PFO in Cryptogenic Stroke Patients

The lead neurologist investigator from the REDUCE trial discusses his perspective on how cryptogenic stroke patients should be approached.

Scott Kasner, MD, is Professor of Neurology and Director of the Comprehensive Stroke Center at the University of Pennsylvania. He is also the leading investigator for the REDUCE trial, a prospective, randomized, multicenter, multinational trial designed to demonstrate safety and efficacy of the Gore Helex septal occluder (Gore & Associates, Flagstaff, AZ) for patent foramen ovale (PFO) closure in patients with a history of cryptogenic stroke or imaging-confirmed transient ischemic attack. The study includes up to 50 investigational sites in the United States and Europe.

At the recent International Stroke Conference (ISC) in Los Angeles, you called on cardiologists and neurologists to commit to the randomization of cryptogenic stroke patients with PFO and to cease aggressive treatment of those patients outside of clinical trials. What is currently happening with most cryptogenic stroke patients who have PFOs?

Dr. Kasner: Well, things have changed since November with the announcement of the CLOSURE I trial results at the American Heart Association Scientific Sessions. Prior to those results, patients with PFOs had a lot of choices. They could see a doctor who let them know that they had suffered a stroke and that tests revealed that the patient has a PFO. Some doctors would recommend that the patient go on aspirin therapy, others would recommend that the patient go on warfarin therapy, and some were recommending closure of the PFO, despite the fact that there is no device approved for PFO closure or for stroke prevention. In general, neurologists took a more conservative stance, whereas cardiologists were more likely to favor closure.

In November, the results of the CLOSURE I trial (sponsored by NMT Medical, Inc., Boston, MA) were announced, which showed that PFO closure was no better than medical therapy. There are a number of flaws with the CLOSURE I trial, which I will address, but the study appears to have produced two very different responses by physicians, again along specialty lines. Among neurologists, many have concluded, "I should stop worrying about PFO, I should stop looking for it, I should stop caring about it, and I should stop referring these patients for closure."

Among aggressively inclined cardiologists, there appears to have been a very different reaction that has focused on the flaws in CLOSURE I, while continuing to close PFOs in these patients. My remarks at this year's Stroke meeting were to both specialties: I think that trials need to continue to determine whether PFO closure is beneficial to carefully selected stroke patients. In the meantime, given the data that we have from the CLOSURE I trial, it is impossible to recommend PFO closure as a routine matter of course, and we should not be closing anybody except in the context of a clinical trial. The burden of proof is now on the devices and the people who close these PFOs to show that it works.

How do you convince your neurologist colleagues that, despite the unfavorable results of CLOSURE I, they still need to refer patients to the two clinical trials presently enrolling patients: REDUCE and RESPECT (AGA Medical Corporation, Plymouth, MN)?

Dr. Kasner: There are several things that neurologists should keep in mind. First, CLOSURE I was a single trial, and we seldom make decisions in medicine based on a single trial. The REDUCE and RESPECT trials are both enrolling patients, and we need both studies completed to properly evaluate this procedure. Second, there are potentially very important issues of patient selection in the CLOSURE I trial. One issue is that CLOSURE I included patients who did not have a verified stroke on magnetic resonance imaging or other means. If these patients did not clearly have a cerebral embolic event in the first place, then closing the PFO is probably not particularly important, and those patients were also very unlikely to have a stroke in the future. It also seems likely that some patients in CLOSURE I had

strokes due to other causes and, again, PFO closure may have been irrelevant for those patients. Therefore, both of these groups of patients do not really inform us about how to treat the cryptogenic stroke population.

There were also important device-specific considerations. Many of the strokes that occurred in the device arm of the CLOSURE I trial appeared to be related to the device itself, including strokes related to clots forming on the device or irregular heart rhythms that occurred as a result of the device placement. It is possible that a safer device might tip the balance in favor of PFO closure, but we do not know that yet. This is all the more reason to say to neurologists, "You should refer these patients for participation in trials," and to say to cardiologists, "You shouldn't be closing PFOs with the tools that you have unless those tools are proven in the trial." We are still in a state of what we call *clinical equipoise*, in which we do not know the answers to these issues, and the only way to answer these questions is to continue to randomize patients in clinical trials.

Before the CLOSURE I results came out, was it still challenging getting neurologists to refer patients for these PFO studies?

Dr. Kasner: Yes. Before CLOSURE I, many patients with stroke and PFO were referred directly to invasive cardiologists to fix the "hole" in the heart. Now, I think neurologists need to step back and first ask themselves, "Am I convinced that the patient has no other good explanation for their stroke other than the PFO?" and "Have I really looked extensively at all potential explanations?" If they have really looked hard and have not found any other cause for the stroke and they attribute it to the PFO, their next step should not be referring the patient to an invasive cardiologist or bailing out and saying "just take an aspirin and you'll be fine." They should be telling the patient that they have had a stroke, that they have a PFO, we do not know what the best therapy is, and they should see somebody at X institution who is investigating whether there is an effective treatment for PFOs.

