The RESPECT Trial

Robert Sommer, MD, and John Rhodes, MD, share their insights on the recently presented data and how this will influence clinical practice.

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What are the significant take-home points regarding the data from the RESPECT trial?

Dr. Sommer: From an absolutely purist point of view, and in a pure statistical analysis, the intent-to-treat design of the RESPECT study, which is how all superiority trials are designed, did not show a statistical benefit of using the Amplatzer device (St. Jude Medical, Inc., St. Paul, MN). The *P* value was .08, and that was with nine strokes in the device arm and 16 strokes in the medical arm. So, had there been one less or one more stroke in either of the groups, statistical significance would have been reached.

The RESPECT study has, in its design, ongoing follow-up until 5 years or until the device receives approval from the Food and Drug Administration. It is very possible that with another year of follow-up, the difference between the two groups could be statistically significant.

That being said, there was also a significant dropout in the medical arm of this group, much more so than in the device arm. I'm not a statistical expert, but by statistical analysis, this made the actual analysis of those numbers difficult to interpret. The original design of the trial had also built in two secondary analyses—an as-treated analysis and a per-protocol analysis—for just such an event, because they knew the trial was going to take a long time. Both of those groups had a strongly positive statistical value favoring device closure. Of course, the caveat to the whole thing is that three of the patients who had strokes in the device group never received a device. So, this does taint the original data somewhat.

If you are performing a statistical analysis, you have to say that so far, the study has been negative. However, it is very difficult to ignore the fact that we not only have outcome analyses that show benefit in the way we treat patients (eg, treatment with the device and medical therapy is better than treatment with medical therapy alone) but also that the study has given us statistical evidence for the first time that there are certain patient characteristics that would lead operators to favor closure over medical therapy. These include those who have experienced peripheral cerebral stroke, those who have a large right-to-left shunt, and those with an atrial septal aneurysm. We had already suspected some of these as being risk factors, but now we actually have the data, which will perhaps allow us to begin to determine which patients would most benefit from the closure procedure versus remaining on antiplatelet therapy.

Dr. Rhodes: I would point out that this is a well-done study with a large patient population, but in an environment with off-label use and other insurance-related issues that potentially make it difficult to enroll and make the enrollment period longer. I think knowing

that, and what the outcomes were, it is a good study that gives us a lot of information about which direction to move toward regarding therapy for patients with cryptogenic stroke.

How do these results compare or contrast with the results of previous trials?

Dr. Sommer: CLOSURE I was the only other original, randomized, prospective trial that was completed. There

St. Jude Medical's RESPECT Trial for PFO Closure Presented at TCT

October 25, 2012—St. Jude Medical, Inc. (St. Paul, MN) announced that results from its RESPECT trial were presented during a late-breaking trial session at the TCT 2012: Transcatheter Cardiovascular Therapeutics conference in Miami, Florida, by John D. Carroll, MD, of the University of Colorado.

According to St. Jude Medical, the data from RESPECT, which is evaluating the company's Amplatzer patent foramen ovale (PFO) occluder in the prevention of recurrent cryptogenic stroke, show that the primary analysis was not statistically significant but trended toward superiority, while additional analyses demonstrated superiority. Stroke risk reduction was observed across the totality of analyses with rates ranging from 46.6% to 72.7%.

"The patient population affected by cryptogenic stroke tends to be relatively young and healthy," commented Dr. Carroll. "PFO closure with the Amplatzer PFO occluder is potentially a novel prevention strategy that may be superior to medications alone. Stroke is a devastating disease, and we now have compelling evidence that shows a 46% to 72% risk reduction in recurrent strokes, which is meaningful for this otherwise healthy patient population with a long life expectancy."

St. Jude Medical stated that the RESPECT trial is a prospective, one-to-one randomized, event-driven study that began in 2003 and enrolled 980 patients at 69 centers across the United States and Canada. All patients in the study experienced a stroke, confirmed by magnetic resonance imaging, which was ruled cryptogenic before participating in the trial.

Participants were randomly assigned to one of two groups. One group received the Amplatzer PFO occluder and medical management, and the other group was treated using the current medical management standard of care alone, which consists of receiving medicine to prevent clots and potentially decrease the risk of another stroke.

Enrollment was stopped when 25 primary events (stroke and all-cause mortality) occurred. All patients were monitored at 1 month, 6 months, 12 months, 18 months, 24 months, and annually thereafter. Patients enrolled in the trial will continue to be followed until a regulatory decision is made by the US Food and Drug Administration (FDA).

St. Jude noted in its announcement that the RESPECT trial's design assumed that both randomization and patient follow-up would be equal between the two arms for the duration of the study. During the trial, a difference in lost-to-follow-up patients between the two arms was observed and therefore, the raw count analysis (the intended primary endpoint analysis) was unduly biased. As a result, AGA Medical Corporation (Plymouth, MN) disclosed to the FDA this unequal bias while still blinded to the primary endpoint data and reiterated that final analysis would include three additional, protocol-specified analyses. AGA Medical, which developed the Amplatzer device and initiated the RESPECT trial, was acquired by St. Jude Medical in October 2010.

