

Steven R. Messe: Welcome to this podcast called Getting to the Heart of Stroke, Evolving Views in PFO Management. My name is Steve Messe. I'm a vascular neurologist at the University of Pennsylvania. This podcast is part of a series being produced by the American Heart Association, HCA Healthcare is proud to be the national supporter of Getting to the Heart of Stroke. In this episode, you'll learn about current approaches to evaluating and managing patients with PFO and stroke, and the views and opinions are those of the speakers and they reflect our interpretation and synthesis of the current science. So content should not be considered official policy of the AHA.

Briefly reviewing the learning objectives for this podcast. After listening to it, we hope you'll be able to better demonstrate the knowledge of the basic stroke workup, identify patient demographics and clinical features associated with higher likelihood of PFO associated stroke, and describe the importance of shared decision making when pursuing PFO closure.

I'm joined today by two terrific experts in this field. They recently participated in a satellite symposium on this topic at the International Stroke Conference. First, we have a vascular neurologist, Dr. Megan Stevens. Megan, please introduce yourself.

Megan Stevens: Hi, I'm Megan, and I am a vascular neurologist at Erlanger University of Tennessee Chattanooga.

Steven R. Messe: Excellent. And we also have a structural interventional cardiologist, Dr. Molly Szerlip. Molly.

Molly Szerlip: Hi, I'm Molly Szerlip, very happy to be here. I am currently the director of our regional structural heart program at Baylor Scott and White, the Heart Hospital - Plano.

Steven R. Messe: Excellent, thank you. So, all right, we're going to get started and hopefully have an interesting discussion today. I'm going to set the table, we're going to talk a little bit about what we've learned about PFO as a possible mechanism for stroke and some evidence about how we can best reduce the risk of stroke recurrence and how we're selecting patients for PFO closure in particular. So going way back to the late 1980s, there were a number of case control studies that were published that identified increased likelihood of seeing a PFO in younger patients with otherwise cryptogenic stroke. So Molly, can you tell us a little bit about what A PFO actually is?

Molly Szerlip: Yeah, of course. In order to understand the PFO and stroke, I guess we have to go back to fetal circulation. And basically what A PFO is an open foramen ovale. And what the foramen ovale is when we're being developed in the mom's uterus, there's a placenta. And the placenta brings blood from the umbilical vein to the fetus and that's how blood is oxygenated. And so the blood goes into the baby's IVC or inferior vena cava and then into the right atrium. And instead of then going to the lungs like it does once you're outside of the uterus, it flows across into the left atrium through the foramen ovale. And the right-sided pressure is always higher

than the left-sided in utero. And so that's why it flows that way. Once the baby is born, however, this changes and the left-sided pressure goes higher and that foramen ovale is supposed to close. In about 20% of the population, it doesn't close. And that's okay because the left-sided pressure is high, but in some certain instances you can have a stroke from that, which is what we'll be talking about today.

Steven R. Messe: Awesome, thank you. So yeah, it's presumed then that paradoxical embolization is the primary mechanism that PFO can lead to stroke. And what that means is that a clot would form in the venous circulation, perhaps in the legs or in the pelvis, and then that venous blood clot would pass, go up to the heart and pass through the right to left shunt and become an arterial embolism and leading to stroke. And so logically it was thought maybe if we closed that shunt, if we closed the PFO, we could reduce the risk of stroke recurrence. And early on, patients were being referred to surgeons to have open heart surgery to suture the PFO closed. In the early '90s, they started to use devices that could be placed percutaneously. These devices were initially developed and designed to close atrial septal defects, which is a little different than a PFO. Molly, can you describe the difference there?

Molly Szerlip: Yeah, so an atrial septal defect is when there is actual tissue that does not grow between the two chambers, the right and left atrium, and actually forms a true hole. So there is a space there. Whereas with the PFO, it's more of a tunnel. And so that's really the big difference between the two.

Steven R. Messe: Got it. It's sort of a tunnel that almost has a flap-like closing and opening with the pressure, right? Yeah. So these ASD closure devices were placed in the PFOs and they seemed to stop the shunt from happening in most patients, which was exciting, but we really didn't have evidence that reduced the risk of stroke. And for the next two and a half decades, we had devices available that could close a PFO, but we didn't know if it really did reduce the risk of stroke. And these devices were being used in clinical practice and there were PFO specific devices that were developed as well. And there were trials that were going on to see whether or not closure really worked or not. And there was slow enrollment over this long period because a lot of patients were getting closed outside of trials.

