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

Melanie Cole, MS: Dr. Kasner, thank you so much for joining us. We spoke briefly in a previous podcast about the SELECT2 trial, the findings for which were published in the New England Journal of Medicine in February of 2023. For those who haven't listened to that episode, can you give us a little bit of a recap of the study?

Scott Kasner, MD: Sure. Thanks for having me here. The SELECT2 is a landmark trial that immediately transformed our care of stroke patients. So first, I guess just a quick little bit of background. Since about 2014, we've been doing thrombectomies in patients with stroke due to a large vessel occlusion—initially only in the first up to six or eight hours. Then starting in 2017, we expanded that window up to about 24 hours based on other research that Penn participated in.

In all of those prior trials, patients who had very clear evidence of large territory infarction were excluded, with the idea that the damage was too severe, that we couldn't help those patients. So, in clinical practice, that's what we followed, and we didn't treat many patients with large cores. Core meaning, again, this territory of the injury that was too big.

The purpose of SELECT2 is to readdress that question and say, “Could we effectively treat some or all those patients with thrombectomy, even if they have a large core?” There was a lot of debate before this trial was done about whether or not this was likely to be effective. Because we didn't know, we did a randomized trial of about 350 patients who were randomized to either get thrombectomy or not. The key selection criteria was that they had an acute stroke (or within 24 hours) and had a large core infarction, which could be determined by their baseline CT scan or CT perfusion. The non-contrast CT is the most commonly used test for patients with suspected stroke really to rule out hemorrhage. But, we can see early infarct changes and we can score those from zero to 10, where 10 is a normal scan and zero would be a patient who has a very, very large infarction. The prior trials excluded patients with five or less, so this SELECT2 trial included those with three to five, so a large infarction, but not massive. The alternative was we could use CTP or MRI to see the territory

that's not getting enough blood flow and is likely the core of the infarction. And there, we used a threshold of 50 milliliters or 50 ccs.

We randomized these patients and the original goal was to go to nearly 600 patients, but the trial got stopped early because of overwhelming efficacy. After 178 patients were assigned to thrombectomy and 174 to medical care, the odds of a good outcome was far in favor among those who were treated with thrombectomy, so the trial was stopped. And efficacy was observed in a rating scale called the Modified Rankin score.

Modified Rankin scale scores patients from back to normal, mildly impaired, moderate deficit, severe deficit or dead. In this trial, the patients who became functionally independent despite having this really large stroke was 20% in the thrombectomy group, 7% in the medical group, so a tripling of the people who were independent. And perhaps more importantly, because many stroke patients end up severely disabled enough that they can't walk, especially with these large strokes, here the number of people who had independent ambulation was about 38% with thrombectomy and only 19% with medical care. We doubled that too, this substantial proportion of patients back to independent status, so not wheelchair-bound or bed-bound.

Those are really the main results. Because of this substantial efficacy, certainly not perfect, we're not getting everybody back to normal, but we're making a lot more people independent or ambulatory, we immediately adapted this into our clinical practice and we are now treating patients with large strokes across our entire network. That's it then in a nutshell.

Melanie Cole, MS: How many strokes would qualify for this treatment?

Scott Kasner, MD: Well, thrombectomies altogether, it's probably somewhere in the range of 20-25% of all strokes. That's roughly the number with the large vessel occlusion, significant deficit who arrive at the hospital in time. There's still some who come in too late. There's sometimes people who have a clot, but it's in a branch that's further out in the tree and we're still developing strategies and technologies for treating those better. This trial substantially expanded that population who's eligible for therapy.

Melanie Cole, MS: It sure did. It's so interesting, Dr. Kasner. What were some of the findings that surprised you? Was it interesting to learn that it wasn't associated with reduction in mortality compared with medical therapy? Speak about the outcomes following treatment that are more quality of life-related, disability, functional independence.

Scott Kasner, MD: That was a great question. So, we really didn't see a significant difference in mortality. Unfortunately, stroke is far more often disabling than it is fatal, particularly for these large strokes. Mortality was still substantial, about almost 40% on average, with maybe a smidge better in the thrombectomy group, but nothing significant.

The real reductions were we substantially reduced the number of people who were severely disabled as kind of mentioned before. We looked at some other things like the likelihood that somebody's more likely to go home. We looked at some quality of life scores related to mobility, depression, social and cognitive functions, all of those things trended in the same direction as the overall effect that there were improvements in quality of life, in ability to return home and attain functional independence. So, these are all the things that we all want. We ideally want to make all these strokes go completely away. Again, this is a population in particular who already had substantial irreversible damage and we're able to show that, despite that, we could still make meaningful, incremental improvements in their outcomes.

Melanie Cole, MS: How important Dr. Kasner, was the imaging method used to measure the volume of infarcted tissue and SELECT2? Can imaging affect outcome?

