Melanie Cole (Host): Welcome to the podcast series from the Specialists at Penn Medicine. I'm Melanie Cole. And joining me today is Dr. Scott Kasner. He's the Vice-Chair for Clinical Affairs and Neurology, the Ruth M. and Tristram C. Colket, Jr. President's Distinguished Professor of Neurology at Penn Medicine. He's here to highlight the SELECT2 Thrombectomy Study and Penn's role in this study.

Host: Dr. Kasner, it's a pleasure to have you join us. Thank you so much. I'd like you to start by walking us through the SELECT2 study and Penn's role in this study. What drew your interest in participating? And Dr. Kasner, could you briefly tell us a little bit about what the findings mean for stroke patients in our care?

Scott Kasner, MD: Well, thanks for having me, and I'm excited to talk about this trial.

The goal of the SELECT2 trial was to determine if we could expand the indications for thrombectomy to a broader population of stroke patients. When thrombectomy was first really established as a therapy for stroke in about 2014, we used to only treat people who could be treated within six hours after the onset of their stroke.

In 2017, two big studies called DEFUSE3, which Penn participated in, and DAWN, showed that we could treat selected patients up until 24 hours. In both of these trials, the imaging criteria were really critical, in that we would only treat patients who had really very little evidence of damage on their initial scans, and or a very large penumbra. By this I mean, we would look at the initial CAT scan. We'd make sure that there was a really small area of hypodensity and then ideally in some of these trials, used advanced CT imaging with CT perfusion to show that there was a large territory, larger than the area that was damaged, that was penumbra, that was at risk, and that we could potentially treat that.

After that, we expanded our thrombectomy indications to 24 hours—we could treat potentially fifteen-ish percent of the patients in the US with this therapy. But, there were lots and lots of patients who just arrived in the hospital with really extensive damage and we said, we can't treat them, there's no benefit, and we can only cause harm.

SELECT2 sought to really evaluate that question a little bit more and said, rather than assuming that these patients are too far gone, maybe we could create some benefit. Such the trial was born.

It was led by Amrou Sarraj at University of Texas in Houston. There were 31 sites around the world that participated. We were a critical component of that, enrolled a large number of patients. The criteria here were that these were patients who presented with an acute stroke within 24 hours and had either extensive damage on their CAT scan, defined as something called the ASPECT score (where it's scored from zero to 10, 10 is a normal scan).

You lose points for increasing areas of damage. Zero would be a scan showing of very widespread early infarction. We also use CT perfusion, which is a technique that is commonly used at many centers to assess how much territory is core damaged and how much is penumbra at risk, but not permanently damaged. Either of those could get patients into the study.

They just had to have a large core, greater than 50 milliliters or an ASPECT score of three to five to get into the trials. These were all large strokes. In fact, the average core volume was about 70 ccs, which would be considered quite a large stroke and would've been exclusionary in many of the prior trials.

So with those inclusion criteria in mind, these patients were then randomized to get thrombectomy or not. Again, this was a real paradigm shift. We previously didn't really treat any of these patients. So suddenly, we are now treating half in the context of this trial. Outcomes were defined as the modified Rankin scale, which is a scale that goes from zero, where patients are completely back to normal with no residual symptoms, to six, which is death. Three is kind of an important, defining point, where patients with three or better can walk and patients with worse than three cannot walk independently. About 352 patients were randomized, again, half to thrombectomy and, and half not.

They were typical of a stroke population. The median age was about 66 to 67. These were very severe strokes. The NIH Stroke Scale, which is a scale of stroke severity, was 19, indicating quite severe impairments. The average core volume was about 70 ccs. They ranged quite substantially.

The key result here was that there was a significant improvement in clinical outcomes, over the range of the modified Rankin scale. I should probably explain what that is just again, for a minute. I mentioned what the scale is, but when we look at outcomes here, you can do this in a couple of ways. You could sort of say like, I'm only going to look at the number of patients who are zero, one or two, which would be really good outcomes versus all others. Or you could look at the full range of scales and look for kind of a shift towards better outcomes. The primary outcome was this shift where any change towards the better was considered a substantial improvement.

Using that approach, the benefit of thrombectomy in this population was an effect size of 1.51, so patients were 50 percent more likely to have a more favorable outcome at three months after their stroke. Three months is a typical time point. Notably, if we dichotomize the score with functional independence or independent ambulation, those were still two to three times more likely with thrombectomy than with medical care.

So this was a huge win, and in many ways, a surprise. Obviously, some people were hugely enthusiastic about this and thought that we could make a difference, others were really skeptical and thought that we couldn't, based on what our prior notions were.

