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Stroke Prevention in TAVR: Reviewing New Findings from the PROTECT-TAVI Trial

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You're listening to ReachMD, and this Medical Industry Feature, titled "Stroke Prevention in TAVR: Reviewing New Findings from the PROTECT-TAVI Trial," is brought to you by Boston Scientific. And now, here's your host, Dr. Janar Sathananthan.

Dr. Sathananthan:
Good afternoon. I'm Janar and I'm the Chief Medical Officer for Interventional Cardiology at Boston Scientific. And welcome to the Windy City. We're here at ACC 2025, and I'm joined today by three friends and colleagues. And we're here really, to talk about a very important study, the BHF PROTECT-TAVI study, which was one of the SEMINOLE late-breakers at ACC. A very important study in interventional cardiology. And we're joined by Dr. Rajesh Kharbanda from the University of Oxford, who was the PI for the study, Dr. Samir Kapadia from the Cleveland Clinic, who of course, set off the SEMINOLE study in the randomized space in this therapy with the PROTECT-TAVR study. And we're joined by Dr. Mike Rinaldi from Charlotte, North Carolina, a very renowned Interventional Cardiologist in the US.

So, we're going to have an informal conversation today, but obviously, in the space of TAVR, stroke is a very feared complication, and you know the therapies going to younger and younger patients. It's something we worry about. We had a series of publications in the last year. Dave Cohen had an STS series publication with more than 400,000 patients. We had a US sub cohort of yours, Samir. But really, today is the largest randomized, control trial in the space.

So, Raj, maybe I'll start with you. If you could just give us a brief description of the design of the study, and then what the key take-away lessons and findings were from the study?

Dr. Kharbanda:
Yeah. So, it was a randomized trial. We powered it on a 3% event rate, which was right at the time, and about a 30% efficacy of the device. So, a 3% down to 2%. And we needed about 7,700 patients to power that study, so it was larger than the other studies. And that speaks to the low frequency of the event, really.

The trial recruited very well. The primary endpoint was stroke, very analogous to PROTECT-TAVR. So, stroke at 72 hours, or discharge if earlier. And stroke was adjudicated by an independent adjudication committee. So, it was TAVI, randomized sample, low set, and stroke discharge or 72 hours.

The trial enrolled well, and at the third interim analysis, the Data Monitoring Committee recommended that we discontinue further enrollment because of futility. By that time, we'd enrolled 7,635 patients, so just over 3-and-a-half thousand in each group. Well-matched for baseline clinical characteristics; 80-year-olds, severe aortic stenosis, 40% female, 80% were bicuspid anatomy. And procedural characteristics were very successful; 99% of them got the valve as intended. Success rate was 87.5%, and the key outcome was that all stroke was 2.2% in the control group and 2.1% in the set group. Absolute risk difference of 0.01%, which didn't reach significance.

And in terms of disabling stroke, the rates were – well, it was 53 events versus 47 events. Again, didn't reach significance. The other secondary endpoints included death, non fatal stroke, TIA. No difference. So, this was a neutral study, and the subgroups; we investigated a series of subgroups. Again, there was no group we could identify where there was a beneficial effect.

Dr. Sathananthan:

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OK. So, a lot to unpack there. So, let's take it in sequence, starting with the design. Samir, I'm interested in your thoughts. The studies sound similar, endpoints are somewhat similar. In your view, what do you think is key differences or similarities between your RCT and this new one that was presented at ACC?

Dr. Kapadia:
I think, very, very similar trials in big picture, that all patients were enrolled in both trials. There is one difference that in US at that time, we had the device available commercially. So, some of these study sites may have enrolled patients that were not really – you know high-risk patients were not enrolled in the trial initially and only the low-risk patients were enrolled. Because people were using central device. So, there is some bias that could've been introduced in the United States because it was. But at the same time, people were using the device, so there were – at least 25 devices had to be used before we allowed them to use the device or put them in the trial. So, there was some kind of a criteria used to – who can do the procedure in the US trial, initially, because this was the first trial.

So, there was a bar set to say that we have to do 25 cases before you can start enrolling in the trial. And the stroke definition is very similar, but at the same time slightly different in the sense that these strokes, when the strokes happened in the PROTECT-TAVR trial, they had to be seen by the neurologist and then do the analysis with whatever imaging studies had to be done.

If I'm correct, in the PROTECT-TAVI trial, they had a questionnaire that asked the patient that if this questionnaire was positive, then they involved the neurologist. So, this was not all. Is that accurate?

Dr. Sathananthan:
Yeah. So, we used a validated questionnaire to ensure stroke-free status. So, rather than have neurology, everybody, we had a daily screening process to pick up events. And the event rate actually, that we've demonstrated. We weren't missing events. I think that the rates are similar to the National Registry, so it wasn't that we were not picking up events with our approach, just to reassure. I think that's important. You're right, it's a subtle but important distinction.