The protocol-specified analyses performed on the data included the raw count analysis and three Kaplan-Meier (time-to-event) analyses.

In the intent-to-treat raw count analysis, there was a 46.6% risk reduction of stroke in favor of the device ($P = .131$). However, patients were counted in the arm they were randomized to, regardless of receiving treatment; this assumes a similar study population was maintained in each arm. But because the populations are different, this analysis is no longer valid.

In the intent-to-treat Kaplan-Meier analysis, there was a 50.8% risk reduction of stroke in favor of the device ($P = .089$). The Kaplan-Meier analysis adjusts for any drop out differential between study arms to more accurately compare the two outcomes over time. Patients were included based on the arm they were randomized to, regardless of receiving treatment.

In the per-protocol analysis, there was a 63.4% risk reduction of stroke in favor of the device ($P = .034$). The per-protocol analysis evaluated patients according to whether the study treatment protocol was followed (eg, inclusion/exclusion criteria, medical management protocol, etc.).

In the as-treated analysis, there was a 72.7% risk reduction of stroke in favor of the device ($P = .007$). The as-treated analysis evaluated patients according to whether they actually received the treatment (eg, device or medical therapy only).

are some significant differences between CLOSURE I and RESPECT. The first is that CLOSURE I included transient ischemic attack (TIA) patients, whereas RESPECT only included stroke patients. Second, the devices used are significantly different. The device used in the CLOSURE I study, the StarFlex device (NMT Medical Inc., Boston, MA), is known to have had significantly higher rates of residual shunt, device thrombosis, and atrial arrhythmias, which could potentially add to the stroke risk in this treatment group.

We also know that the Amplatzer patent foramen ovale (PFO) device, used in the RESPECT study, is better on all accounts, based on data from previous randomized comparisons. One of the critiques of the CLOSURE I study was that there was a very significant number of device-related issues in the device-treated arm that led to strokes. Had some of those not occurred (ie, we had a better device), there may have been a more positive outcome.

The other big difference was the study design. CLOSURE I had a specified 2-year follow-up, whereas RESPECT was an event-driven trial that was adaptive to allow for a specific number of events before analysis.

I think it is important to contrast RESPECT against CLOSURE I because there are significant differences between the two studies, which may be why there is a difference in the outcomes.

Dr. Rhodes: I definitely agree. The most important thing about comparing RESPECT to CLOSURE I is that we now have a safer device—a device with a much better profile and a lower risk for atrial fibrillation, thrombus from the device, or residual shunting. That was the most beneficial thing about CLOSURE I.

Another aspect that was interesting about CLOSURE I was that the recurrent event group did not have a tendency to be those with the larger shunts, and this may be due to including patients with TIAs. I think without including TIAs in the RESPECT trial, the study was able to tease out that the larger shunts may actually be a risk factor.

Dr. Sommer: Interestingly, it wasn't statistically significant in CLOSURE I, because it wasn't designed to analyze this. But, if you look at the CLOSURE I data, the larger the baseline shunt, the lower the risk of recurrent stroke in the CLOSURE group. This may mean that they are not related. But, it may also mean that in the patients with smaller defects, which made up approximately 40% of the population in the CLOSURE I trial, the stroke or TIA was related to a different mechanism. And, the patients who really derived benefit were the ones who were more likely to have had a stroke due to a big shunt, which was consistent with RESPECT.

How are these data going to affect clinical practice?

Dr. Rhodes: The impact on clinical practice for neurology and cardiology may be slightly different. It is difficult to know how it will affect practice, but I would hope it results in a more focused interest in finding the right answer for this patient population and continuing to enroll in the ongoing clinical trial, REDUCE. Also, maybe the impact will be to move toward other ways to investigate these patients, such as combining data from various trials to see if there is a patient population that is at higher risk.

Dr. Sommer: In terms of my specific practice, I see a lot of these patients in consultation. I think that one of the things that has changed for us since the RESPECT data came out is that we are much more aggressive in evaluating shunt size in all of the patients that we see. We are now performing transcranial Doppler on everybody to get an idea of how big the shunt is. Based on the RESPECT data, if the shunt is small, there may not be a real difference between whether you treat with aspirin or whether you treat with closure, whereas if the shunt is very large, there may be a benefit to device closure.

Are better or differently designed studies needed?

Dr. Rhodes: Clearly, in some patients with PFO, the defect is pathologic, so looking at other study designs is important. There is the ongoing REDUCE trial, which we are still enrolling. It is an international trial with enrollment in Europe, Canada, England, and the United States. I think the REDUCE trial will help us to answer the question regarding antiplatelet therapy versus device closure. However, the REDUCE trial will be negatively affected if the enrollment is only the lower-risk patient. It is very important for us to realize that there is still equipoise and that we need to enroll these patients right now and not close all of these defects "off label."

