Finally, Success Reducing Recurrent Stroke With PFO Closure

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PRAGUE, Czech Republic — Two new clinical trials showing a reduction in recurrent strokes with the closure of a patent foramen ovale (PFO) look set to change clinical practice.

The CLOSE trial and the Gore-REDUCE trial were both presented here at the 3rd European Stroke Organisation Conference (ESOC) 2017.

Both trials were conducted in carefully selected stroke patients in whom PFO was suspected to be a cause of their strokes. The Gore-REDUCE trial showed a 77% relative reduction in recurrent strokes with PFO closure, with a number need to treat to prevent one new stroke of just 28 at 2 years. It also showed a 49% relative reduction in new brain infarction on MRI.

The CLOSE trial showed similar results with a 5-year absolute risk reduction for recurrent stroke of 4.9% in the patients undergoing PFO closure, with one stroke avoided at 5 years for every 20 patients treated.

The issue of whether to close a PFO in a patient who has had a stroke without any other known cause has been a long-running subject of debate in the cardiology and neurology communities.

Presenting the Gore-REDUCE trial, Scott Kasner, MD, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, explained that 1 in 4 individuals have a PFO — an opening in the wall between the left and right atria of the heart — but most do not experience any problems as a result. However, it is thought that a PFO could increase the risk for stroke in some individuals by allowing a blood clot to cross from the right to the left atrium and then to the brain.

Dr Scott Kasner

Dr Kasner reported that PFO is twice as common in patients who have experienced a cryptogenic stroke as in the general population, and observational data have suggested a reduction in recurrent stroke rates with PFO closure. Three randomized trials of PFO closure have been conducted, but none have shown a significant reduction in stroke risk in the primary analysis, although meta-analysis has suggested a benefit.

Experts suggested that the reason the two new studies have succeeded in showing significant reductions in recurrent stroke after closing of the PFO was probably selection of the most appropriate patients for inclusion.

"The key is trying to figure out which patients had their first stroke as a result of a PFO vs another cause," Dr Kasner noted. "We had very strong criteria to exclude patients with other cardiac sources, such as AF [atrial fibrillation], underlying coronary disease, or small vessel disease."

The CLOSE trial selected patients believed to at highest risk for a stroke from a PFO based on having a PFO with a large shunt or an atrial septal aneurysm, whereas the Gore-REDUCE trial included patients with a range of different shunt volumes (80% moderate to large shunts).

Commenting on the results for *Medscape Medical News*, Alistair Webb, MD, University of Oxford, United Kingdom, said, "These two studies will have a big impact. This is very exciting data that is expected to change clinical practice.

Dr Alistair Webb

"After years of controversy on whether to close these PFOs in stroke patients, these new trials suggest that by selecting patients carefully there does seem to be a benefit in certain patient groups — those with an atrial septal aneurysm or a moderate to large shunt," Dr Webb noted. "The debate will continue, however, for patients with small shunts and no aneurysm."

Gore-REDUCE

The Gore-REDUCE trial randomly assigned 664 patients from seven countries in a 2:1 ratio to PFO closure with the Gore *Helex* or Gore *Cardioform* (WL Gore & Associates) septal occluders or to antiplatelet therapy alone.

The trial had two co-primary endpoints: freedom from recurrent clinical ischemic stroke through at least 24 months and incidence of new brain infarct (defined as clinical ischemic stroke or silent brain infarct detectable on MRI through 24 months).

Results showed 6 new strokes in the closure group vs 12 in the medical therapy group. Dr Kasner said, "As we had twice as many patients in the closure group, there were a quarter of strokes in this group compared to the medical therapy group."

There was also a significant absolute reduction in new brain infarcts of 5.6% in the closure group.

Table. Gore-REDUCE: Main Results

Endpoint	Closure Group (n = 441)	Medical Group (n = 223)	Hazard Ratio (95% Confidence Interval)	*P* Value
Annualized recurrent stroke rate (per 100 person-years)	0.39	1.70	0.23 (0.09 - 0.62	.001
Brain infarct present, n (%)	22 (5.7)	20 (11.3)	0.51 (0.29 - 0.91)	.024

In terms of safety, the rate of AF was higher in the closure group (6.6% vs 0.4%), and 6 patients (1.4%) had a "serious device adverse event." These were 3 device dislocations, 2 cases of device thrombosis, and 1 aortic dissection.

