EVEREST II: Mitral-clip device noninferior to surgical repair or replacement

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Atlanta, GA (updated) - Much-anticipated results from the Endovascular Valve Edge-to-Edge Repair Study (EVEREST) II show that the novel MitraClip (Abbott) device—a percutaneous version of edge-to-edge mitral-valve repair—may lead to fewer early adverse events than traditional valve repair or replacement, with "noninferior" efficacy out to one year.

The results were presented here during the opening late-breaking clinical-trials session of the American College of Cardiology 2010 Scientific Sessions/i2 Summit. "The MitraClip procedure is an important therapeutic option for selected patients with significant mitral regurgitation, given the demonstrated safety, effectiveness, and clinical benefit," investigators for the trial conclude.

Speaking with heartwire, lead investigator Dr Ted Feldman (Evanston Hospital, IL) characterized the clip not as something that would supplant surgery but as an additional option for patients deemed suitable for this percutaneous approach. "The cases that are most likely to be successful are the ones where the jet of the mitral regurgitation is central and relatively discrete and when there is a flail leaflet, where the gap between the two leaflets is not too great."

During the late-breaking clinical-trials session, Feldman acknowledged that patients in EVEREST II were a highly selected group, but that close attention to appropriate selection is also key for surgical patients.

And in the past, he continued, "many [patients] have been excluded because they are not good candidates for surgery; we have an algorithm now that traditionally only involved medicine, repair, and replacement. And today we have another option."

The MitraClip device emulates the edge-to-edge repair technique pioneered surgically by Dr Ottavio Alfieri, in which the free edge of the anterior mitral-valve leaflet is joined to the posterior leaflet, creating a point of permanent coaptation and a double orifice. With the MitraClip, the device is threaded via the femoral vein to the right atrium and passed into the left atrium via transseptal puncture. The device is then passed through the mitral valve into the left ventricle. When the clip is deployed, it essentially clothes-pegs the free edge of the anterior mitral-valve leaflet to the posterior leaflet, creating a point of permanent coaptation.

Results from earlier studies established the safety and feasibility of the procedure, but EVEREST II is the first trial to directly compare outcomes with the device against the gold standard, surgery, in a randomized trial.

Summiting EVEREST II

In EVEREST II, 279 patients with significant mitral regurgitation (3+ to 4+) were randomized 2:1 to the MitraClip procedure or to surgical repair or replacement at the surgeon's discretion. To be entered in the trial, patients had to be symptomatic or, if asymptomatic, to have documented LV dysfunction. The trial was conducted at 37 centers and included patients with both functional mitral regurgitation (27%) and degenerative mitral regurgitation (73%). Primary end points of the study were major adverse events at 30 days (designed to show superiority) and clinical success rate, defined as freedom from a combination of death, mitral-valve surgery or reoperation for mitral-valve dysfunction, and an improvement of at least two
grades of mitral regurgitation at 12 months (designed to demonstrate noninferiority of the clip device).

As Feldman showed here today, the primary safety end point (a wide-ranging combination of adverse events including death, major stroke, reoperation, urgent/emergent surgery, MI, renal failure, and blood transfusions, among others) in the per-protocol analysis significantly favored the percutaneous procedure at 30 days, with less than 10% of patients experiencing a major adverse event, as compared with 57% of the patients treated surgically (p<0.0001). Need for blood transfusions was the main driver of the safety end point, with a difference of 8.8% vs 53.2%. For the primary efficacy end point in the per-protocol analysis, the overall clinical success rate was numerically higher in the surgery group, at 87.8% compared with 72.4%, but this difference, statistically, met the prespecified noninferiority hypothesis of 31%.

Results followed a similar pattern in the intention-to-treat analysis.

**EVEREST II: Safety and efficacy end points**

<table>
<thead>
<tr>
<th>End point</th>
<th>Clip (%)</th>
<th>Surgery (%)</th>
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<tbody>
<tr>
<td>Safety, per protocol</td>
<td>9.6</td>
<td>57.0</td>
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<tr>
<td>Efficacy, per protocol</td>
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<td>Safety, intention to treat</td>
<td>15</td>
<td>47.9</td>
</tr>
<tr>
<td>Efficacy, intention to treat</td>
<td>66.9</td>
<td>74.2</td>
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All between-group differences statistically significant

Clinical and functional improvement

Individually, the pattern of benefit was similar for the different components of the efficacy end point. While reductions in mitral-regurgitation grade were greater in the surgery group, improvements in left ventricular volume, left ventricular dimension, and NYHA class were similar between the two groups.

"The surgeons correctly note that the clip is not as effective in reducing mitral regurgitation as surgery is—that is, there are more patients at the end of the year who have [grade] 2+ mitral regurgitation with the clip than with surgery," Feldman told heartwire. That is not an acceptable result for a surgeon mindful of the risks of open-heart surgery, he noted.

But from the patient's perspective, mitral-regurgitation grade is not so important, Feldman continued. "The one-year functional outcomes, including NYHA class, SF-36 quality-of-life surveys, and importantly LV dimensions, are favorable in both groups at a year, and this suggests to us that while we have many patient with 2+ mitral regurgitation at one year, they are doing really, really well clinically. The bottom line for the patient, is, they don't care what their mitral-regurgitation grade is if they feel well."

