients. So we'll see how that goes, as well.

So switching gears a little bit to talk about endovascular therapy-- so the IMS III trial has gotten a lot of publicity lately. It was one of the a tPA plus endovascular therapy studies. This really kind of, prior to these studies, has become one of the options that we have in these stroke patients that if they're not getting better after tPA, we consider sending them to endovascular therapy. And so they wanted to do it in a more structured way.

And so this study was occurring over the past four or five years, and was looking, again, at IV tPA patients treated within three hours. And they were randomized to either just the IV tPA alone or stopping that tPA at 2/3 dose. You can see the kind of common theme here where if we're doing something else, sometimes people like to give a little less tPA. And then do additional endovascular therapy.

And you can see along the bottom there that that endovascular therapy was a little bit left up to the discretion of the interventionalist. So some of the patients were getting IA tPA, just tPA dripped into the artery. And then others were receiving these other mechanical devices.

And if we can forward to the next slide, these are some of the devices. I'm sure people have heard about some of these because they're really neat. The first one up in the left corner is the MERCI retriever, and that's the corkscrew one. That was kind of the first degeneration device that was available. And the good thing about it is it goes in, it corkscrews through the clot, and it pulls it out.

But the bad thing is those pointy ends can rupture vessels. And so it's not necessarily the best way to do it. It's kind of like a Roto-Rooter, but it's not, you know, necessarily the safest when you're talking about cerebral blood vessels.

The second went up to the upper right is the Penumbra device, and that one's kind of a aspiration suction vacuum device with a wire at the end to break up the clot. And again, those pointy edges sometimes have some side effects of rupturing the vessels. And so those two were the main devices used in this trial.

Of course, with every technology as the trial goes through, that stuff's a little bit old news now. So the bottom is the Solitaire stent retriever device, which is a stent. It opens just like a stent, but then it captures that clot against the walls. And then after a couple minutes of letting that clot integrate into the stent, you pull the stent out.

So there's definitely some benefits of that above the other two in that you quickly pass through the clot and open up to cause recanalization much earlier in the process. And then also you're getting all of it out without showering some pieces forward. So that device, although it was allowed in the study, was really only available in the last few months of enrollment. So this study is not really talking about those new up-to-date devices.

So here we have the results, and they were a little bit discouraging. So we see that at the primary endpoint of functional status, the Rankin score of 0 to two, there wasn't a significant difference between those receiving IV tPA alone, versus IP plus endovascular therapy. But they wanted to look-- you know, I think we all know that there are some people that this is good for, and there's some people that definitely get better when we do this.

So looking a little closer into the data, looking at time to reperfusion, they saw that every 30 minutes matter. So just like IV tPA, every minute matters and time is brain. It's the same thing with endovascular therapy.

So they saw that with every 30 minute delay in reperfusion, there's a 14% relative reduction in probability of a good outcome. And they also looked into what characteristics of patients made them better interventional candidates. And I know that that's still something we're working out a little bit, but I think the bigger vessels, the larger clots have a better outcome.

So what about MR-RESCUE? So that's one trial that was done around the same time the second study came out called MR-RESCUE. And this one is looking at the same thing, IV tPA plus endovascular therapy. But they wanted to try to categorize patients by perfusion imaging. So you can use CT perfusion or MR perfusion to help evaluate which patients have this penumbral pattern, which I'll show you in a second.

And so you can see, it's pretty similar type of structure of their study. And with the penumbral patterns, you can see the top-- they have a computer program that helps you interpret this perfusion data because a lot of times we get this data. And it's all sorts of colors all over the brain. And we don't really know exactly how to use that. So their computer program gave us those predictive maps in the middle to help you figure out which of these are truly a favorable pattern or a non-favorable pattern based on previous studies.

And so the top row there is this favorable penumbral pattern. So you can see, the red area in the middle is the tissue that's already thought to be dead. And then the green area is tissue that's thought to be at risk, so maybe tissue that we can save if we go in and open that vessel up.

The bottom is this non-favorable penumbral pattern. So you can see that the red and green pretty much overlap, so you're really not saving that much if you go in and open up that vessel. And, in fact, you may be putting them at extra risk because this is all tissue that's at risk of hemorrhagic transformation. So they thought that this was a really great way to structure patients and see if we could figure out beforehand which ones will benefit.