Has the CLOSURE I study actually made it easier to enroll patients now?

Dr. Kasner: Well, we don't know yet. Part of the reason we are in limbo right now is because CLOSURE I was announced at AHA in November, but it has not been published. I think many neurologists and cardiologists are waiting to see the final publication. With the full publication of the study results, we will get a more detailed look at the findings than just the 10-minute snapshot of the initial presentation—we will have a chance to digest it and try to decide what it means. I think the results from AHA were fairly clear, but I was there and able to see the presentation. Others, who were not there, may have read about the results of the trial in a news brief somewhere and may not have a chance to think critically about the implications of the trial.

If the RESPECT trial produces results similar to CLOSURE I, what impact do you think that will have on enrollment for REDUCE?

Dr. Kasner: Certainly, that would be another nail in the coffin for PFO closure, but it depends on exactly what those results show. If RESPECT also shows no difference between PFO closure and medical therapy (and the event rates are very low in both groups, the groups are well matched, etc.), then maybe we shouldn't be treating these patients at all. However, if it turns out, as in the CLOSURE I trial, that a substantial proportion of the strokes that occur in the device closure arm are attributable to the device itself, it then becomes even harder to justify PFO closure in practice, or even in trials, unless there is good evidence that any new device being studied (or device being studied in an ongoing trial) has a markedly better safety profile, particularly with respect to causing clots or causing atrial fibrillation.

By the time that the RESPECT data are presented, the REDUCE trial should have enrolled a substantial enough number of patients to have some idea about device-related complications and atrial fibrillation. If the numbers look very good in the GORE REDUCE trial, and they do not look so good in RESPECT (and didn't look so good in CLOSURE I), then there is still room for moving forward in trying to answer this question.

Do you know if the standard of care of the PFO cryptogenic stroke patients in the United States differs from that in Europe or Canada?

Dr. Kasner: Somewhat. In the United States, where we are predominantly a fee-for-service system, there is an undeniable motivation for doing procedures. In systems where there is less financial motivation, there is less pressure to do these procedures.

In Europe, there appears to be much less PFO closure off-label, although it varies from country to country and is somewhat based on their economic models. In Canada, from what I understand, PFOs are rarely (if ever) closed outside of a clinical trial because it is just not supported in practice or guidelines.

For neurologists, there are several possible impediments to the use of PFO repair for patients with cryptogenic stroke, including, as you have already mentioned, a lack of convincing controlled data and difficulty obtaining coverage for an off-label indication. In your mind, would a positive finding in the REDUCE trial showing benefit of Helex over best medical therapy be enough to encourage most neurologists to refer patients for repair?

Dr. Kasner: I think it depends on how positive the REDUCE trial is, and relates back to the previous question about RESPECT. We already know that CLOSURE I showed no benefit for closing PFOs using the NMT device. If RESPECT also showed no benefit, but REDUCE does show a benefit, the first response will naturally be skeptical, that REDUCE is only one of three trials and that it is a fluke. We would then have to go back and again try to dissect these trials in detail. If RESPECT, which appears to be a very well-designed trial, shows no benefit and the results cannot be explained by device complications, then there is going to be a fair amount of skepticism about this procedure. However, these scenarios are difficult to foresee unless we see what the data actually show and what explanations we can come up with for why there are differences among the trials. Of course, if REDUCE is a slam dunk—showing a dramatic benefit to PFO closure with a low risk from device implantation—it will change clinical practice regardless of the other trial results.

There are also one or two trials going on in Europe, the status of which I do not know very much about. These will also add to the overall body of literature and add to our understanding of the efficacy and safety of PFO closure.

How would you weigh the risks and benefits of medical therapy versus interventional treatment for secondary stroke prevention in the PFO patient?

Dr. Kasner: That is what we are still trying to figure out. It appears that the risk of stroke on medical therapy is relatively low, probably in the range of 1.5% to 2% per year. That is pretty low and, in the short-term, could be hard to beat.

On the other hand, we are talking about a population of patients who are generally young (some of them in their teens, 20s, or 30s). So, a 1% or 2% annual risk over the next 30 years could be very frightening if the numbers are really that high, although we do not have much long-term data, and that may be an overestimate. Nevertheless, cutting that risk in half would be a very meaningful benefit.

One of the advantages of the REDUCE trial design is that it follows patients for up to 5 years, so we should have a longer view than the other trials. ■