

AMY GUNK: Thanks, everyone, for coming and listening to us talk a little bit about stroke. I know it's a little bit off-topic, but certainly a lot of the patients with cardiac issues have strokes as well. So I think it's good to hear a little bit about it from this end. And we'll talk a little bit about our Telestroke Network that we have here at Wake Forest Baptist and just a little bit about acute stroke care in general today. So we wanted to go over a few different things about stroke. We'll talk a little bit about the signs and symptoms of stroke, talk about the importance of the golden hour in terms of treating acute stroke, talk about our Telestroke network here in North Carolina, and then some other advances that are occurring in stroke care and the future of stroke care.

So I certainly don't have to tell anybody that here in North Carolina we're right kind of in the stroke belt-- stroke buckle even, if you will-- of the country. You can see on this diagram that the areas with the stars are areas of increased mortality across the country in terms of stroke and increased morbidity. So not only is stroke a really large problem in terms of the fourth leading cause of death right now, but there's a huge burden of morbidity in these patients. So even if you don't die from stroke, there's a significant amount of disability that leads to increased health care costs. Obviously it decreases patient quality of life, caretaker quality of life and is a really huge burden on patients and the community.

So what about the symptoms of stroke? So this is kind of the commercial version of it. So FAST is easy acronym to remember-- face weakness, arms, speech, and time. So it's an easy way to remind our patients and the community that if you see any facial droop, any arm or leg weakness, any speech problems, you have to really pay attention to the time, because you have a short amount of time that we can potentially intervene and help these symptoms.

But there's more, so it's not as simple as that. There's altered mental status. There's bilateral weakness. Is that really stroke? Well, typically no, but occasionally dizziness is one of those tricky symptoms where we're always trying to decide if this is a posterior circulation issue, or if this is something in an ear or if it's just dehydration. There's certainly a wide range there. Double vision and hearing loss, nausea, vomiting-- these are all kind of nonspecific symptoms, but things that we have to think about.

And so I included on here some information about when we really determine it's stroke, and so you can see on the bottom is the posterior circulation. Those, I think, are typically the trickiest ones to think about, and you can see the blood vessels there in the brain stem. It's not the entire brain at the bottom there, and that shows us that the blood vessels that are in the brain stem in the back part of the brain are really close to all the cranial nerves.

So when do we think that these nonspecific findings are really stroke-related? It's when we see some associated findings of cranial nerve weakness, either double vision or, with the nausea and vomiting, if there's anything specific, anything more focal that tells us that there's a specific part in the brain that we're having problems in. That's when we really start worrying about stroke. And the other picture up in the top corner that you can remember from a minute ago when the slides were showing shows the different other vascular territories in the brain. So really what we're thinking about is acute onset of symptoms, of symptoms that start right away-- you can remember the moment that it started, or you wake up with these symptoms-- that fit in a pattern, that makes sense with the vascular distribution in the brain.

And that's what makes it a little more difficult. So I guess the next question is, how do we tell that it's a stroke and that it's not just other symptoms? And you'll see on your slides that it's really acute onset, focal findings, makes sense in a vascular territory, and it's not really explained by something else. So if there's an old area of stroke and they're having symptoms that fit with that old area of stroke, that's not necessarily something that we're worried about, an acute problem. It's something older.

So the next slide talks about core stroke, and you've all heard before time is brain. And this really is important because every minute that we don't treat a stroke, potentially two million neurons are lost. That's a huge amount, and obviously that can mean more or less depending on the area of the brain that it's in and the symptoms that that can cause. But that's a lot of time, so we really want to be managing this as quickly as possible and gathering all of our resources together to do so. And you can see in the picture that there's an area, typically a core area of infarct-- I know it's difficult to see on these small slides, I apologize-- surrounded by an area of ischemic penumbra.

And that's the area that we think of as once the patient comes in, there's probably going to be an area of core infarct that we're not going to be able to do much to reverse. But then there's an area of tissue at risk in the surrounding area that potentially if we reverse that clot or are able to intervene, that that area is salvageable. It's an area that's been stunned but hasn't yet had an official stroke, hasn't really infarcted, and the tissue hasn't died yet.