This was really very compelling data to show us that we could lead to better outcomes. It's worth pointing out that we really didn't change mortality, in a significant way. That wasn't the primary goal. And these severe strokes, many patients consider severe disability a fate even worse than death, but we didn't change mortality.

Very few patients with these large strokes ended up with a modified Rankin score zero or one, meaning that they were back to doing everything they were doing before. Again, not surprising, they all had substantial damage, but there was a huge improvement in the number of people who were still functionally independent or at least ambulatory compared to before.

And that is just an enormous boon for these patients. Some important secondary outcomes were quality of life scores, which also were better in the treated patients in terms of mobility, social activity, cognition, and depression. So all those, also supported the primary result that thrombectomy leads to better outcomes.

So in terms of safety, our big concern was that these patients with large strokes might have an increased risk of intracranial hemorrhage, because we've just opened an artery in a big area of injured tissue. It turns out that that wasn't the case at all.

The risk of clinical worsening due to intracranial hemorrhage or a symptomatic intracranial hemorrhage was only one out of 178 patients in the thrombectomy arm and two out of 174 in the medical care arm. So really, no significant difference at all. It looks like there was maybe a little bit of early neurologic worsening in the thrombectomy patients.

But, they had better outcomes in the long run, and that's an interesting result that we are still exploring. Why did they get worse early, but then do better in the long run? Maybe they had more swelling. When we do a thrombectomy procedure, sometimes you move the big clot from a big artery, but it's sort of breaks up and lands in another—so we're still exploring that.

What we really care about are these long run improvements or long run outcomes. So this is sort of secondary result, but it is noteworthy and requires further exploration. Other complications were quite low.

So overall, this trial was atom smashing. It took the paradigm of what we could and couldn't treat and just cracked it wide open and said, now we can treat these patients with large strokes, and this potentially increases the proportion of strokes who can get thrombectomy from, again, fifteen-ish percent to maybe 25 or more. It opens up big questions about how late can we treat patients because maybe, if we can treat people with this much damage, then maybe we can treat them even far out beyond 24 hours. That still needs to be further established, but is tantalizing. These results jive with the results from a large Chinese trial that came out at the same time, and a Japanese trial from earlier that suggested similar results. So adding to a global picture of our ability to treat these large strokes.

Host: Well, thank you for that comprehensive explanation, Dr. Kasner. Such an interesting study. How long has this approach with thrombectomy plus medical care for larger strokes been available at Penn Medicine's Comprehensive Stroke Center? And how important is it that stroke patients and their clinicians be attentive to the clinical studies taking place at Penn Medicine?

Scott Kasner, MD: This is a huge issue for us. So, we started this trial in late 2019. So, that means we've been doing this for over three years, at least offering it to patients, right? It was a clinical trial, so it's optional. People always have the decision and their families, to decide if they want to participate or not. But, this has been an option here for three years.

We presented the results of SELECT2 at the International Stroke Conference in February of 2023. So, the rest of the world, the rest of the US, the rest of every place didn't start treating these patients until February 2023. Think about how many patients had a stroke between late 2019 and 2023. Who could have potentially participated in a study like this, had this treatment offered to them and it may have helped move the field faster forward if they had participated in this time window. That could have been huge, and the public health implications of this, as we said, are enormous.

Host: Well, they certainly are. So, I'd like you to just expand a bit on what this means for the local market and patients. How do you envision your research translating to patient care and how could this change the landscape of stroke care? Take us from bench to bedside, Dr. Kasner, and how this care model can really improve and significantly improve the way patients receive their care down the line.

Scott Kasner, MD: When we think about stroke, I just presented SELECT2 and said how this is such a great breakthrough for our patients. Broadly speaking, stroke is still a terrible disease. The status quo, the standard treatments are intravenous thrombolytic agents like tPA or TNK within four and a half hours, thrombectomy up until about 24 hours and now, in a broader population. But, we're still left with a lot of people with severe deficits. We need to do better. Among the patients who have severe deficit or even a mild deficit, we have to worry about their risk of another stroke. We have to help their recovery. So, there are innumerable problems in the stroke field that we need to address.

Here at Penn, we are participating in many trials across this entire spectrum. We have multiple trials for acute therapies, including medications that could be given in addition to thrombolytics or thrombectomy, new catheters and devices to help improve the performance of thrombectomy, and maybe do a better job getting these vessels open. We have novel therapies for secondary stroke prevention and novel therapies for recovery. None of these are really available in routine clinical practice. So if you go to a hospital and they do thrombectomy, but they don't participate in research, then you're getting the standard of care, but you're also dealing with the fact that the standard of care really falls short of what most people want, which is to walk away from their stroke with no deficit and never have another one. We have to do better. The research gives us that opportunity.