So unfortunately again there wasn't that much difference in these patients. And so the top line is-- again, you can't really see it probably because it's far away. But just trust me to know that none of these p values are significant.

So the top line is looking at all-comers. There was no difference between the IV tPA and the IV plus IR. And in the bottom, they structured this based on either favorable or non-favorable penumbral pattern. And even within those, there was no difference.

So is it because the penumbral pattern is actually just a sign of which patients are going to get better anyway? Maybe they have good collaterals, and that's what gives them this tissue at risk image that actually is just tissue that's being saved by those collaterals. It's hard for us to know. And again, kind of some of the same things apply as I talked about with the last study of why this happened and how we can better determine which patients benefit.

So when next? So we talked a little bit about the study limitations. Is it because this is old technology? Now we have these stent retrievers that we think are doing better than the Merci and the Penumbra. But we need studies to better determine that.

Are we choosing the wrong patients? Should we not choose all-comers with a stroke scale above a certain number, but really better choose the patients that are, perhaps younger, perhaps have the right type of clot to go in and retrieve? And what's the role of endovascular therapy at this point outside of a clinical trial?

We don't really know. And that's kind of the debate that's going on now. And I'm sure that Dr. Wolfe will talk more about that later. I think we all agree that there's patients that benefit from this. And we just need to figure out who those patients are.

So now let's switch gears a little bit and talk about tPA exclusions. So these patients that come in either too late or with some exclusions on their tPA candidacy criteria, and we want to do something. What can we do?

So there's a couple different exclusions we'll talk about. So wake-up stroke-- we all have this sinking feeling where if somebody comes in, they just woke up. And they know they had a stroke. They went to bed normal, and you think that it just recently happened, but you can't really tell. And so you can't treat them. Mild strokes, and TIAs, and what about symptom onset over 4 and 1/2 hours?

So wake-up stroke, again, like I just mentioned, most of these are actually thought to occur during those first few hours of the morning. And imaging studies support this concept. So patients coming in with wake-up stroke, stroke upon awakening, the perfusion studies show that they have this favorable for diffusion mismatch.

And I know I just told you that we don't really know exactly what that means, but it helps us know that, perhaps that stroke is not yet completed, versus if they went to bed 12 hours ago, that stroke should be completed by now. So what can we do from these patients? Because right now they're excluded from IV tPA because we have an unknown time of onset.

So a few places are studying this, and they all have different inclusion exclusion criteria, but basically they're keeping either registries or doing randomization of these patients. When they have a CT scan that doesn't look like it's over 1/3 is about the cut off of the MCA territory that's already infarcted. And they're looking at either IV tPA or thrombectomy for these patients to see if there's a group that do still benefit from tPA even though we don't have an exact time of onset.

So what about mild stroke and TIA? So right now there's no clear exclusion for the NINDS criteria for a mild stroke. But I think that we know that there's a certain percentage of strokes with a low stroke scale that have an expected favorable outcome. So who do you want to give the risk of tPA to? And who do you want to maybe try another therapy?

That being said, I think that that's a tough call because there's certainly patients that have a low stroke scale. For example, a stroke scale of one of aphasia is still very significantly disabling stroke. So figuring out what those best cut offs are.

So one thing that we're actually enrolling in here at Wake is the POINT trial. And so this is looking at TIA and mild stroke. We know that TIA patients have a higher risk of second stroke within the first three months. And what can we do to help prevent that?

So, of course, we're going to do all the normal workup looking for carotid stenosis and things like that, but considering giving them dual antiplatelets, versus a single antiplatelet. So typically these patients would just be put on aspirin, and we'd evaluate them, and monitor them carefully. But what about using aspirin plus Plavix in this selected patient population?

So these are patients with either a TIA with an ABCD squared score of greater than four. And that's just kind of a risk assessment tool that we have for TIA patients to see at how great of a risk over those next three months they are, or minor stroke, which is a stroke scale less than three. And they're randomized within three hours. And the outcomes will happen at 90 days like all these other trials.

And we actually have some data from a similar study called the CHANCE trial that was done in China. And this was very similar inclusion and exclusion criteria, as you can see. And they recently finished their trial.

And you can see at the bottom that those on dual antiplatelets did slightly better than those with single antiplatelet. That being said, this is a different patient population. So it's in China where the stroke care is a little bit different. And there's also a higher rate of intracranial stenosis. So I think it's still important to not jump to this therapy just because of one trial.