So this concept of the golden hour is very common in medicine. A lot of times we hear it in the context of trauma and then also, of course, in MI. So we really want to be treating as quickly as possible, and by giving us this guideline of an hour I think that kind of keeps us all accountable to our time. And ideally we would want this to be the first hour from symptom onset, because that's really when we have the best chance of recovery.

But I think that realistically we only have control of this first hour from ED presentation, and so that's what we typically use as this golden hour. And you can see from this figure that as time goes on, the minutes from onset of stroke symptoms, the efficacy of TPA, of thrombolysis to wipe that clot and really prevent that stroke from becoming a true infarct and not just that area of penumbra that I was trying to talk about-- that the benefit of that decreases. So even though we have this hour of onset, we have a time window where we're able to use this medication, sooner is always better. It's always going to be better to do it at an hour than two hours, or two hours than three hours, even if you have that little extra time.

But there's, of course, some barriers in acute stroke care. It's not as easy as I make it sound with that golden hour concept. So we have this need for rapid data collection, but we have a limited patient population to do this in. A lot of times these patients come in either aphasic or not able to tell us what's going on, altered mental status, so it's really difficult to get the information that we need to be able to treat them in a timely manner. A lot of times the family members that may have witnessed this or other people that see this if it happens in the community don't come along in the ambulance ride with the family member, so by the time they get there it's a further time out. So we need to figure out how to get that information accurately and quickly, and that brings up the point of this inaccurate data collection, too.

So EMS picks up the patient. They say this happened 15 minutes ago. They bring him to the emergency room and say this happened 15 minutes ago. Well, now it's 30 minutes ago, and then the ER calls the stroke doctor and says this happened 15 minutes ago. Well, now it's an hour and 15 minutes ago, so you can see how that can kind of get perpetuated-- so really figuring out what's most important in that time. And because of this we have this coordinated code stroke effort, and it's really a team effort because all the different components really need to be involved to make this happen as quickly and as efficiently as possible.

And that includes EMS. It includes the emergency room staff, neurology team, radiology, of course-- to be getting the patient to see a CT scan as soon as possible-- pharmacy to be mixing up the drug if we're able to give it, the neurointerventional team, if this is somebody that's going to potentially be an IR candidate, which I'll talk about in a minute, and others. And even beyond this 60 minute time frame, we've broken it down further to give ourselves time goals for each point along that golden hour of acute stroke, I think very similarly to that kind of hour door-to-needle door-to-cath time in a acute MI.

So what do we get during that time period? We really want to get a brief but thorough history and physical, and that key question is time. So like I said, we don't want to say 15 minutes ago; we want to really get a time and stick with it. And so the question I always ask instead of when did this happen is, when were you last totally normal? Because that's the last moment I can guarantee that you weren't having a stroke. And just changing that phrasing really helps us figure out what time work we're able to use.

And then we do an NIH stroke scale, which is a brief version of the neurologic exam that has some standardization so that we're all doing the same thing, so that when the resident sees the patient in the emergency room they can tell me with the stroke scale is and I have a guesstimate as to how bad the stroke is. That being said, there are certainly some limitations. So a lot of the neurologic exam is based on the ability to follow commands, and if the patient's aphasic are not able to follow commands, just by that alone they're going to have a much higher stroke scale than somebody who's having equal deficits on the other side of the brain.

So this number, you kind of have to take with a grain of salt. I certainly can't say that a stroke scale of 10 is twice as bad as a stroke scale of five, but I'm able to use it as kind of a guesstimate and to track a patient over time, that if they're getting better or worse I can see what that number is. And it's easier for us to keep that number in our head than the specific symptoms. But there are some other stroke scales, and these are typically used by EMS. There are things that are a little bit more simple and a little bit less thorough.

So there's the Cincinnati Pre-Hospital Stroke Scale, which I would say is probably the most extensively used out in the field and EMS. And that really only consists of three questions-- so the facial droop, the arm drift, and the speech. As you can imagine, that probably captures a lot of people that aren't having stroke that just happen to maybe be leaning to one side and they count a facial droop and don't want to lift up their arms because we just put an IV in that arm and maybe are a little bit slurred. So there's been some other scales that have been created, including the LA Pre-Hospital Strokes Screen. That one is below that, and you can see that's a lot more detailed.