The first three randomized trials evaluating PFO closure were published in 2012 and in 2013, and these were all neutral or negative for their primary endpoint, although the second two did have some suggestions of reduced risk of stroke, although not statistically significant. Definitive evidence for the benefit of closure for stroke prevention was not seen then until 2017. And we had publication of three more randomized trials at that time. There was a closed trial reduce and the defense PFO trial. And I think there's a number of reasons why these more recent trials were thought to be positive compared to the first three trials, possibly related to the fact that off-label closure was less common during this era. And I think patient selection was more refined leading to enrollment of patients who were more likely to benefit from closure.

And I think what's important to note is that all these trials enrolled patients after

they excluded alternative high-risk stroke mechanisms. So I think that's something we could talk a little bit about now, Megan. Optimal secondary stroke prevention, you know this well of course depends on determining the cause of the most recent stroke event. So what do you describe as the basic stroke workup, the general workup that you need to do?

Megan Stevens: So the American Heart Association and American Stroke Association did set out guidelines for what constitutes a basic workup, and that's the 2021 guidelines. And that includes brain imaging, so either a head CT or brain MRI, vascular imaging, so potentially a CTA of the head and neck, MRA of the head and neck, or some combination of those studies with carotid ultrasounds such that you would have both cervical and intracranial blood vessel anatomy characterized. You also should have basic labs drawn. So they even go so far as to say what those basic labs are in the guidelines. So a CBC, physical therapy, physical therapy, PTT, troponin, creatinine, glucose, hemoglobin A1c, and a lipid panel. And with these you also need some cardiac testing. So either an ECG or the mandated 24 hours of cardiac monitoring if your evaluation is occurring on the inpatient side. And also the echocardiogram which the American Heart Association sets out as at first being a transthoracic study. And within that the workup can be further expanded.

Steven R. Messe: Got it. So we can talk a little bit more about when it should be expanded, I guess. Do you think the workup should change at all if it's a younger patient who's being evaluated for a stroke?

Megan Stevens: Absolutely. With younger age you're going to have different stroke etiologies be more likely. And so whether that is a young woman who is pregnant, there are stroke risk factors with that state. Additionally, whether you have a congenital heart presentation or you have an inherited coagulopathy or vasculopathy. But again, for the purposes of this discussion, most prominently really we have PFO as being a potential cause for stroke in young patients. And so to characterize that, we do need to expand the workup from a trans esophageal echocardiogram standpoint, but we also do need to do more prolonged cardiac monitoring to rule out atrial fibrillation.

Steven R. Messe: Yeah, I think that makes a lot of sense. And AFib we know is age related. The incidence goes up as the patient is older, so I definitely think we need to monitor older patients. Do you have a threshold for what age you don't monitor for Afib, a younger age when you wouldn't do it?

Megan Stevens: I am a very cautious person, so I try not to think that my knowledge is better than what the test will eventually show because patients can absolutely have atrial fibrillation at a younger age, particularly if they have a history of alcoholism. They may also have a predisposition genetically in their family, particularly those people who are of Northern European descent are more likely to have that genetic preposition to AFib. But we do at least have to do 28 days or 30 days of monitoring for patients if they're in that category of 50 to 60. And that's per the guidelines that were put out by the American Heart Association as well as a JAMA study. But when you're in that area of teens to age 50, the amount of AFib that you need to screen

for is potentially up to the discretion of the physicians.

Steven R. Messe: Got it. Molly, any thoughts on AFib monitoring and your patients that you're seeing?

Molly Szerlip: Yeah, it's actually an interesting thing because the more and more I do this, you're right, people can have AFib when they're younger, but they don't tend to have strokes from the AFib when they're younger. So that starts going into a full other category. Typically people that we have strokes from atrial fibrillation have big atria and that's why they develop clots in their left atrial appendage. That's the whole reason why we look for atrial fibrillation. So I don't think we know, but if a younger person who has a structurally normal heart has atrial fib, I don't know if we know truly what the risk of the stroke is for from atrial fib in a much younger person with a structurally normal heart.

Steven R. Messe: Yeah, I think that's a great point. I think this is an area that needs more investigation for sure. AFib found after stroke is different than AFib found before stroke in terms of the risk. All right. But I got us off on a tangent where he got away from PFO here. So you mentioned, Megan, the echoes are important and a TE as well. Who should get a bubble study with their echo? I think that's a question that clinicians often ask. Does every patient need a bubble study to look for that right left shot?

Megan Stevens: Absolutely. Well, that gets us to really looking for PFO. And so typically we would say that if you're less than age 60, you should have a bubble study. But there can be different protocols at different hospitals and there can be up to the echocardiographer's discretion when they do the bubble study. So absolutely, it should be done when you're less than age 60 and a stroke patient because we know that without the bubble study, the color doppler does not consistently pick up PFO. But when it comes to, if those people who are older, many times we will ask for the bubble study, particularly if they are early 60s. And that gets to the difficulty here, which is where is the edge and are there patients that we're missing when we are coming up with criteria for patient selection for PFO closure?