If you come to Penn, then all these options are at your fingertips. We assess everybody to see what they might be eligible for. We offer it to them. It's totally voluntary. We're not forcing anybody to do anything. But it's nice to know that you have options. Sometimes we have patients who are offered a trial who say, you know, "I'm really excited about this. I want to do something above and beyond what I can do. Sign me up." And we also have people who say, you know, "I'm sorry. I don't want to commit my family member to this research project. This sounds a little scary to me." That's understandable too. "But I really appreciate knowing that you've done everything that you could and even went to the point of offering me something above and beyond that." And I think people are grateful for the opportunity or super excited when they hear that not

only were they able to get this opportunity, but they got the new thing and the new thing turns out to be the way we now treat everybody. How amazing is that? The more of these trials that we do, the faster we solve these problems for the future.

Host: Dr. Kasner, I'd love for you to tell us about a patient who saw a positive outcome from this expansion. How are they doing now?

Scott Kasner, MD: So, one of our patients, I remember quite well, a 63-year-old woman, generally pretty healthy, but smoked, who presented with a very severe stroke to another hospital. When she got there, she was not really protecting her airway, they had to intubate her. They transferred her over to us. Her NIH stroke score was 28, so almost off the charts as high as you can go. She was not able to consent on her own behalf to the trial, but we contacted her family who understood that again, the alternative was a very dire situation. They agreed to have her participate and she was randomized to thrombectomy before it was available in routine practice. She had quite a rocky course in that she actually had some other complications in the hospital, not related to the procedure itself, but due to some other medical problems. In the end, we got this blood vessel open. Despite a relatively large stroke early on meeting the criteria for this trial, she ended up being able to resume all of her normal activities. She still had some deficits. Again, that's what we expect in these people who already have extensive damages that they're going to have some deficits, but she was independent in taking care of herself, resuming the vast majority of her activities. I think she did not resume driving, but otherwise was back fully engaged in her prior social life, her other activities. This is only at 90 days. I mean, people are still even improving beyond that. It's now about a year out and she continues to improve. Super gratified with her outcome, as is her family who had to make a difficult decision on the spot, as is often the case in these very acute trials.

I would really like other providers to know that there is enormous opportunity to improve outcomes for stroke patients at all levels. And referring them to Penn in the acute setting, in the subacute setting, in the chronic setting, offers them opportunities that they might not get elsewhere. And by having people come to us with an open mind about participation in these projects, we hopefully get to answer sooner, which then applies to everybody and that leads to better outcomes nationally and globally. Research is hard. It's a concept that is challenging for patients or families, for doctors. We all wish we knew all the answers, but we just don't. Encouraging people to think about participation in research really has enormous benefits for all of us.

Host: Absolutely amazing, Dr. Kasner. This is such an interesting study. As we're talking about the expansion for more patients, more strokes that you can care for. What are the expectations for those patients who fit into this expanded category?

Scott Kasner, MD: I think a lot of patients would've fit this category previously, would've ended up in the situation where they went to a local hospital, saw their stroke team, or maybe used telemedicine, telestroke to see them, and they would've said, sorry, it's too late. There's nothing for us to do, and now the expectation should be, you know, strong consideration for thrombectomy in this patient population.

There are still some caveats. While we took large strokes, there's large and then there's giant. The people with really giant strokes, we need to look at this a little bit more, but they maybe benefit less. That wouldn't be surprising. Is it still worth a shot, maybe? So, those are some of the clinical considerations, but most importantly, we really just cast this much wider net for patients who we could potentially treat.

Host: Great points that you made, Dr. Kasner. Wrap it up for us. What would you like other providers to know about the SELECT2 Thrombectomy Study and really how important this is for the future of stroke patients?

Scott Kasner, MD: I think this tells us a lot about what's going on in the brains of patients with stroke and that this is still a very dynamic process that we can treat people later, bigger, worse than we thought we could before. This may change even further as our technology and imaging and other things improve.

But for now, we should not write anybody off. And we should really be exploring aggressive therapy more for a much broader population of patients.

Host: Thank you so much Dr. Kasner, for joining us and sharing this study with us. That was absolutely fascinating. To refer your patient to Dr. Kasner at Penn Medicine, please call our 24/7 provider only line at 877-937-PENN. Or you can submit your referral via our secure online referral form by visiting our website at pennmedicine.org/referyourpatient.

That concludes this episode from the specialists at Penn Medicine. I'm Melanie Cole.