So while all the patients that are identified by this likely have stroke, it doesn't necessarily include all stroke patients. It's only ones that are very specific. For example, even the age over 45 years-- that certainly would cut out a portion of my patients that I see on service, because there's a lot of patients, especially in the stroke belt, that have strokes even before they're 45, unfortunately. The men's is over to the side and that's just another example of a stroke scale that's kind of somewhere in between.

So we have all of these different ways to kind of get the information that we need to identify these patients quickly without spending an hour and a half doing a thorough neurological exam. We also want to get some lab tests, making sure that they're eligible for TPA. We don't want patients with a higher bleeding risk getting the medication. And then there's always some other tests that we want to get on these patients when they come in, things like EKG, chest X-ray, other things. Those are, of course, important in evaluating the patient, but they're possibly not essential right in that acute stroke period. So sometimes we'll forgo those in favor of the CT to start with.

So talking about the CT scan-- so the reason that we do that is it's quick, it's fast, much faster than an MRI. And really the purpose of the CT scan is to rule out bleed, not to diagnose stroke. So initially an acute stroke won't necessarily have any signs on a CT scan. A bleed, however, will. But sometimes there are some hints on the CT scan as well, and we can consider CTAs and CT perfusion to give us some more information as well.

So these are just pretty clear cut examples of bleeds. So you can see the large area of intracerebral hemorrhage with the arrow pointing to it, as well the subarachnoid hemorrhage, all of the white area in the ventricles on the other panel. So those are patients that, of course, would be very high bleed risk. Their symptoms would be due to bleeding, and we wouldn't want to give them TPA. That's really the main purpose of a code stroke, is to figure out if this is really a stroke and if it's caused by ischemia rather than bleeding.

But like I said, there are some hints that we can get to see if this is an ischemic stroke. So on the left, you're going to have the hyperdense MCA sign, so in that area you can see-- I'll try to point to it here; oh, I guess that doesn't work. But you can see in the blood vessel, kind of in the middle of the brain, that it's brighter on one side than the other, and that area is an acute clot.

So when that acute clot shows up, you even see it on the non-contrasted CT scan. And so if that fit with the patient's symptoms, I would say, well, that's where the clot is. We really need to be giving this patient TPA as soon as possible. And then on the other side, you'll see some early ischemic changes. There's some blurring of the grey-white junction sometimes, loss of the insular ribbon. It's really hard to see on this side, so I'll show you the next one.

This is a good example where we're comparing CT images and MRI images. So I know it's kind of difficult to see on these monitors, but if you look at the top panel, you really don't see a whole lot of difference in the CT scan when you're comparing one side to the other. But through B, you see a bright, white area. That's on DWI on the MRI, and that shows the area of acute stroke. So then if you go back up to A and remember where that is, you can kind of see that it's just a little bit darker there and it's a little bit more blurred. There's not as much distinction between that ribbon right along the cortex of the brain-- again, really difficult to see on these monitors, so I apologize.

And that would fit in with the last panel in B where we're seeing a cut-off of one of the blood vessels. In C, you can see if we don't do anything about it, what would happen? So you can definitely see in C a lot of more hypodense darker area on the side of the stroke with even some midline shift pushing over to the other side of the brain. The brain is an enclosed space, so if we're not able to prevent that stroke from evolving then you can have swelling and shift and that can cause herniation and death.

So what do we do? So the stroke guidelines are really to give TPA as soon as possible. In 1995, the studies were done to look at TPA and acute stroke, and in 1996 the FDA approved for treatment within three hours of onset of an acute ischemic stroke. In 2009, the American Heart Association expanded this treatment window to 4 and 1/2 hours based on some extra data we have. And then in 2013, they adapted the guidelines to really reinforce this door-to-needle time, the golden hour of less than 60 minutes.

So we see improved outcomes at three months. This isn't something that you're necessarily going to give a patient and they're going to wake up right away and come back to normal. It's really the three month time point that we see the most benefit. You're certainly going to have some patients that respond very quickly, but other patients may just not have as drastic a deficit as we would have seen without TPA. So we don't think that it doesn't work if it doesn't work right away.

But there's other things we can do as well. So if there's a patient that we give TPA to and they don't come back to normal, or we see that hyperdense artery, we see a large area of clot and we know that it's one of the bigger blood vessels, there are some devices that we can do. And certainly this has been adapted from cardiology, where the first panel up in the top-left corner is called the MERCI retriever. It looks kind of like a corkscrew. And we're able to go in there and take this corkscrew, run it through the clot, and essentially pull that clot back, just like you would with a cork and a wine bottle. You can see potentially some less optimal outcomes with this.