Scott Kasner, MD: The imaging with any of those techniques mentioned before helps us identify which of the patients already have substantially large cores. And so, that was a criterion for selection in the trial. We are still unraveling some of the bigger questions here. So, one view might be, “Well, now you've done prior trials that used highly selective imaging and showed that that led to benefit. Here, you took the patients with the large cores and you still saw a benefit. So, why do we need any of this imaging? Why can't we just treat anybody with a large vessel occlusion with this therapy?” And that could be one interpretation of these results. But of course, this is one study in the context of others and there are other studies that are looking at this question. And even within this study, there's some work looking at how much that size of the initial core affects outcome.

And while it looks like the odds of more favorable outcome increase regardless, it does seem like the patients with a very, very large cores, say greater than 150, probably don't really achieve the level of Independence that we are hoping for. We might still treat them, but there may be differences in that sort of judgment and value as to whether or not going from severely disabled to moderately severely disabled is a big enough jump to make it of value to patients and families and all. So, those are still open questions. Fortunately, there's very few

of those. Most people have more of the kind of moderate core and, again, are reflected in the overall results with a substantial improvement. But there may still be limits as to what we can achieve for those with truly massive infarcts.

Melanie Cole, MS: Doctor, SELECT2 was an important international trial, and Penn Medicine was one of only five medical centers on the east coast participating. Can you speak briefly about why your program was a site for this trial? What does it mean for both clinicians and the public to have a regional center involved in such an amazing clinical trial as this one is?

Scott Kasner, MD: We were chosen because we are a high-volume center with a focus on research. There's certainly lots of places in the country that are doing lots of thrombectomies, but you needed to pair this with a team that sees clinical care and clinical research as being seamlessly integrated so that we treat everybody with the best available care and then, and we explore our research options and try to find opportunities for our patients to participate in. And we were very effective at that and we have been for many other trials as well. Being part of this for us is obviously huge, right? We want to be part of the team that is changing the outlook and the future for stroke patients. And this was a critical trial for us to join.

Melanie Cole, MS: Well, thank you for that. And it is really such an important trial. As we get into this, Dr. Kasner, are there any changes EMS and emergency care providers should make in light of this study?

Scott Kasner, MD: For the EMS providers, I think the message is still pretty straightforward, which is anybody with a bad stroke, motor deficit, severe aphasia, severe neglect should be brought to a comprehensive stroke center, where they can get appropriate imaging and thrombectomy if appropriate. It's really hard on clinical grounds out in the field to figure out who's got a big core or not.

For the EMS providers, the emergency medicine providers, they need to know that we have a bigger population that we can treat, broader inclusion, exclusion criteria, and they need to work with their stroke teams to make sure that they are identifying these patients and getting them to comprehensive stroke centers because patients can show up at any hospital. And even though EMS tries to bring the big bad strokes to the comprehensive stroke centers directly, people will show up anywhere. Those are really the key messages there.

I will say that SELECT2 opens up a broader question. If we can treat patients who already have well-developed infarction on their scan, then how wed are we

to the idea of 24 hours? Future research may yet tell us that we can treat these patients even beyond 24 hours. This kind of goes back to the question of where do academic centers fit in?

If somebody comes to us this time next year and their last known normal was a day and a half ago, we will hopefully be enrolling them in a trial of thrombectomy versus standard of care to see if we can push the window from 24 hours to 72 or longer. If they go to a place that's not involved in the trial, and it's more than 24 hours, they will get no therapy for sure. Going to the leading academic centers that are engaged in the research gives people an opportunity to at least have this conversation and, gives them the choice to participate in that trial or not and hopefully get something that will ultimately prove to be more effective down the road.

Melanie Cole, MS: Such good points you made. Final thoughts, Dr. Kasner. What's on the horizon for clinical studies in stroke and stroke therapy? What would you like the key takeaways to be?

Scott Kasner, MD: There a lot of changes on the horizon. One I just mentioned about pushing the window beyond 24 hours. The technology for the catheters and other approaches to these vessels is evolving. People trying to make catheters that can reach out into smaller and smaller blood vessels, which means we can reach clots further and further out into the brain, and potentially do this with less risk of causing some secondary injury from the catheters or anything else like that.

Many years ago, there was a concept of neuroprotection, medications that you could give to the brain that would help it survive while waiting for the blood supply to be returned. Countless trials were done, and neuroprotection failed repeatedly. But that idea is coming back now with the expansion, very rapid expansion of thrombectomy to so many more people, I said 25%, but it could potentially end up being a lot more, about trying to couple neuroprotective therapies with thrombectomy. Once you get the artery open, then you give the neuroprotectives into that area of damaged brain, and maybe that could substantially improve outcomes as well. All of these things are on the horizon, and it's just a really exciting time and a very optimistic time for stroke.

Melanie Cole, MS: Well, it certainly is exciting and both optimistic. And thank you so much, Dr. Kasner, for joining us and giving us a good overview of the importance of the SELECT2 thrombectomy trial. Thank you again.

That concludes this episode from the specialists at Penn Medicine. I'm Melanie Cole. Thanks so much for joining us today.