Steven R. Messe: Absolutely. Hopefully we'll have a little bit of time to talk about that more at the end. I think that's a really important question. And then some people do recommend TCD with bubble study. Do you use that in your practice at all to look for shunting?

Megan Stevens: I don't use it in my practice. And that is because we are lucky in that we have a very good relationship with the cardiology group and they are able to perform transesophageal echocardiograms very frequently, and there's ease of access and there is some superiority of TEE over transcranial doppler in that you are able to evaluate for other causes of stroke beyond just potential for A PFO.

Steven R. Messe: Yeah, I totally agree. I think TCD is a very helpful adjunctive test when it's available. It's not available at many sites, and I think it's particularly helpful if you don't feel that you got a good assessment. The bubble study wasn't a good one, they couldn't

do a good Valsalva, and you want to look further for shunting, but it also looks for other causes of stroke and it confirms that it's an intracardiac shunt, because about 5% of shunts or so are actually in extrapulmonary shunts. And going for PFO closure in that setting is probably not helpful. Is that right, Molly?

Molly Szerlip: Yes, exactly. So when we do this, you do want to make sure that there's not an intrapulmonary shunt. So there's ways on the bubble study that you can tell that there is more than likely a intrapulmonary shunt, it's how many cardiac cycles it takes for the bubbles to come through. But yes, you need to rule that out as well.

Steven R. Messe: Yeah. And Molly, do you require a TEE before you go in for the procedure of closure?

Molly Szerlip: No. No. So the only time really that I get A TEE would be if I think that there's a PFO, but my TTE is negative and then I go and look for it. Or if very often I get sent patients where they tell me that there's a PFO because it's around where A PFO is, but it turns out it's really an ASD. So on those people, I will get a TEE so I can better characterize whether it's a hole or a tunnel.

Steven R. Messe: Got it. So the patients that you're seeing are referred often by neurologists, not all of them necessarily though have had a TEE, is that correct?

Molly Szerlip: Correct. Correct. A lot of times we get a lot of patients that had a year prior and then they get to their primary care doctor, a new primary care doctor that's like, "Oh, you had a stroke." And then they'll get an echo and they'll do a bubble study and they'll go, "Oh, you had A PFO," and then that will come to me.

Steven R. Messe: Great. Okay. All right. So we're going to move on. Let's talk a little bit more about the evidence that is now available to us that helps refine our patient selection. And in 2021, there was a patient level meta-analysis of all the randomized trials of PFO closure published in JAMA, and it evaluated the utility of two approaches to determine whether the PFO was related to the stroke and also thereby how likely they are to benefit from PFO closure. So I'm specifically talking about the RoPE score and the Pascal classification. Megan, can you tell us a little bit about these approaches to categorizing risk of PFO relatedness and likelihood of benefiting from closure?

Megan Stevens: Absolutely. So the RoPE score was developed by doctors, Thaler and Kent and colleagues, and you get points, max of 10 for being young, having a stroke that looks on imaging like it could have been related to A PFO, so cortical as opposed to lacunar. And you also get points for absence of vascular risk factors. So the higher the score, the more likely that your PFO is associated with the stroke that you had. And it also quotes your overall all-cause stroke recurrence and TIA recurrence rate. And so if you have a high score, you're actually going to have a low all-cause stroke recurrence rate. So I think sometimes it's helpful to have an example of what that would look like. And so if you had a 70-year-old man who had diabetes and high blood pressure, was a smoker, had a previous lacunar infarct, had another lacunar infarct, that gentleman would get zero points. Therefore a 0% chance that this was

associated with PFO but would have a 20% all-cause stroke and TIA recurrence rate.

So on the flip side, if you had a 32-year-old woman who did not have any vascular risk factors and had a cortical stroke, that patient would get nine points and that would be associated with 88% likelihood that the stroke she had was related to PFO and her all-cause stroke and TIA recurrence rate would be 2%. And so-

Steven R. Messe: I could just say, I think that's one of the great paradoxes of PFO though is that the more likely the stroke was due to the PFO, the lower the risk of another stroke happening. I think it's hard for people to wrap their head around that and therefore you're like, "Why do we care about finding A PFO? If it's likely related to PFO, it's unlikely to have a stroke recurrence." It still does have stroke recurrences. And the question is, can we make it even lower, that what I think is important people understand, but thank you. Keep going.