And we're still continuing the POINT trial to get more information. It's also a little bit different. Even though they were treated for three months, they only got the dual antiplatelets for 21 days. So there's some differences, but it's an interesting kind of encouraging finding that the POINT trial will be interesting to follow up on. And, again, this just shows the significant difference in ischemic stroke and no different in hemorrhagic stroke.

So what about those who come in after 4 and 1/2 hours? The have a big clot. Maybe IR is not available. What can we do?

So desmoteplase is actually bat saliva, derived from bat saliva. And there's been some studies that have been done using this medication, which have indicated that perhaps the ones that benefit most from it are those with a vessel stenosis or occlusion in the proximal cerebral arteries. So this study is looking at giving desmoteplase three to nine hours after stroke in the selected patients listed there. So higher stroke scales, Rankin score less than two, and they're currently enrolling that at 89 sites the last time I checked.

So what about other exclusions? So I think it's tough that there's patients that are getting better in front of us, these rapid improvement patients. And we don't necessarily know what to do with them either. Also we're waiting on the INR and the PTT, and we don't know exactly what to do with those patients.

So the recent literature for those have been suggestive of treating. So for those with rapid improvement, a lot of times we see them getting better, but they're not 100% better. We still think that they may have some deficit. And if you watch them over time, there's a hint that they may end up getting worse again.

So they're getting a little bit better because you're treating their blood pressure and giving them fluids in the emergency room, but then you wait until the window's expired and don't give them tPA, and they're getting worse again. So we recommend treating those patients even if they're getting better. Of course, not if they've resolved entirely. But there's a possibility that they'll get worse again.

Those awaiting and INR and PTT-- so if you're not on Coumadin, and you really have no reason to have an elevated coag labs, then it's possible to just treat, and wait for those labs to come back, and stop it if they are out of the realm of normal. And that's actually been recommended in some of the more recent guidelines.

So when is it time to reevaluate this criteria that we have the inclusion exclusion criteria? And there's actually some places and studies looking at some of that, as well. So it'll be interesting over the next couple of years to see how that changes.

So switching gear to stroke prevention-- so we talked a little bit about antiplatelets with a minor stroke in TIA. And just another slide or two about that, I wanted to talk about kind of what the standard is now. So aspirin, clopidigrel, Aggrenox, those are pretty much the antiplatelets that we have available to us.

And if you ask 10 neurologists what the best one to use is, you'll probably get five or 10 different answers. So it's a little bit of patient preference and personal selection. There are some studies that narrow it down a little bit. But for each individual patient, I think you just need to think about what's best for them.

Typically, aspirin, you know, there's also this question of which does is the best dose. 81 is probably OK for most people, but there are certainly people that either have different metabolic enzymes or things like that that really won't benefit from 81. So if they can handle 325, if they don't have any bleeding problems or anything like that, I usually go ahead and give them 325 because there's not that much more risk, and there's potentially more benefit.

Clopidogrel is often used in cardiology. So if patients have cardiac comorbidities or particularly peripheral vascular disease, I think that that's really the one to go to. And then Aggrenox-- the tough thing about Aggrenox, even though it has been shown to be slightly better than aspirin alone in some trials, and significantly, so-- I say slightly, but it's significant-- it's a twice a day dosing. So if somebody's, already you're trying to get them to take their aspirin every day, they might not be taking their Aggrenox as needed.

And then also it can cause headaches in the first couple months. Usually if you get past that first couple months, you're able to be OK. And you don't want to give it to patients with CHF. So, again, it's patient selection based on each individual patient criteria, but those or what we have available right now.

We do have a little bit of data, though, because, you know, if one antiplatelet is good, is two better? Well, no, not really. So the SPS3 trial looked at lacunar strokes within 180 days. And they randomized to either aspirin plus placebo or aspirin plus clopidogrel. And they also looked at blood pressure as well. So the primary outcome was recurrent stroke.

And in this next slide, on the left you can see the antiplatelet arm. And so you can see that those lines are very close together. There's no significant difference between dual antiplatelets and single antiplatelet in ischemic or hemorrhagic stroke.

And to the right is the blood pressure arm. And the lower blood pressure, so less than 130, rather than 130 to 149 was, though not statistically significant at a p value of 0.05, it was 0.08. There's a suggestion that those patients might do better in lacunar strokes for a second stroke.