I've had patients who literally could not walk across the road without getting shortness of breath and who go home after this procedure and in less than a week, are doing water aerobics.

For the quality-of-life end point specifically, 12-month improvements were similar between the two groups; the only conspicuous difference between the MitraClip and surgery groups was for the physical quality-of-life scores, which improved significantly within 30 days for the percutaneously treated patients, but, not surprisingly, declined significantly in the surgery group within this early period, "consistent with the recovery from open-heart surgery," ultimately rebounding to catch up to the clip group at one year.
"The most striking thing in our experience is the remarkable clinical response," Feldman commented. "I've had patients who literally could not walk across the road without getting shortness of breath and who go home after this procedure and, in less than a week, are doing water aerobics."

Of note, the EVEREST investigators saw no differences in outcomes between the degenerative mitral-regurgitation patients vs the functional mitral-regurgitation patients. "So etiology, in our growing experience, is less important than valve morphologic features," Feldman said. "We didn't realize this would be so effective in functional mitral-regurgitation patients when we started."

What defines success?
Commenting on the EVEREST II results for heartwire, Dr Craig Smith (Columbia University, New York, NY) predicted, "This is going to be considered banner news at a cardiology meeting, but it's not terribly surprising for sites that have been involved in the trials."

Smith, a surgeon, who said he himself was not involved with EVEREST II—although Columbia was an enrolling center—made the point that Feldman anticipated, that the device was not as good as surgery at reducing mitral regurgitation. But he agreed that the clinical results were "good enough," in his opinion, for the procedure to gain traction in the US, assuming the device is approved. His only concerns centered on the "time-consuming" nature of the procedure and on how the clip repair would stand the test of time. He has personally treated a patient who underwent percutaneous repair with the MitraClip four years ago and upon reoperation, found the clip and surrounding tissue "clogged" and scarred, ruling out surgical repair. One of the claims made repeatedly by investigators in successive MitraClip studies has been that use of the device does not rule out future surgeries. While it may be true that surgery is still an option, says Smith, he questions just how many of these will be eligible for repair after three or four years have passed, leaving replacement-valve surgery the only option.

"Time will tell," he said.

Dr Scott Millikan (Billings Clinic, MT) who discussed the EVEREST II results following Feldman's presentation this morning, congratulated the investigators, calling the clip device "a very important innovation in one of the holy grails of valvular therapy," but he, like Smith, also expressed concern that patients, needing reoperation years later, would be "relegated to replacement, as opposed to repair," due to leaflet deterioration over time.

He also called into question the "definition of success" in EVEREST. Summarizing some of Feldman's charts for the audience, Millikan pointed out that in the clip group at 12 months, over half of the individuals had 2+ to 4+ mitral regurgitation, as compared with only 16% in the surgical group, and one-fifth of patients had 3+ or 4+, as compared with only 3% of the surgical group.

"There are very few surgeons who would leave an operating room with a 2+ mitral regurgitation after an attempted valve repair and feel good about it, and I think there are even fewer cardiologists who would consider sending patients to surgery for 3+ mitral regurgitation and have them return with 2+ insufficiency in one year and be happy," Millikan said.

He, like Smith, questioned the inclusion of blood transfusions in the safety end point. "I think weighting blood transfusion the same as death or stroke just doesn't make sense. If blood transfusions for cardiac surgery are a major adverse event, maybe we should consider radiation exposure similarly."

Rolling with the punch, Feldman replied, saying that his point about radiation was "well-taken."

"In that spirit, I might say that sternotomy could be considered an adverse event as well," Feldman quipped.
In fact, Feldman noted in a morning press conference, even if the surgeon's definition of major bleeding was used instead of all transfusions, the difference in the 30-day safety end point remained "highly statistically significant."

He also suggested that surgeons who are focusing on the transfusion data may be missing a key point—namely, that there were "zeros" in the death, stroke, and urgent-reoperation categories for the clip patients, something not seen for the surgical patients. "The MitraClip procedures is one of the safest procedures we have ever done, not only in interventional cardiology, but in medicine."

As to the point that the improvement in mitral-regurgitation grade was unsatisfactory, Feldman noted that there were several patients in the study who had 3+ mitral regurgitation after initial therapy and were deemed "failures" but in fact did not go on to have surgery. "And that is because clinically they were doing really well."

Moreover, all of the patients who had 2+ mitral regurgitation following the procedure in fact had diminished LV volumes at the end of the year.

Potential for transformation

If approved by the FDA, the clip-based therapy may prove a welcome alternative to surgery in at least some of the more than 250 000 patients diagnosed with significant mitral regurgitation each year in the US. According to statistics presented by Feldman, only 20% of patients with significant mitral regurgitation actually undergo surgery, with most being managed medically. While drugs may help with symptoms, they typically do nothing to help the underlying pathophysiology or disease progression.

To heartwire, Feldman pointed out that the device is already approved for use in Europe, where the learning curve has proved to be relatively steep, with most operators getting "their arms around the basics" in just two or three procedures.