Dr. Kapadia:
Some distinction. And my point is that, because you also asked for 3% rate, early start, and it was 2.2, so there is a, either a power-related or whatever the ascertainment. So, something to keep in mind, that there was a little difference, that everybody was not seen by the neurologist. So, maybe the minor strokes could not be identified or something. But as Raj points out, that this is a very well-validated questionnaire that they used, but this is a questionnaire that – who answered, how they answered. These are all important questions to keep in mind. Of course, you know they must have all the ultimate data and we'll dig deep as we are planning to do this analysis together. We will have a better idea how we can combine the data and can understand the data better.

Dr. Sathananthan:
Yeah. And I think the two of you are planning a meta-analysis that will be presented as a late-breaker at PCR. So, more to understand from the data combined.

Dr. Kharbanda:
And I think again, it's very combinable data because again, 72-hours stroke rate. Very similar concepts that we have used.

Dr. Sathananthan:
OK. So, Mike, I want to just turn my attention to you here. You're a very busy interventional cardiologist, extremely busy practice. When a patient has a stroke, it's a terrible complication and we've seen data prior to this study, which has shown a benefit, at least, in disabling stroke, which anyone would fear.

Are you surprised by the results of this study?

Dr. Rinaldi:
So, I think, at outset, first, the rates of stroke have come down, but they're not gone and stroke remains a problem in TAVR. So, a lot of different complication rates have come down, but stroke has kind of flattened and it's plateaued, and it's not gotten better. And it's still 1,000-fold higher than PCI. And stroke is probably the thing that patients fear the most, so it's a big deal still. One to 2% sounds low, but it's not nothing, and if you're doing 100 TAVRs a year, that means you're stroking out 1 to 2 patients a year. That's a big deal to those patients and it's a big deal to us as providers.

So, we still need better therapies to reduce stroke. The question is, after a 6,000-patient study that was neutral, does that mean that there's no role for embolic protection? I think that's probably not quite right, in that a randomized trial applies to the patient population that was studied. And we have an important and excellent study that suggested no clear benefit in that population, but we have another trial that was numerically superior in the in the entire field. And then, in the US, it was actually statistically significantly improved, suggesting there may be some patients that do benefit. And we need to figure that out. And I'm hoping the meta-analysis will help sort

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that out.

But given how important stroke is, I think it's important for us to really pay attention in the absence of definitive data, to try to figure out are there patients who are at higher risk for stroke. And you know in a technology that reduces but does not completely prevent stroke, the biggest benefit is going to be in the patient population that has the highest risk of stroke. You have the best chance of reducing stroke, if you are at risk for stroke in the first place. So, we need to start thinking about who are the higher risk patients for stroke. And – And I still think there's a role for this technology and protection in general in the field.

Dr. Sathananthan:
Yeah. OK, appreciate. I mean, there's also a range of procedures people are doing now, basilica or other fancy techniques which have a, certainly, at least theoretically, you would think, logically, would have a much higher risk of debridement certainly with therapies, may be beneficial. So, you know Raj, I'm sure there's a question. Mike alluded to it, right? We're trying to understand different subgroups, and so you know one thing for me that's, certainly, I think for many others as well, from you know David Cohen's presentation at TBT, was they looked at over 400,000 patients. Seemed to be this very strong trend in patients with prior stroke. I think as a field, it's fair to say we don't quite understand the mechanism of why that would be different. But was that a group that you looked at, or could you talk more in detail about the subgroups that you looked at? And I know you mentioned there wasn't one that struck out?

Dr. Rinaldi:
Yeah. So, we didn't predefine stroke, but we looked at age, we looked at sex, we looked at bicuspid valve, we looked at surgical risk score, we looked at pre-dilatation, we looked at valve type. So, the sort of usual ones that you would expect. None of those –I think we need to dig down, and I think that increasing the power with the combined metro-analysis will allow us. Obviously, the individual groups are small when you start looking like that. And I think combining the data sets will allow us to tease out whether there are particular groups that might benefit. We didn't see a benefit in our analysis, but I think we need to delve deeper I think. And it may be that a combined – it may not be that it's just one factor. It may be a combination that you need.

Dr. Sathananthan:
So, Samir, look, I mean, you've been at the start of this field from the very beginning. You've helped generate a lot of the data, you're involved with a lot of the new technologies in this space. What do you think, after this presentation and this data at ACC, are the remaining unanswered questions?

Dr. Kapadia:
So, before we go to the unanswered, I just want to say what we know, and then we say what we don't know. I would say that – So, the problem started – just so we are on the same page, just the history part – that when we published this PARTNER 2A trial, Dr. Schaff, wrote an editorial in *New England Journal*, saying that the main problem with TAVR is that there is going to be more stroke compared to surgery. So, this was in *New England Journal*. And at that time, I was very interested in stroke, so we analyzed stroke with the PARTNER trial and we came to a realization that we were not actually doing the stroke analysis by neurological assessment in every patient, because stroke was not an endpoint in PARTNER 2B. So, the surgical stroke rate was 2.6%, and subsequent trials showed that it was when we really ascertained the stroke, it was 6.2, and it was not 2.6. So, whatever the reasons were. So, my point is that the stroke came to light very early on in the TAVR literature.