Megan Stevens: Yeah, so we of course care because you can have just one more stroke and it can be the worst type depending where it ends up. And so when we are then looking at the RoPE score, what does it not take into account? Well, it does not take into account the anatomic features of PFO. And so the Pascal criteria and classification system helps to rectify that because it takes into account your RoPE score and it breaks it down as either a high score or a low score, so high being seven or higher, low being less than seven, and if you have high risk features with your PFO or absence of those features. And so high risk features are large shunt, which was defined as 20 or more microbubbles crossing and atrial septal aneurysm. And so if you have two positive factors, so a high score on your RoPE and high risk features, then you are in the probable category for PFO associated stroke.

And if you have one of these positive factors, then you are in the possible category. And if you have neither, you're in the unlikely category. And the importance of this classification system is that it not only determines likelihood of PFO associated stroke, but it also determines benefit because it was shown that people in the probable category had the highest benefit of PFO closure. People in the possible category had benefit, but it was less than in the probable category. And those in the unlikely category did not have benefit of PFO closure.

Steven R. Messe: Got it. That is an excellent description. And then did you notice any association between those categories of Pascal classification and risk of adverse events also?

Megan Stevens: Yeah, so you're more likely to have increased risk of adverse events if you're in the unlikely category. And so the classification really does help with patient selection, which is the key to PFO associated stroke is finding those patients.

Steven R. Messe: Yeah, that sounds right to me. We should mention that the confidence intervals around the estimate of benefit in the unlikely category are wide. It doesn't rule out a potential benefit, but the estimate is that there is not a benefit and those other categories it clearly is a benefit. And so I think that's helpful to increase our confidence in who we should be recommending closure, for sure. All right, so

Molly, I think the cardiologist obviously plays a very critical role in managing these patients. So what cardiac findings do you consider to be high risk for stroke recurrence as well as what do you look at when you're thinking about closure? What kinds of things are you paying attention to that are important?

Molly Szerlip: So Megan brought up two of the most important, which are the large shunts and the interatrial septal aneurysm. But there's also other things like a prominent eustachian valve or a large Chiari network. Those things too can put you at risk from having a stroke just from thrombus being formed on those two things. So I think that those are the things that we really look at. When you start getting patients above age 60, we're still looking at those patients, but we look at them a little bit closer for atrial fib risk. But just because you're age 65 or even 70 doesn't mean that you can't have a stroke from PFO. So I work really closely with my vascular neurologist to try to weed that out because I still want to protect those patients, but it becomes a little bit harder.

Steven R. Messe: Got it. And I believe there are two devices that are currently approved for use in the United States. Yes. Is there anything different about the two or anything that people should be aware of and how they're selected for one versus another?

Molly Szerlip: Yeah, so there are two devices, the AMPLATZER device, which is by Abbott Vascular, and then the CARDIOFORM device, which is a Gore device, and they're similar. The AMPLATZER device is two self-expanding nitinol discs and it has a polyester fabric in between it. It comes in four different sizes. We typically use one size, it's a 25 millimeter device. The larger devices from an AMPLATZER we would use if there's a long tunnel or a big intraatrial septal aneurysm. So we tend to use a bigger device. The CARDIOFORM device is a nitinol wire, and then it has EPTFE cloth around it. It comes in three sizes. The theory is that the CARDIOFORM device may have less erosion than the AMPLATZER, but as we've been putting more and more of these devices in, we size them pretty well that even the erosion from the AMPLATZER is pretty low. It is good to mention though, that both devices, there is a small but real risk of causing atrial fibrillation in the future. So that's why we just don't close every PFO that we see.

Steven R. Messe: Sounds reasonable to me. I agree. All right. So obviously neurologists and cardiologists are both critically important in caring for patients with stroke and a PFO and there's a lot of uncertainty though as we talk about some of it. And PFO is very common in the adult population. It's not always the cause of a stroke when we see a PFO, and there are these patients that we encounter in clinic who are not the same patients that were included in the trials. The external validity of these trials is not great. Obviously, patients were very carefully selected for the trials. So I want to hear your guys' thoughts about how you approach patients, particularly the ones who are maybe not clear what to do. What's your approach for shared decision making? Megan, you want to go first?

Megan Stevens: Sure. So at my institution, I work closely with structural cardiologist, Dr. Megan Coylewright, and we communicate at the early stages of stroke workups. So when patients are admitted to the hospital to make sure that their workup includes all

necessary cardiac testing so that we can really quickly identify all stroke risk factors, including whether or not PFO is in fact a risk factor for this patient. And we have to formalize that discussion as well.