So let's talk a little bit about the new oral agents. Again, we all see the commercials. So when should we use them? So cardioembolic stroke is 20% of all ischemic stroke. And AFib is in 50% of those. And so this is a really large population of our stroke patients.

And we've all heard of the CHAD score. So at the top graph, you can see that as the CHAD score increases-- so these are all risk factors for stroke and cardiovascular disease-- as that increases, your risk of stroke increases. And at the bottom, you can see that if your score is two or higher, it's recommended that you use warfarin for secondary prevention. Anybody with two or higher-- so a stroke gives you two points automatically-- so anybody that we see with a stroke is automatically a candidate for warfarin.

So warfarin is a vitamin K antagonists, as we all know. And it's superior to placebo and antiplatelets in the prevention of stroke and other thromboembolic events among patients with non-valvular AFib But we know that it has its limitations.

So there's often an unpredictable effect on anticoagulation. So you give one person and another person both five milligrams, and one person's INR shoots up to three, and the other person stays at 1.1 for five days. So you don't know what's going to happen with those patients.

And there's also the interactions with drugs, and food, and inconvenience and safety issues with INR. So a patient eats spinach one week, and they have to change their medication. And in the next week, they don't eat spinach, and you have to change it again. So there's also a risk of major bleeding. And there's certainly those patients that we see that, you know, despite our best efforts to monitor that INR, it's just not doing what we want it to do.

So the new oral anticoagulants are kind of categorized into two classes, direct thrombin inhibitors and the factor Xa inhibitors. And you see a lot of names on there, but the ones with the stars by them are the ones that have been FDA approved for prevention of stroke.

So the coagulation cascade-- I promise I won't go through this in detail-- but warfarin is kind of like using a grenade, whereas the factor Xa inhibitors and thrombin inhibitors are like snipers. They go after a specific point in the cascade. And so those are both in the common portion down at the bottom, right-hand corner. Rather than kind of having multiple effects on the coagulation cascade, they're really pinpointing that final common pathway.

So the first trial, we'll just talk about briefly, is the RE-LY trial, and that was looking at dabigatran versus warfarin. And you can see that they used actually two different doses of dabigatran in this study. And the primary outcome was stroke or systemic embolism. And I won't go through all the details, but I have them there. And I'm happy to talk to anybody about all the details afterwards.

So you can see that in those with the dose of dabigatran of 150 milligrams-- and this is a twice-day dosing-- there was a decreased rate of stroke in systemic embolism, which is their primary outcome. Those given the 110 milligram dose did not have that same benefit. So we'll just talk from here on out about the 150 milligram dose.

So some of the data reported in the study-- so you can see that there was a significantly decreased rate of stroke or systemic embolism in the dabigatran group, and that also included a significant reduction in stroke, which is, of course, what I'm most interested in because I like to save the brain first. And you can see that's hemorrhagic and ischemic, non-disabling and fatal stroke. So all strokes subtypes had a decreased rate of outcome with the dabigatran dose.

That being said, there's a slightly higher rate of MI in the dabigatran group. They went back and looked at this again, looking at their data. And their revised data says that that was an error. And that it wasn't actually the case when they looked back at patient charts.

But, of course, we don't always trust it when you go back and look at patient charts with the idea that we want to find less MIs. So there is a risk of that. So in your patients that have a high rate of heart attack or cardiovascular disease, you might want to avoid this medication.

So what's the bleeding risk? That's, of course, the big important thing here, too. So major bleeding was less with dabigatran. And that includes life-threatening bleeds. That being said, GI bleeds were increased with dabigatran. So you have to be aware of that.

But none of these were fatal or major bleeds. So that's good to know. There's also a decreased rate of intracerebral hemorrhage, which is, of course, important to neurologists.

So what's the summary? So there's some pros and some cons with all of these medications. And I'll try to give you a little bit of a list to determine which one's best for each patient.

So this was actually not only noninferior to warfarin, but superior to warfarin in reducing the risk of stroke and systemic embolism. And the other good thing about the dabigatran is that it's statistically significant decrease in ischemic stroke specifically. So that's, of course, important to us.

That being said, there's an increased risk of GI bleed. There's no known reversal agent, which we'll talk about a little bit more in a couple minutes. It's BID dosing, and there was an increased rate of discontinuation of dabigatran versus warfarin. And that was primarily due to dyspepsia, which was not associated with GI bleed. So it's more discomfort than true GI bleed, but it's still something to be aware of when you're prescribing this to patients.