Dr. Sommer: I think that is going to be assisted by the fact that insurance issues are complicating the use of off-label devices. For many of these patients, the REDUCE trial may be the only option.

Dr. Rhodes: I just returned from Copenhagen where we had the European investigator meeting for REDUCE, and in the northern European countries, they are randomizing everyone. The only option for stroke patients with PFO is to randomize to the trial. If you fail randomization, and they feel there is an indication to close, they might consider closing it in what the United States would call off-

label. But otherwise, they enroll everybody in the study, or they are not treated with the device.

What are the criticisms of the RESPECT data that need to be addressed?

Dr. Sommer: Well, the RESPECT data in general are excellent. It was a very well-run study. The major issue for somebody reading these results would be that the intent-to-treat analysis led to a result in which a third of the patients who had a stroke in the closure arm never underwent closure. This obviously confounds the results of the study. But, from a statistical point of view, if that aspect of the trial is invalid because of unequal dropout in the two groups, and if the intent-to-treat analysis and per-protocol analyses are not valid either because you affect the randomization and there is potential bias introduced into the study, then potentially none of the outcomes are statistically significant.

When I talk to neurologists and other cardiologists who are skeptical about these outcomes, I like to point out that this is a study that took 8 years to accomplish. The chances that another company is going to invest the tens of millions of dollars that it would take to do another randomized study from scratch is virtually nil at this point. There are some really important data in RESPECT that we need to underscore for the Food and Drug Administration: yes, there is potentially going to be a population of patients with certain definable characteristics that really benefit from this. Maybe, going forward, we will be able to design registries for that high-risk group of patients and compare it historically to the control arms of RESPECT, REDUCE, and CLOSURE I stroke patients. We now have a fair number of patients who have been randomized, and we do have some good data.

Dr. Rhodes: One thing I've noticed that I want to carry into how we're conducting the REDUCE trial is that approximately 25% of the patients who were enrolled in RESPECT had what was considered to be a grade 1 shunt, which means one to nine saline particles, as determined by transesophageal echocardiography. Then, when you looked at the final outcome, a grade 1 shunt was considered closed. It's difficult to think about the fact that 25% of your patients are entered into the trial with a certain amount of shunting considered pathologic, and that same amount of shunting is considered normal in the end. For REDUCE, it may be important for us to avoid enrolling patients with a grade 1 shunt, but we also have to take into consideration the limitations of assessing shunts in this manner.

Dr. Sommer: Just from a common sense approach, it is hard to imagine that patients with a tiny pinhole defect are as likely to have recurrent embolic events as patients with large right-to-left shunts.

Another issue that is making answering some of these questions difficult is that the number of these stroke events is fairly small. There is a pretty low recurrence rate after therapy has been instituted, which means that any trial, by definition, is going to either need a lot of patients or a very long follow-up period. One of the concerns that I have about the REDUCE study is the number of patients who are being enrolled. Based on the preceding two trials, both of which had larger patient populations, one had no statistical difference, and the other one sort of just missed. I wonder whether, based on these data, the REDUCE study should be increasing the number of patients who are being followed or extending the follow-up time. The REDUCE study, as designed, has a 2-year primary endpoint and ongoing follow-up up to 5 years. Perhaps the primary endpoint should be adjusted to a longer period of time. It would be a shame to get through the entire REDUCE trial and end up with another negative outcome, having not used some of the lessons learned from the other trials.

Dr. Rhodes: The other issue in the way that the RESPECT trial was designed is that it included patients in the medical arm who were on warfarin. I think if you're randomizing warfarin as a therapy versus device closure, the real risk/benefit balance is going to be long-term risk of bleeding complications from warfarin rather than recurrent stroke on warfarin. If 25% of your medical arm is on warfarin, that 25% in the follow-up time period that they had may not have had an adverse event of recurrent stroke but would have a significant and well-understood risk of bleeding adverse events in the years to come. So, 25% of your medical arm may be less likely to have the endpoint of recurrent stroke compared to the aspirin or clopidogrel arm.

Dr. Sommer: If you do commit these patients to a life of warfarin therapy, while they may not have very significant bleeding risks in their 30s, 40s, and 50s, by the time they get to be 70 and 80 years of age, they're going to have all the same bleeding risks that other elderly patients have on anticoagulation.

Because of the small number of recurrent events, the long-term follow-up on these patients is really important. We're still hoping to see if we can do a late follow-up study on the CLOSURE I patients to see what's happened to them down the road. Now that some of the immediate complications related to both the procedure and the device fade into the background a bit, we may have a much better idea of what the actual difference is between having a PFO closed and having a PFO open later in life. ■