And we meet monthly, and that's usually an opportunity to bring up some of these cases that you're alluding to, which are perhaps more challenging, maybe not as straightforward, maybe at the edges of where our current guidelines and research are able to shed light on what we should do. And we are able to discuss whether or not the associated factors at a patient's presentation and all the other testing is really consistent with A PFO stroke. And we're able to also talk with the patient at our clinic visits to really confirm more than once that where is this patient headed? Are they feeling like they would really rather have a PFO closed or would they rather wait and not have a device placed?

Steven R. Messe: Yeah, I think that makes a lot of sense. And I agree. I think getting to what the patient, where their mind is at, is really important. And I've seen patients who desperately want everything done for a possible stroke prevention and having this PFO really bothers them psychologically. And then other patients are morbidly afraid of having any procedure, and that's their priority, is avoiding all procedures at all costs, and those people are coming from very different places. Molly, do you have any other thoughts about the kind of patient's conversations you're having?

Molly Szerlip: Yeah, so we have a very similar program to what Megan describes. We have a stroke center with vascular neurologists, and we routinely discuss with them as and then back with the patient for the same thing to decide what's the best course of action. And you're right, it really depends on the patient. Some patients really, really just need to have this closed and then others don't want to have a device. It's nice to have a group effort on this though, because we see a lot of 65, 70, 75 year olds who have had stroke, and those are tough. Or even the people who are hypercoagulable who need to be on lifelong anticoagulation but still have a PFO and do you close those? So it's really good conversation and it's really good learning, and I think as we do more and more, I think we're going to learn more and more.

Steven R. Messe: Yeah. Molly, you brought up a bunch of interesting points there. To wrap this part up, I would say I think patient education is critically important in getting to understand what the patient prioritizes and building these bridges and communication channels between cardiology and neurology is critically important, and that's going to lead to the best outcomes for patients for sure. All right. So you brought up some challenging edge cases here. We're getting to the end of this podcast. So what do you guys think about these patients who are over 60? The randomized trials primarily enrolled patients under 60 years of age, and as you said, Molly, we're seeing patients who are 65 or 70 or even 75 who got a bubble study. They found that they had a PFO, maybe there was something about that case. Maybe they also had a DVT and an acute PE at the same time. So it really was a compelling story that it was a paradoxical embolization. So should we be closing these PFOs in older patients? What do you guys think?

Molly Szerlip: Well, I think if you have somebody like that that you said had a DVT, a PE and had a cryptogenic stroke, I do think that you should probably close that mainly because the risk of PFO closure is so low. And so there are some guidelines out there. Skye has a really good PFO guideline that we worked together with our neurology counterparts and went through lots of, I know you were giving a, but I think it's a good beginning basis to be able to then have a good conversation with your neurologist. Again, I think that's what's important about this. I don't think anyone should make the decision by themselves. I think it needs to be discussed with vascular neurologist or a neurologist who specializes in this sort of thing, the patient themselves, and a structural cardiologist. I think it needs to be a discussion because I don't think we know the answer to a lot of these questions.

Steven R. Messe: Yeah. Megan, anything you want to add on that question?

Megan Stevens: Well, I think it is interesting. I don't want anyone who's listening who's thinking about hypercoagulability and why we haven't really mentioned it. And the reason is that in the past, we did not close patients who had a defined hypercoagulability that was going to require lifelong anticoagulation. But things have really changed within the last few years. And so we're at a point now where we're actually having studies show that the combination of being on anticoagulation and getting PFO closure in the setting of thrombophilia is better than medical therapy alone.

And so what we used to take as truth or best guidance is changing right now. And so when it comes to these cases, it is good to talk with the patient to let them know that we're really at a point where we're still gathering information as a community of physicians and providers, and we're not yet at a point where we can definitively say what would be best, but that there are some signals in the data that perhaps having both PFO closure and being on anticoagulation for some of these thrombophilia patients is a good idea. And some patients will want to do both, have the closure as well as be on anticoagulation. Some patients will just want to do the anticoagulation, but again, it's including patients in the discussion between your specialists so that you can get to a decision that was really consistent with the patient's wishes.

Steven R. Messe: I totally agree. I think those lifelong anticoagulation patients are challenging. The data is unclear, at least for me right now. And again, it gets back to the shared decision making and patient priorities for sure.

Megan Stevens: Absolutely.

Steven R. Messe: Awesome. Well, I think we're at the end of our time unfortunately. It has been a great discussion. I appreciate Megan and Molly joining me here today, and I thank you for listening. We hopefully shared some important thoughts about management of patients with PFO and stroke and to claim credit and get additional information, please visit learn.heart.org. Thanks very much.