So if a corkscrew has a pointy end and you're in these delicate brain blood vessels, that could be a bad thing. We don't want to cause bleeding. So they've adapted these a little bit along the way. And in the top-right, you see what's called the penumbra, and that is a catheter that has a little agitator that sticks out of it. It's essentially something where you go up against the clot and pick apart at the clot, and then that catheter has some vacuum suctions so it's picking back those pieces of clot, not letting them go forward and cause further stroke.

So that's good. That's a benefit. But you're still poking at it, and you're still potentially shattering off little tiny pieces of clot, so still not optimal. So instead, the newest generation, if you will, of mechanical thrombectomy is the bottom picture, and that's a retrievable stent. So basically what we do is they'll take a stent, push it through the clot, and open it up, and that clot will kind of intercalate into the chicken wire of the stent. Keep it there for a couple minutes, let it all get in there, and then when you pull out the stent it has the clot right on it.

And so the great thing about that is twofold. One is you're really getting every piece of clot. You're not poking at it, and just hoping that it gets vacuum-suctioned back. And also, right when you go through the clot and open it up, you're restoring blood flow right away. So even before you're pulling the catheters out, you're restoring blood flow to that part of the brain. So potentially, the time to opening the blood vessel is shorter with this device than with others, and so that's really been a game changer, I think, in stroke.

So in summary, there's really a clinical mandate to use this golden hour time and really get patients care as quickly as possible. Time is brain. Earlier treatment is still better. Even though we have expanded the window to 4 and 1/2 hours, that doesn't mean we wait until 4 and 1/2 hours and collect more data. We still treat as quickly as possible. We really have to avoid all delays, and that includes transport to other facilities. We have to make sure that we have the systems in place to be able to give TPA.

TPA, we have the three hour window and then three to 4 and 1/2 hour window in selected patients, and then there's these other interventional therapies. But unfortunately, there's many areas in the state, and certainly in the country, where there's inadequate stroke experience. There's not a lot of neurologists on acute call 24 hours a day, and so that's where our Telestroke Network comes in. We can see that because of some of those deficits in stroke expertise and in neurology coverage, as well as a lot of other barriers, I think, the nationwide stroke treatment rate with TPA is only 3.1%.

So of all patients that have a stroke, only 3.1% of them get TPA, and that's very, very low. Certainly there's lots of reasons that is. We can't always control patients getting to the hospital within that time window. That's certainly a large component of this, but then there's also certainly places that just aren't comfortable giving TPA in this rapid manner. And that's what we're trying to help with the Telestroke network. So I'll let Rayetta talk about that for a little bit.

**RAYETTA
JOHNSON:**

Anyway I'm glad to be here, and thanks for inviting me, Lee and Amy and everyone. I have had the privilege of working with Telestroke since the beginning. We actually began our Telestroke network in December of '09, so we're coming up on our fifth year anniversary. So we're very excited about that. And you can see how it's grown greatly since we began.

So again, just to reiterate, every minute counts when you're having a stroke. Time is brain. 1.9 million brain cells are dying every minute after stroke happens, so we're in a big hurry. We train EMS how to take care of stroke patients. Also, pre-notifying us before they get to the hospital is huge.

They pre-notify us, then we can run down to the ED, be there at the door, waiting for the patient to come in, examine them quickly on the stretcher as they fly down to the CT scanner. Because that's the first thing we got to do-- got to get that scan, rule out a bleed. They don't have a bleed, their stroke scale is positive, and they meet all the administration criteria for TPA. We get that TPA going in 30 minutes, maybe, and what is our goal? Less than 60 minutes.

Yesterday we did two TPA patients, and they were both less than 60 minutes. I think the more practice you have, the better you get. So we've really kind of expedited that whole process, so that's great. And then this morning, those two patients that we gave TPA yesterday to has almost totally resolved their symptoms. So that's always a great thing. Love to celebrate the successes.

Dr. Guzik talked about we have a gap and access to stroke neurologists. A lot of these small little hospitals-- there's not stroke specialists there, are there? And we know pretty much across the board that ED physicians are a little bit reluctant in giving TPA. Why do you think that is?