So I'm not going to go through this in detail, but the recommended dose-- they have a renal dose. But that hasn't been studied as well, so they're still kind of monitoring that. What do you do for surgery? Hold it for one or two days, or three to five days if they have any renal insufficiency. And pregnant patients probably should not get this medication.

So one quick point about the anticoagulation levels-- so how do we know if they're taking it? It's really tough. So it does prolong the PTT, but it's unreliable. So you can't say that this number on the PTT means that they are or are not taking it.

The ECT and thrombin time, those are labs that usually take hours to a day to come back. So they're not something that we can track as easily as an INR. So that is one of the drawbacks of these medications.

So rivaroxaban, this is another one of the medications, Xarelto, you've heard of. And so pretty much the same thing here in terms of what the study was looking at, primary endpoint of stroke or systemic embolism. And there's a decreased rate of stroke or systemic embolism with rivaroxaban, too.

So how is this different? So, again, you can see significantly reduced stroke or embolism and significantly reduce stroke. But if you look down to ischemic stroke, it's not significantly different. MI, there's no difference, so that's good news on this one. And the all cause mortality, there's no difference. So that's OK.

So what's the bleeding risk? So there's no difference in major bleeding. That's what we like to hear. And there is a significant increase in GI bleed, just like for dabigatran. Interestingly about the bleeding risk of rivaroxaban-- so although there is a decrease in fatal bleeds with rivaroxaban, there's an increase in bleeds needing transfusion and with a hemoglobin drop of two.

Each one of these trials didn't have exactly the same outcome, so we can't compare them head to head. But you have to be aware that these bleeds needed transfusion. So that's something to think about. And there was a decrease in intracranial hemorrhage.

So the summary for this one, we basically talked about everything. There's only noninferiority. There's no significant difference in ischemic stroke. There's an increased risk of GI bleed in transfusions, but there's a decreased risk of fatal bleeding.

And then, again, the anticoagulation levels is the thing I'm going to pinpoint on here, is that factor Xa is really the best way to evaluate if they're taking this medication. But, again, that's a send-out lab usually that doesn't come back right away. It does prolong the PT, but again, in a non-reliable way. So you can't say that this number means yes, they're taking it. And they're therapeutic. And this number means no, they're not.

Interestingly, when the FDA approved this medication, they added an additional warning, which is a little bit strange because even though it's the same type of class of medication as dabigatran, they added this note that discontinuing the medication can increase the risk of thrombotic events. And also that you can have epidural or spinal hematomas if you do procedures while on this medication, which you'd think would be kind of common sense. All these medications are trying to prevent thrombus, and they may cause bleeding if you do other procedures while on them. But there is this additional warning on this medication.

So last, but not least is apixaban. And this, if you remember, is also a factor Xa inhibitor, so it's in the same class as rivaroxaban, but the different one from dabigatran. This is also a twice a day dose, five milligrams.

And in this study, they actually even included patients with renal insufficiency at a lower dose. So this is the only one that really looked at those patients within the scope of the trial. And again, their primary endpoint was stroke or systemic embolism.

So what makes this one different? So, again, significant difference in their primary endpoint, the stroke rate for ischemic stroke was the same in both groups. So no difference there. Major bleeding was reduced with apixaban, and intracranial hemorrhage was reduced with apixaban. And importantly, this one had no difference in GI bleed.

So that makes this one a little bit different. Again, we're nitpicking because they all look about the same. So how do you determine which one's different than the other?

And, again, pros and cons-- I'm not going to go through this in too much detail because there's not as much information about apixaban. But the high points are no significant change in GI bleed and significant reduction of stroke and systemic embolism. So this one, again, like the rivaroxaban prolongs the PT, but in an unreliable fashion.

So how do we compare them? This is just a comparison of the different trials. So we won't go into too much detail about that. But at the bottom line, you can see the discontinuation rates of all these medications. So you can see that apixaban had a higher discontinuation rate, but their warfarin patients had a higher rate of discontinuation, too, so you can't really go on that too much. But it's important to know that there is a percentage of all of these patients that stopped taking their medication. So, you know, some medication is better than not taking one. So if they discontinue one, consider another.