And then when we look at all the TVT data, it was very clear that stroke causes death, 15%, 16% death at 1-year. People don't go home. And the stroke rate was, even though coming down, as Mike says, is still so much higher than angioplasty. So, people feel angioplasty – that's what they are doing because they're awake, they're going home next day. So, stroke is an important problem.

So, now, from there, when we did the PROTECT-TAVR, primary endpoint was negative. Again, the stroke rate was down. Our sample size was small and our hypothesis was that it's 4 to 2%, and it was not 4 to 2%. So that's why. We were negative.

We saw some indications in the US population, some indications in the disabling strokes. And then, we analyzed with David Cohen's entire TVT registry, and whatever way we cut it, we find a little bit of a difference. So, we find whether we do the analysis with matching or we do the IPW analysis. Either way, we found the difference in the number of strokes. Positive, although small, but positive.

And then, personally, we are also very active interventionalists doing these procedures. We are doing 700 TAVRs in Cleveland Clinic and I have been using, and my colleagues are using, every day uh embolic protection devices. And our stroke rate is less than 1% and we don't have a major stroke in the last 4 years. So, if the safety of the device is not questioned. So, when I look at the data, I say OK well, this device at least didn't cause more strokes. That is for sure with the PROTECT-TAVR or with PROTECT-TAVI. And at least in our personal experience right now, we are not seeing large amount of strokes when we are using this device. So, the cost is an issue. But other than that, at least clinically, we are not hurting anybody by using this device. And we are not seeing strokes.

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So, before we change that which patient population we use it, we should analyze the data to understand that which exact patient population is more likely to have stroke before I say that, OK, I don't want to use it, but I'll use it only in basilica patient, or in high calcific patient, or in this patient. So, the unanswered question is that which patient population is more likely to benefit from a Sentinel device. And the Sentinel device is one of the devices. Maybe there are newer generation devices. So, in Sentinel devices, there are aortic arch, there is something not very good that may not protect or partially protect. Or all these different questions will come up and some of them we will be able to answer. Some of them, we may not be able to answer. But if we have a better idea that these are the patients who are at high risk of stroke who are likely to benefit, or high risk of stroke that may or may not benefit, these are the patients that we would use the device.

But currently, before we know that, I don't know how to change my practice, to be honest with you, to say that, how am I going to now, all of a sudden – I have two options. One is to use the device in everybody or not to use device in anybody, because I have no idea to know which patients are likely to have better benefit or not. And if it is not hurting the patient, and if at least, personally, I have not seen a problem and I think, at least in my mind, that we have seen some benefit, it's very hard for me to, currently, change all of a sudden to moving to no use of the device from all the use in device. That's my personal bias. But again, I think we need to learn from the data a little bit more, too.

Dr. Rinaldi:
I would agree. So, safety is there, ease of use is there. It doesn't make your procedures longer. So, if you feel comfortable with using it, there's no compelling reason not to use it. But what the real question is for those who aren't using it, is to understand if you're not going to use it in everybody,

if you have concerns about efficacy in the all-comer patient, we need to determine who is at highest risk. And maybe a score can be developed that really stratifies out that high-risk patient where there's the greatest potential for benefit.

Dr. Kapadia:
I completely agree, yeah. And what I think that, again, this is a little bit of a question to me that why there is geographical variation? Why there is variation, and then, whether there's a learning curve or volume relationship, or whether there is some aortic arch that has some relationship. I don't know that. All those questions, unanswered questions, are all these questions. There are some procedural things that can be modified, or patient selection processes that can be modified.

Dr. Sathananthan:
Yeah. I mean, I think one take-away for me is that this is a tremendous opportunity for more research, right? I mean, it's very rare in interventional cardiology to have a device with more than 10,000 randomized control trial patients. I mean, it's probably one of the most studied devices in terms of patient number, from an RCT perspective. So, I know the two of you are working on that. And so, over to you, Raj, maybe for the final word. Obviously, your take-aways from ACC. Congratulations again on your late-breaking presentation. But very excited to hear what's next in terms of where you're thinking about this therapy.

Dr. Kharbanda:
Yeah. Look, I think I respect everyone's comments. It's a really interesting field, I think, and we come at it from slightly different angles. I come from a healthcare system that I can't use the device if I want to. It's a different approach. So, but for me this is an opportunity. So, coming back. Stroke remains important. Disabling stroke is a catastrophe. We're going to do a group of patients who are going to be younger and lower risk, and the consequences of stroke are more. We still need to understand much better how to reduce stroke, so it is still important.

I think the ease of use, the familiarity, the volume of data that we have, we need to really understand which patients are at higher risk and if embolic protection is effective in those patients still. I think those are the things that I hope we can – As you say, we've got a huge wealth of data that we should use wisely to understand how we best use this device. And whether it's effective in a particular subgroup.

Dr. Sathananthan:
That's great. Well, I want to thank the three of you for joining us today. It's been a great discussion and look forward to hearing more data coming out of this very, very deep well of clinical research here. So, thank you again and have a good day.

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