AUDIENCE:

Can be dangerous.

RAYETTA Can be dangerous, right. What's the biggest complication of TPA?

JOHNSON:

AUDIENCE: Bleed.

RAYETTA Bleed, yeah. About 6% of TPA patients do have a cerebral hemorrhage, but from the literature I've read, still,

JOHNSON: sometimes there's more of an issue with not giving TPA than giving TPA. Anyway, so there's lots of factors.

Another big factor-- patients don't get in time to the hospital, do they, to be treated, because we only have that three to 4 and 1/2 window that we can give IV TPA. And why aren't patients getting to us in time?

AUDIENCE: Denial.

RAYETTA Denial, exactly. It's different. Heart, you have pain. With stroke, you usually don't have so much pain, unless it's a

JOHNSON: cerebral hemorrhage, and then you may have a severe worst headache of your life. But ischemic strokes usually don't cause a whole lot of pain. It's more paralysis, weakness, inability to see or inability to speak.

So I think that's a huge thing, because pain is a big motivator. But if you're just a little bit weak in your arm or leg or maybe your speech is a little bit slurred, a lot of patients say, well, I'll just go take a nap and see if I'm better when I wake up. But if it's a real stroke, it's not going to happen, is it? It may have even gotten worse. So community education, public education is a huge piece of this, and I think we as health care providers can certainly be out there trying to educate the community.

I know for heart and stroke, it's kind of the same thing. Ms. Susan and I do a lot of community education, so it's a lot of fun to do that. And the community is very receptive to all those educational efforts, I think. So we wanted to improve stroke care, we wanted to increase access and use of TPA, and we wanted to encourage our hospitals to actually keep their patients. At first, they thought we just wanted to take all the patients, but we didn't want to do that.

Number one, we couldn't take care of all those extra patients. So we really encourage the network hospitals to keep their patients if they can. If they feel like they're able to deliver that level of care to the stroke patients, they can certainly stay at their facility in their home community. But if they need a higher level of care, we are happy to have them and take care of them, which you'll see that we do. It's about 50/50. About 50% stay in their home hospital; about 50% of those patients are transferred to us.

I just want to show you this, because I thought that was interesting. There was a study that came out of the University of Melbourne that showed if we could just save one minute-- remember we said every minute counts for stroke, save every minute that you can-- so one minute would equal almost two extra days of healthy living. So for every minute we save and we get TPA going, we can maybe offer that patient two extra days of healthy living. So that works out to about a month for every 15 minutes saved.

So I think that's a pretty dramatic difference. So what did we end up with, with our Telestroke? We have 24/7 Telstroke coverage. We now, at the present time, have eight board-certified vascular neurologists that provide service. It usually takes five minutes from time that we get the beep until one of our physicians is on the Telstroke computer at the hospital.

And you can see there, to the right, Dr. Tegeler. Dr. Guzik and Dr. Tegeler are now co-directors of our Telestroke program. So that was Dr. Tegeler probably when we just first started our Telstroke network, so he's there in his office on the little laptop. His beeper's gone off. He's gone to his Telestroke computer, beamed into the robot.

You see the robot on the left-hand side. So this little robot's about my height, about 5'5. So he is remotely driving that robot along the side of the stretcher that the patient's in going down to the CT scanner, I'm guessing. He will evaluate the patient quickly doing our NIH stroke scale, talk to the ED physician nurses, and make a decision about whether that patient is a candidate for TPA. So they can get the TPA going at the network hospital, and then if they need a higher level of care or they do not maybe have a stroke neurologist at their hospital, or even a general neurologist, they may be transferred to us, either via air care or ground ambulance.

So this is just a snapshot of what Telstroke looked like in North Carolina in 2010, when we just first started. So you see there's very few sites there. And then look what it looks like now in January of this year-- a lot more of exploded. Telestroke has kind of exploded throughout the state. We actually covered the whole state of North Carolina. We're from the western part of the state to the eastern part.

Our most western hospitals are Allegheny, Caldwell, Wilkes, and then we go across the state, all the way to Morehead City to Carteret Hospital at the coast. We have a couple more hospitals that will probably be coming on board pretty soon, so we're still growing and experiencing a lot of great success with our network. This is what our network looks like now. So you can see in the red dots are our medical centers that we're presently in discussion with, and then the little areas that have the little actual robots are where we are currently having our networks in-progress.

