COAPT at 5 Years: MitraClip Benefits Persist

The COAPT Trial Evaluated the Transcatheter Edge-to-Edge Repair Procedure (TEER) in Symptomatic Heart Failure Patients With Secondary Mitral Regurgitation

CLD talks with Gregg W. Stone, MD, FACC, MSCAI.

Can you describe how mitral regurgitation develops in cardiomyopathy patients?

Mitral regurgitation (MR), particularly secondary MR, which was studied in the COAPT trial, develops in patients with heart failure usually due to left ventricular (LV) dysfunction and dilatation in about 9 out of 10 cases. In the remaining 1 out of 10 cases, the development of secondary MR may be due to a primary left atrial myopathy due to longstanding atrial fibrillation. Usually, however, the development of secondary MR is due to left ventricular dysfunction and dilatation, which geometrically displaces the papillary muscles. Papillary muscles are connected to the cords. The cords are connected to the anterior and posterior mitral leaflets, and when that happens, the cords tether the leaflets, or keep them from closing or coapting. The leaflets normally coapt or approximate. If the leaflets are pulled apart because the LV increased in size, then that causes secondary MR.

These patients were more likely to live longer because of the reduction in their mitral regurgitation.

If you treat these patients effectively with heart failure medications, then that will tend to shrink the ventricle, and the papillary muscles and the cords may help coapt the leaflets again and reduce the amount of MR.

Patients who have cardiomyopathy are routinely undergoing transthoracic echocardiograms for evaluation, usually on at least a yearly, if not bi-yearly basis. MR is one of the standard abnormalities that might appear on a transthoracic echo. Transthoracic echocardiography is the standard technique to assess the severity of MR, although that assessment can be complex. We recommend that hospitals follow the United States American Society of Echocardiography guidelines, which have a published "multi-parametric" approach to diagnosing the severity of MR. Multiple different parameters are measured, including looking at left atrial and LV size, effective regurgitant orifice area, width of the vena contracta, reversal of the pulmonary systolic venous flow pattern, and other such parameters. Collectively adding all the different measurements allows you to arrive at a judgment regarding the severity of the MR, whether mild, moderate, or severe.

What are the challenges in these patients that led to the creation of COAPT trial?

We have known for a long time that patients who develop secondary MR have a worse prognosis. They are more likely to die, more likely require hospitalization for heart failure, and have a worse quality of life. We have never known whether this was a marker of a bad LV, where the LV just keeps dilating and then causes MR, or whether the MR itself, once it occurs, causes additional volume overload of the LV, further worsening the cardiomyopathy and the patient's symptoms, and decreasing forward cardiac output. We didn't know whether fixing the MR might improve the patient outcomes even if the underlying LV dysfunction remained. There have been multiple studies done with surgery to fix secondary MR. Mitral valve surgery is a great procedure to fix primary MR when the problem is the valve itself, such as mitral valve prolapse, Barlow's disease, endocarditis, fibroelastic deficiency, or rheumatic disease. For secondary MR, surgery has never been definitively shown to be helpful and so is not routinely done. Mitral valve surgery is a significant procedure in these patients who are already quite sick. They tend to be elderly, have LV dysfunction, and often have multiple other comorbidities such as renal failure, anemia, and chronic obstructive lung disease. Therefore, the COAPT trial was designed to evaluate a less risky, less-invasive therapy, the MitraClip (Abbott Vascular), which was the first approved transcatheter therapy for transcatheter edge-to-edge repair (TEER). Until the COAPT trial, we did not know whether the MitraClip would help in secondary MR, where the main problem is the underlying LV dysfunction.

Can you tell us more about COAPT and its final results?

COAPT enrolled 614 patients with heart failure and a LV ejection fraction between 20% to 50% (the mean was about 31%), who remained symptomatic despite being tried on all class one-indicated heart failure medications. These patients had also been treated with electrical therapies like cardiac resynchronization therapy and implantable cardiac defibrillators, if that was appropriate, but were still experiencing heart failure symptoms, so they were not doing well. Patients were randomized to either stay on their medical therapy alone or be treated with the MitraClip. They were followed for 2 years, which was the time of the primary endpoint, and then out to 5 years.

The final 5-year results from the COAPT trial were presented at the 2023 American College of Cardiology Scientific Sessions and simultaneously published in the *New England Journal of Medicine*.[1] We found that the success rate of this procedure was high, on the order of around 97%, and it was successful at reducing MR. All the patients had severe MR at baseline that was reduced to moderate, mild, or even less than that in >95% of the patients. It was a durable repair, lasting throughout the 5 years. There were very few complications from the device itself, only 4 complications (1.4%), all within 30 days and none after 30 days. We found that after MR reduction with the MitraClip, patients immediately felt better. Within days to weeks, the curves of the primary endpoint of heart failure hospitalization separated and these patients were less likely to be admitted to the hospital. Their quality of life improved, as measured quantitatively with the Kansas City Cardiomyopathy questionnaire, New York Heart Association, and other measures. Their exercise tolerance improved. Most importantly, over time, patient mortality was decreased. These patients were more likely to live longer because of the reduction in their MR. All of the primary and secondary endpoints were met at 2 years, we followed the patients after 5 years, and found these benefits persisted out to 5 years. There was actually quite a marked improvement in quality of life, freedom from heart failure hospitalization, and survival in these patients. Nonetheless, a lot of patients in both groups still have adverse events because these patients are, on average, about 72 years old and have multiple comorbidities. Almost 70% have renal insufficiency and more than 50% have anemia. About half have had a prior myocardial infarction, percutaneous coronary intervention, coronary artery bypass surgery, chronic obstructive pulmonary disease, and stroke. This is a very sick