And I tried to bold some of the main points here. So dabigatran, the high points are that ischemic stroke is decreased. There's decreased vascular mortality. Though, all cause mortality is not different. And there's the side effect of dyspepsia that you have to consider.

Rivaroxaban, there's that increased rate of transfusions, which I think is a little bit of a concern. And with apixaban, there's no change in GI bleeds. So that's good.

So, that being said, there's still definitely concerns about these medications. So this is a report of the FDA Direct reports. So if you have a problem with a medication, you can tell the FDA directly, and they keep track of how many concerns there are.

And dabigatran is higher than all of these medications over the past 10, 20 years, including Coumadin. So is that because it's new, and everybody's worried about it? Or is it because there really are this many problems? And they're continuing to monitor that.

The biggest concerns are in the inability to reverse these agents, right? So when somebody comes in with a bleed, and is on warfarin, there's at least theoretically some guidelines on how to reverse that. That being said, I think that if you have a major bleed, and kind of the horse is out of the barn, even reversing warfarin doesn't necessarily help people.

But what are the reversal recommendations for these new agents? So none of them have a reversal agent available. Dabigatran is dialyzable. So you can dialyze, but I think it would be difficult to convince somebody to put in a dialysis catheter in somebody who is actively bleeding all over the place from dabigatran. You can also consider factor concentrates and things like that, but there's no true data that says that this is going to help. I think we do it because we want to try to stop that bleeding. And, of course, considering platelets if there's thrombocytopenia, as well. But this is something that needs to be monitored a little more closely, and figure out that really the best way to be managing these patients.

So what about tPA? So a patient comes in, and they say, you know, I'm on dabigatran, but I didn't take it yesterday. And now I have a stroke. How do you know if they're anticoagulated or not? And if it's safe to give them tPA?

So the new guidelines for ischemic stroke actually made a little bit of a recommendation on that. That being said, it's really confusing and doesn't necessarily help. So it's not recommended unless sensitive laboratory tests are normal, or the patient has not received a dose for two days.

What are these sensitive lab tests they talk about? I'm not entirely sure. So we talked about how, in general, if you take dabigatran or a direct thrombin inhibitor, if you have a normal PTT, it usually means that it's not therapeutic. And with the factor Xa inhibitors, usually if there's a normal PT, that means there's no medication.

So everybody has their own kind of system. I've heard people before that say if a patient says I haven't taken it in two days, and their labs are normal, then they'd be willing to give tPA. But not if either one of those is not true. But, you know, that's individual preference, and there's certainly no guidelines to follow for that.

So what do you choose? And again, I think that it's kind of patient-specific. I think there's a really great role for these medications in patients whose INR is never consistent.

So in those patients that come in one day, and their INR is five. And the next day, and their INR is one, and they're on the same dose, and you just really don't know what's going on, I think these medications have a more consistent level of anticoagulation. So I think that's a positive.

In terms of which one to use, I think that they're all very similar at the end of the day. You know, I went through telling you all the discrete differences, but I think at the end of the day, they're all pretty similar. And again, it's patient-specific.

So if it's a patient that you might think is at a higher risk of an MI, maybe don't give them dabigatran. If there's somebody who might get a GI bleed, again, you're probably considering not giving them Coumadin or these new agents. But if you decide to give them, then maybe apixaban might be the best because there is no increased rate of GI bleed. But it kind of remains to be seen exactly which patients benefit from each type of medication.

So just to stop talking about the anticoagulants and talk about one more study that's happening here at Wake Forest. So Cheryl Bushnell, the director of our stroke group, is actually doing a really interesting prevention or recovery study on beet juice-- so something that's very safe and potentially has a lot of benefits.

So there's been some preliminary research that shows that a high-nitrate diet might result in increased cerebral blood flow in elderly patients. So the thought being that these nitrates transform into nitric oxide, which acts as a vasodilator. And so can we enhance recovery post-stroke using this supplement?

And so they're currently enrolling into an 80-patient preliminary study. And I think that's a really interesting study. So it's something I kind of wanted to throw in.

So we talked about a lot. And I'm happy to answer any questions, but I think that you can see that there's a lot of change potentially coming in the next couple of years in stroke, and a lot more possible treatments that we'll have to be able to treat a larger portion of patients, and potentially treat patients more effectively and better. So let me know if you have any questions.

[APPLAUSE]