This is a snapshot of our regional network activity, so this is something we go every month. We have quarterly meetings with each of our network hospitals, and we go over this data. So what was that number that Dr. Guzik showed us? TPA administration was what, like, 3%? Yeah, 3%. Look at that last column at the very bottom.

Our TPA administration rate is 45%. That's huge. I looked probably a couple years after we were into this Telstroke network, and I looked back at the hospitals at that time. Before they joined our Telstroke network, their rate of administration of TPA was, like, how much you think, zero to about 2%. So I think that's dramatic.

That tells volumes about the success of our network. So we have increased the administration of TPA, I think, tremendously. And you can also see there the number of patients that remained at network hospitals. I guessed about 50%; it was 48% as of the end of August, and then 33% were transferred to Baptist. And you can see for our total network we've had about almost 1,200 activations now across the whole entire network, and so you can see there how we exponentially kind of increased our network activity and our robot consultations from January of '10 until July of '14.

And you might wonder what our outcomes are or what happens to these patients after they get TPA and they get treated via this telemedicine robot. You can see there that the discharge dispositions of those patients that remain at their network hospital-- there's about 71% of those patients are discharged to home, another 14% are discharged to a skilled nursing facility, and about 7%, it looks like, are discharged to rehab. So that's pretty good outcomes, and then you can see of those patients that are transferred to us it's pretty equal. We have 65% that go home, and 11% go to rehab. Another 11% go to an extended care facility.

And we just received an award, so we're kind of proud of that. InTouch Health is our vendor for our Telectro robots. So we were just awarded outstanding achievement throughout the country. We were one of three that were chosen to have outstanding achievement in our Telectro network, so we were kind of happy about that.

Future directions-- stroke remains a huge health challenge. We have time-limited acute therapies, but we're always trying to improve and create new strategies. As you saw, Dr. Guzik talked about the interventional procedures that we can do which expand that time window of treatment up to six, maybe even eight, hours. So Telectro addresses gaps in access and avoiding delays in treatment and transport.

So we feel like we've accomplished our goal, and telemedicine is changing paradigms for delivery of medical care. And we think that stroke is just the tip of the iceberg. There's so much more we could do with telemedicine, and I'm sure you guys could think of numerous ways that we could use telemedicine in other areas. But again, it's been a great pleasure and honor to be part of this. It's been a lot of fun. So I'll let Dr. Guzik finish up.

AMY GUZIK:

Well, thanks, Rayetta. I just wanted to talk a little bit about a couple studies that are coming down the pipeline. We know that TPA works well. But it doesn't help everyone and it doesn't help everyone completely. So what else can we do?

And I think of this as kind of a TPA-plus. So we know that TPA works. We don't stop using that, unless we find something that's significantly better. But there's been a lot of studies, a lot of which are taken from the cardiology world as well, about things that we can do. Certainly the blood vessels in the vasculature in the brain is very different than the heart, but there's, of course, a lot of similarities as well.

So one study that's been done is called CLEAR. It's TPA plus integrilin essentially, the thought being that TPA works quickly and it really only lasts in your body for about 15 minutes or so, so is there something that we can give to continue that clot lysis possibility. And so this was a phase 2 safety study. They're working on getting this into a phase 3 study, where it will actually be able to get larger numbers where we can see if this is really something that's beneficial, and it's comparing TPA by itself to TPA at a lower dose. Because we were worried about the bleeding risk with TPA plus another medication, plus, then, a continuous drip of integrilin.

And this was patients that were receiving TPA within three hours, had a stroke scale greater than five, so maybe not those tiny little strokes-- something that was a little bit more significant in aged 18 to 85. And at this safety end point, what the researchers showed us is that there was an equal amount of symptomatic intracerebral hemorrhage between the two, so this was safe. This was something that we could potentially do, and there is some preliminary efficacy, certainly not large enough numbers of patients studied that we're going to go put this into practice today.

But preliminarily, we see that there is potentially an increased percentage of patients getting a functional scale, which is this modified Rankin scale, the MRS scale. That's a functional assessment of stroke patients at three months. A higher percentage of them had a lower stroke scale, or a lower functional scale, which means a better outcome at three months than those getting TPA alone-- so definitely an exciting thing that I'm kind of keeping my eye out for.

