Perspective on CCSVI: What's Next?

PREMISE trial Principal Investigator Adnan H. Siddiqui, MD, PhD, shares his insights on the key findings of the study and what we should demand from future trials.

What are some of the unique challenges in studying a possible multiple sclerosis (MS) treatment?

Dr. Siddiqui: MS treatment trials are extremely well defined. There are generations of MS neurologists who have focused on this disease for their entire careers and have developed some really good tools to assess the effect of treatment on MS.

For someone who is not an MS specialist—I'm a neurosurgeon and endovascular interventionist, so I'm not an MS expert—it was important for me to partner with physicians who were experts in treating MS and experts in evaluating MS, particularly given the trials. The PREMISE trial was the brainchild of an incredible collaboration among neurology, radiology, and interventional neurosurgery, where we really put our heads together to see what was the best way to study this procedure and disease. We also partnered with psychologists, functional MRI experts, pharmacologists, and biostatisticians to create a great team that was completely engaged in the work without any personal benefit.

Minimal grant support was received, and it went directly to the hospital to recover the costs for these procedures in terms of hospital stay. The hospital was very generous and allowed us to complete the study without charging the patients or recouping the entire cost. The patients were not charged anything, and the physicians were not paid anything.

How would you summarize the design (screening, diagnostics, intervention, follow-up) of the PREMISE trial?

Dr. Siddiqui: The design was a double-blinded, randomized, prospective, sham-controlled trial comparing venous angioplasty versus sham angioplasty of large head and neck veins in patients who had MS and had attributes of chronic cerebrospinal venous insufficiency (CCSVI).

The screening process consisted of a visit with an MS neurology expert, Dr. Bianca Weinstock-Guttman, who determined the diagnosis, degree of disability, and type of MS based on the patient's history. The second part of the screening was to make sure that there were actual lesions on the MRI of the brain that were consistent with the diagnosis evaluated by Dr. Robert Zivadinov. Third, we established the presence of CCSVI based on the Doppler criteria of variability evaluated by Karen Marr, RVT.

If you met all these criteria of active disease, particularly the relapsing-remitting types of these two, and were on some standard form of therapy (other than for natalizumab [Tysabri], which we excluded because it's relatively new and supposedly quite effective), then we screened the patients for additional studies and for the actual intervention.

The diagnostic part included MRI studies, functional MRI studies, Doppler studies, cerebral blood perfusion studies, CT venography studies, a variety of blood work, a variety of quality-of-life assessments, psychometric assays conducted by Dr. Ralph Benedict, clinical examinations, functional assays, sleep assays, and additional assays that have been associated with MS research.

For the intervention, we brought the patients to the hospital for the procedure and sedated them quite heavily before performing a right femoral venous access. Through that access, we obtained an angiogram of the azygous vein, followed by the right internal jugular and then the left internal jugular, to assess if there was evidence of > 50% narrowing on angiography or by intravascular ultrasound.

At that point, we proceeded with randomizing the patient either to sham angioplasty or venous angioplasty. We created a variety of distractions for the patients at that time to confuse them from being able to recognize how they had been randomized. We assessed for the blindedness the next morning, establishing that > 90% of our patients had no idea what was done, confirming that we had a good blinding process.

The follow-up of the trial was a 1-week phone call followed by a 30-day visit with a variety of imaging studies, Doppler studies, and MRI. We also had 3-, 6-, and 12-month follow-ups.

Was the trial in any way affected by the increased scrutiny surrounding CCSVI in recent years (eg, enrollment or progress)?

Dr. Siddiqui: Initially, we had a massive outpouring of interest in enrollment in the trial. The increasing availability of commercial enterprises, however, where venous angioplasty was being offered in both inpatient and outpatient office settings significantly delayed our expected trial enrollment—we initially thought we'd be done within a couple of months, but it ended up taking us more than a year and a half to enroll all the patients.

How did this trial differ from other studies focusing on CCSVI?

Dr. Siddiqui: Compared to other studies that were single-arm, prospective, and nonblinded, this was a double-arm, randomized, sham-controlled, prospective, and double-blinded design, which is about as good a design as you can use to assess for effective therapy. Given the nature of the remarkable results that have been reported in the literature far and wide, we were extremely enthused that we were going to see something quite remarkable.

What were the key findings of PREMISE?

Dr. Siddiqui: The key findings of the PREMISE trial were that the procedure, both sham and true venous angioplasty, could be performed without any major serious adverse events in our limited population of patients. That was our primary endpoint—to establish safety—which we did.

There were a variety of different secondary endpoints. When we looked at the clinical scale in terms of disability, there was no effect from venous angioplasty compared to sham angioplasty. When we looked at MRI-based findings, there were significantly increased new lesions in patients who had venous angioplasty compared to those who had the sham procedure. Finally, looking at the psychometric assessments, there appeared to be no significant difference between the two groups.

The primary finding from our study was that even though the procedure is safe, there appeared to be more MRI-based disease activity in patients who were treated with venous angioplasty than those who were treated with the sham procedure.

Were the results of the trial surprising to you? What stands out most in the findings?

Dr. Siddiqui: Yes, they were very surprising to us. We were expecting a positive study based on everything that we had heard, seen, and read, and we were quite shocked. We had to double, triple, and quadruple check all our data to make sure that we did not miss anything, due to the fact that this was a small study. However, the results are what we have reported, which were increased MRI-based disease activity in those who were treated with venous angioplasty.

I think that is the most important finding from our study. It cautions patients from routinely undergoing this procedure. I do not believe this is an unequivocal establishment of the deleterious effects of venous angioplasty. I think instead, it is the first serious concern in a properly conducted trial that there may be potential harm to this procedure, and this needs to be investigated further in much larger, better-populated studies than the one that we did as a pilot.

What do you anticipate will be the enduring impact of PREMISE on the endovascular treatment of CCSVI?

Dr. Siddiqui: We hope that this will result in a more serious collective effort. I know there are trials that are ongoing or have been initiated in the United States and in Europe, including Dr. Paolo Zamboni's trial in Italy, that are specifically looking at a randomized, double-blinded design to assess if there's promise to the procedure. I think it would be very useful to see what the results of those larger trials are, but I think the enduring effect of PREMISE would be that it has given us pause and caution from blindly following the initial enthusiasm of a relatively simple procedure to cure a very complex disease.

What is needed from future MS/CCSVI trials? What study design elements must be considered?

Dr. Siddiqui: It is critical that future trials be randomized, blinded, and evaluated blinded. That is extremely useful, particularly in a disease as complex and difficult to evaluate as MS.

I believe there is a whole new field that we have been exposed to in light of the work done by CCSVI researchers and led by Dr. Zamboni. We're now starting to seriously look at the veins, particularly those in the head and neck, and the spinal fluid pathways where we're striving to evaluate other aspects of the brain's circulation. I think that is going to open up new avenues of research and intervention in a variety of neurological disorders, hopefully including MS.

PREMISE was a highly thoughtful endeavor to investigate the very interesting association that Dr. Zamboni introduced to us. I am certain that there will be a lot more work that's going to come out of this. We have shown a negative effect, and in my opinion, a negative effect is an

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effect that establishes a relationship. It may not be in the same direction as desired, but it does show an effect from the intervention on the disease, and, therefore, there is an association. Thinking that a simple balloon angioplasty is going to fix something as complex as MS is, at best, naive. ■

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