group of patients, so they are prone to have events, but all event rates were substantially reduced by the MitraClip without directly affecting the underlying LV. We don't cure patients from heart failure because the LV dysfunction remains, but by getting rid of the secondary manifestation of the extra volume overload of the MR, it increases forward cardiac output, and decreases pulmonary pressures. All of that has favorable long-term effects on both quality of life, freedom from hospitalization, and survival.

What else did we learn from COAPT's 5-year results?

The results we saw at 2 years persisted out to 5 years. There was somewhat of a less magnitude of effect between 2 and 5 years, and this was because of a protocol-specific process where we allowed patients in the control group (medical therapy alone) who had survived to two years, who had the same amount of MR and the same symptoms, to cross over and receive the MitraClip. About half of the patients who survived out to 2 years took advantage of that protocol. Their prognosis was markedly improved from the 2-year period forward, and was actually very similar to if they had received the MitraClip 2 years earlier in the randomized arm. Analyzing by intention to treat actually somewhat decreased the curves spreading over time because we helped the control group.

The important point is that up until that 2-year endpoint, almost half of the control group patients had died. While those control patients who survived still benefited from the MitraClip, they could have benefited a lot earlier and we could have kept more of those patients alive had they been identified earlier and treated earlier. We should look for appropriate patients that are failing medical therapy. There are a lot of such patients and if they are appropriate, they should be treated as early as possible with TEER.

How does the MitraClip work and what is necessary to support patients undergoing these procedures?

In the MitraClip procedure, a catheter is threaded from the femoral vein up into the right atrium. An interatrial septal puncture is done, and then the catheter is passed from the right atrium to the left atrium. The catheter is passed from the left atrium across the mitral valve into the left ventricle, and is then opened. The catheter has fabric-coated grippers to capture the mitral leaflets and clip them together, and a clip is left behind. The MitraClip procedure takes these leaflets that are not coapting anymore because they have been stretched apart, grabs the edges, and clips them together. It makes what we call a butterfly repair, because it looks like a butterfly, or a double orifice repair, and decreases the extent of the MR. In some cases, the MitraClip may eliminate the MR altogether, but in most cases, it will markedly reduce MR. It is a safe procedure in the cath lab, is used in about 800 hospitals, and now that people have experience with it, the MitraClip has a very high success rate. The procedure definitely has a learning curve and requires not only an experienced interventional cardiologist, but an outstanding imaging specialist. It is a team approach to do these procedures. Even before undergoing a MitraClip procedure, patients need a heart team consisting of a heart failure specialist, interventionalist, imaging specialist, and in many cases, a cardiac surgeon to identify the right patients for intervention versus surgery, who meet the appropriate criteria and in whom you can be confident there would be a benefit. These patients need comprehensive care from a heart failure specialist before TEER therapy, best medical therapies to identify the right patients, and then to be referred to either intervention or occasionally surgery. After their treatment, these patients require care from a heart failure program, a valve program, interventional cardiology, cardiac surgery, and excellent imaging.

What are the future plans for study?

There is a second TEER device being studied right now for these types of patients. It has been approved for primary or degenerative MR, and is being compared to the MitraClip for secondary MR. There are other new approaches such as annuloplasty and other transcatheter approaches, and a whole host of transcatheter mitral valve replacement devices have been developed. These devices have the benefits of virtually eliminating MR in almost all cases, but are a little trickier to use, may result in more complications, and require anticoagulation. It remains to be seen whether the additional benefits from transcatheter mitral valve replacement are worth the additional risks.

In addition, there are significant numbers of patients who did not meet the exact inclusion and exclusion criteria for the COAPT trial, so the trial results don't apply to patients who are either sicker than those in COAPT or less sick. For example, we did not study those patients without symptoms who have severe MR or patients who are in cardiogenic shock, are bedridden, or are end stage. We also didn't study patients with moderate MR. It could be that TEER will prevent the progression to severe MR. All of these are open research questions that require their own randomized trials to adequately answer. ■

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Reference

1. Stone GW, Abraham WT, Lindenfeld J, et al; COAPT Investigators. Five-year follow-up after transcatheter repair of secondary mitral regurgitation. *N Engl J Med.* 2023 Jun 1; 388(22): 2037-2048. doi:10.1056/NEJMoa2300213.