Hypothermia-- so even though this has kind of been in debate lately, there are certainly lots of benefits in hypothermia in terms of stalling cell death and letting us have a little more time to be fixing things and figuring out what's going on. And here you can just see the red lines show all the different areas in cell cycle death, essentially, that hypothermia potentially has protection with. So it's hitting lots of different targets. And so the ICTuS study is looking at hypothermia after TPA at a bunch of different centers, and they are looking at TPA within three hours again, stroke scale of greater than seven but less than 20-- so not the sickest of the sick patients.

We really want to be able to monitor those neuroexams a little more closely, So we don't want to necessarily give them hypothermia and some medications for shivering. These aren't patients that need to be intimated or anything, but they're monitored closely and cooled for 24 hours to 33 degrees. And the primary outcome is, again, 90 day Rankin scale of zero or one. And so that's ongoing. We don't have the results of that yet, but the initial smaller scale trials that led up to this have shown some promising data that it's at least safe, if not effective.

I'll skip through these a little bit, but CLOTBUST-ER and this transcranial laser therapy are newer ways that people are trying to use other methods to bust up clots, essentially, from the outside. So CLOTBUST-ER, you can see the picture in the bottom where basically it's like a headband that you would wear, and the ultrasound is delivered through this headband to potentially break up some of those clots. And so that's been shown to be certainly safe. It's safe even if this potentially is a bleed, and we're looking at the outcomes of, again, 90 day functional status as well, so we're still waiting on that a little bit.

The great thing about this, I think, for the future, as well as the laser therapy-- it's kind of the same thing-- is if this is safe in both ischemic strokes with clots and bleeds, it's potentially something that could be done in the ambulance on the way to the hospital. So this is something that they could put on, we could potentially be lysing that clot even before they get to the hospital, and then we could go through the rest of our work once they get there. So that's really exciting as well.

We've had a couple studies that have looked at TPA plus endovascular therapy, and that's come into question in the past couple years. And so we know that TPA works. We know that it's better than placebo. We know that interventional in some settings works. We certainly know that it's able to take clot out, and we have some data that the patients have better outcomes as well. So why don't we combine them?

Well, potentially there's an increased risk of bleeding and some other potential side effects. So this looked at the combination together, and unfortunately it didn't show a big difference of TPA alone versus TPA plus endovascular therapy. But it was relatively safe. MR-RESCUE was another study that was done recently that said, well, OK, maybe for all comers TPA plus intervention isn't better than TPA alone, but we know that we can get these perfusion scans. And maybe if we see a mismatch where there's a larger area of penumbra, that area that's not the core dead tissue but that tissue at risk, maybe those are the patients that are going to do better with interventional therapies.

And so this looks at some of those penumbral patterns. You can see the top row is a, quote, favorable penumbral pattern where the area of red or dead core tissue is smaller than that area of green or tissue at risk. So potentially those are the ones that can really benefit from this. But again, we didn't see a whole lot of difference. So, well, what went wrong?

Remember when I was showing you the different devices? So these were all done in the old generation of devices. So that MERCI retriever corkscrew and the penumbra vacuum device-- these were all done before that Solitaire stent retriever, the ones that were opening up those arteries right away and getting that clot back. So I think we've got to go back to the drawing board a little bit with that to get a little more information.

I think that we've all seen, anecdotally, patients that do really well with this. I think we just don't know who the perfect patient population is to receive both therapies or to receive this endovascular therapy. And I think that what this has reminded us is that TPA is really a great drug and we need to focus on getting that to as many people as possible as quickly as possible.

So just to recap a little bit, I know we talked about a lot of different things involving stroke in the past hour, but really the summary is if you see an acute onset of focal symptoms, think stroke. And remember that time is brain, so really our biggest barrier is getting patients to the hospital. I think that we all have optimized our golden hour, once patients get to the hospital, pretty well, especially with Telestroke in different, smaller hospitals, which is really bringing us to the patients rather than using that transport time to get them here.

And TPA we can give zero to three or 4 and 1/2 hours, depending on the patient population, but faster is always better. We don't want to expand our work into that extra amount of time. And there's potentially some other treatments in the pipeline that I think are really exciting. So thanks for listening, and I know it's the end of a long day but we're definitely able to answer any questions.