# PFO in Cryptogenic Stroke Patients

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

**A Q&A with Scott Kasner, MD**

***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 patent foreman ovale (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 may have potentially changed a little bit in November with the announcement of the CLOSURE I 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 cardiologists were recommending closure of the PFO, despite the fact that there is no device approved for PFO closure or for stroke prevention.

In November, the results of the CLOSURE I trial (sponsored by NMT Medical, Inc., Boston, MA) were announced which showed that (in their trial) PFO closure was no better than medical therapy. There are a number of flaws with the CLOSURE I trial, which I can address, but the study appears to have produced two very different results. Among neurologists, many basically said, "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 cardiologists there appears to have been a very different reaction focusing 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 still go on to try to address whether PFO closure is beneficial to 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 is 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 issues of patient selection in the CLOSURE I trial, mainly that the

study included patients who did not have a verified stroke on magnetic resonance imaging or other means. And therefore, many of those patients may never have gone on to have another stroke, so they are not really fully representative of the cryptogenic stroke population.

There were also important device considerations in that many of the strokes that occurred in the device arm of the CLOSURE trial, meaning the patients who had their PFO closed with an NMT STARFlex device, had strokes related to clots or irregular heart rhythms that occurred as a result of the device. So a safer device, might tip the balance in favor of a 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 consideration of trials." And again, all the more reason for cardiologists to say, "You shouldn't be doing this 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.

***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 were referred directly to invasive cardiologists to fix the "hole" in the heart. Now, I think neurologists need 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 explanation and they attribute it to the PFO, their next step should not be referring the patient to an invasive cardiologist or just bailing out and saying "just take an aspirin and you'll be fine." Their next step should be to tell the patient that they have had a stroke, that they have this 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 are waiting to see the final publication to determine if the published results are the same as those presented in November. With the publication of the study results, we will get a more detailed look at the findings than just the 10 or 12 minutes of the initial presentation—we will have a chance to digest it and think about 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 read about the results of the trial in a news brief somewhere and may not have a chance to really think 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 a little bit on what the results show. If the results from RESPECT also show 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. However, if it turns out that, as in the CLOSURE I trial, a substantial proportion of the strokes that occur in the device closure arm are attributable to the device itself, it becomes 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 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), 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 of a fee-for-service system, there is less demand to do procedures.

In Europe, there appears to be substantially 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, the PFOs in these patients are rarely closed outside of a clinical trial because it is just not supported in practice.

***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 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. If RESPECT, which looks like a very good trial, shows differences and the results cannot be explained by device complications, I think 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 is a difference between the two trials. Of course, if REDUCE is a slam dunk—showing a dramatic benefit to PFO closure with a low risk from the device implantation—then it will change clinical practice, regardless of other trial results.

There are also one or two trials going on in Europe, the status of which I do not know 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:** I think that is what we are still trying to figure out. It does appear 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 who have a stroke due to a PFO (some of them in their teens, 20s, or 30s). So, a 1% or 2% risk over the next 30 years is really substantial if the numbers are really that high. Cutting that risk in half would be a very substantial benefit.

One of the advantages I think of this design is that it follows patients for up to 5 years, so we will have a little bit of a longer view than we have from the other trials.

***At the 2010 ISC, the big story was the results from the CREST, the NIH funded study comparing carotid stenting with carotid endarterectomy. Has CREST impacted the neurology referral patterns for carotid ischemic stroke?***

**Dr. Kasner:** Definitely, and that's still a work in progress, too, because all the European trials showed that carotid stenting was inferior to surgery for most patients, CREST says they are the same, the meta analyses say that endarterectomy is still

better, and the debate rages on.

Overall, I think it has made neurologists and everybody else feel more comfortable with stenting as an alternative, at least in some circumstances. And I think it leaves open the opportunity to individualize patients depending on their perceived surgical and stenting risks.

I would add one quick side comment about the ISC. Probably the most interesting study presented were the results of the Carotid Occlusion Surgery Study (COSS) presented by William Powers, which is a trial of surgical bypass for patients with a carotid occlusion in their neck where you can't do endarterectomy or stenting. Surgeons can do a bypass procedure: they take an artery from the surface of the scalp, basically drill a hole in the head and attach it to an artery inside the brain. And this was done in mass quantities back in the '70s until a trial published around 1985 showed it wasn't worthwhile.

It kind of made a comeback because of patient selection issues and a bunch of technological issues, but the bottom line is that it didn't work—that bypass procedure was still no better than medical therapy and we really shouldn't be doing it. And that didn't get a lot of press because it was a negative trial, but this was a long awaited trial that's been going on for a decade.

***How has the standard of care for ischemic stroke in the acute setting changed in the past 10 years?***

**Dr. Kasner:** Intravenous TPA is still the standard and in 2008 the ECASS III trial told us that we could treat patients not just until the first 3 hours after onset of symptoms, but also up to 4-1/2 hours, although with a few more selection criteria perhaps.

In addition, the endovascular therapies, such as catheter directed thrombolysis and the Penumbra and Merci mechanical thrombectomy devices, have really exploded, not because new data has come across (because, in fact, we still have surprisingly little data about intra-arterial therapy), but because the number of people who were able to do it has multiplied so much that it's becoming much more commonly used.

I would say these endovascular treatments are still not the standard of care, per se, because they are available in limited centers and we don't have a lot of data to really guide us on which patients are most likely to benefit or which patients are most likely to harm, but it's nice to have it as a tool for treating selected patients in the right circumstances.

***And how about in the hemorrhagic stroke area, has there been much development?***

**Dr. Kasner:** It's frustrating. We've been trying a lot of different strategies over the years, like aggressive blood pressure lowering, factor VII as a procoagulant to try to stop bleeding, various things like that. And none of them have ever clearly been shown to be effective in randomized trials. We've had some hints of efficacy but nothing really compelling. The one thing that has become clear is, if you see these patients who come with a hemorrhage and you write them off as being unsalvageable, and designate them as DNR, then they are obviously going to die. If you try to support them aggressively, even though we don't know specifically what it is that we're doing, but blood pressure support, ICU support, airway support, fluid support, complication support, et cetera, we can substantially reduce mortality in these patients.

So the one thing we know is not treating them is bad, treating them aggressively can save their lives, but the recipe for success is still a mystery. ■

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