CLOSE Trial

The CLOSE trial involved 663 cryptogenic stroke patients with a PFO with an atrial septal aneurysm or a large shunt from 32 sites in France and 2 sites in Germany. They were randomly assigned to three different groups: PFO closure, oral anticoagulant therapy, or antiplatelet therapy. Mean follow-up was 5 years.

Results were presented by Jean-Louis Mas, MD, University of Paris Descartes, France.

Dr Jean-Louis Mas

In the comparison between PFO closure and antiplatelet therapy, results showed 4 recurrent strokes in the antiplatelet group vs none in the closure group (hazard ratio, 0.03; 95% confidence interval [CI], 0 - 0.25; *P* < .001).

In terms of safety, as in the Gore-REDUCE trial there was an increase in AF in the closure group (4.6% vs 0.9%; *P* = .02). Major procedural complications occurred in 14 patients (5.9%) of the closure group. These were AF (n = 9), atrial flutter (n = 1), supraventricular tachycardia (n = 2), air embolism (n = 1), and hyperthermia (n = 1).

In the comparison of oral anticoagulants with antiplatelet therapy, there were 7 strokes in the antiplatelet group vs 3 in the anticoagulant therapy group, a nonsignificant difference (hazard ratio, 0.43; 95% CI, 0.1 - 1.45; *P* = .17). Major bleeding occurred in 5.4% of the oral anticoagulant group vs 2.3% of the antiplatelet group, again a nonsignificant difference (*P* = .18).

One interesting observation in the CLOSE trial was that the risk for recurrent stroke was higher in patients with PFO and an atrial septal aneurysm (2%) than in those with a large shunt (0.5%).

"These data suggest that patients with a PFO and an atrial septal aneurysm may be at higher risk of recurrent stroke, and may therefore be the top priority group to target for PFO closure," Professor Mas commented. "But we can't answer this from this study alone. We need more data."

Changing Practice

Other experts were also excited about the results.

"These are two trials will change practice," chair of the ESOC 2017 meeting, Martin Dichgans, MD, University of Munich, Germany, told *Medscape Medical News*. "They are very reassuring. We will now be much more in favor of closing a PFO, especially when there is a large shunt or atrial septal aneurysm.

"But we need to look more carefully at the data. In the following months discussions that will come from these data will tell us where to go," he added.

Stephen Davis, MD, professor of neurology at University of Melbourne, Australia, added: "This is the first time anyone has shown a reduction in recurrent stroke from closing a PFO in a primary endpoint of a trial. This may be in part because of better procedural excellence. We do need to wait for the details — we're still not sure about the size of PFO — but as a whole, this moves the field forward significantly."

Andrew Demchuk, MD, University of Calgary, Alberta, Canada, commented: "We already knew from the meta-analysis of the previous trials that there was something there in the data, but these two new trials now give us strong evidence of benefit."

He stressed the importance of careful patient selection for the procedure. "These PFO strokes are much more likely to be seen in younger patients who don't have underlying coronary or embolic conditions. In these trials the average age was mid-40s. We would generally consider a PFO in a young patient with a stroke if we can't find any other cause. Now we have to really pay close attention to this."

But Dr Demchuk added that many details need to be ironed out.

"Closure doesn't come without any safety concerns — particularly atrial fibrillation. We'll have to pore over that information. There are going to be some areas of discussion over how large the PFO should be to justify closure and the importance of atrial septal aneurysm. Echocardiographers are going to have to standardize how they look for PFOs and how they define a moderate or large shunt. I don't think we all use the same definitions. We're going to have to sort all this out. We need to zero in on the ideal population in whom to do this procedure. That's going to be the subject of ongoing discussion for a while."

The Gore-REDUCE trial was funded by WL Gore & Associates. Dr Kasner received compensation for his time as principal investigator from the sponsor. The CLOSE trial was funded by the French Ministry of Health.

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