EVEREST II randomized clinical trial: Predictors of mitral valve replacement in de novo surgery or after the MitraClip procedure

Donald Glower, MD,[a] Gorav Ailawadi, MD,[b] Michael Argenziano, MD,[c] Michael Mack, MD,[d] Alfredo Trento, MD,[e] Andrew Wang, MD,[a] D. Scott Lim, MD,[b] William Gray, MD,[c] Paul Grayburn, MD,[d] John Dent, MD,[b] Linda Gillam, MD,[c] Barathi Sethuraman, MD,[f] Ted Feldman, MD,[g] Elyse Foster, MD,[h] Laura Mauri, MD,[i] and Irving Kron, MD,[b] on behalf of the EVEREST II Investigators

Objective: The Endovascular Valve Edge-to-Edge Repair Study (EVEREST II) is a prospective, multicenter, randomized controlled trial comparing percutaneous repair with the MitraClip device to mitral valve (MV) surgery in the treatment of mitral regurgitation. The present study analyzed the patient characteristics and treatment effects on mitral repair versus replacement.

Methods: Of 279 patients enrolled, 80 surgical patients underwent 82 MV operations and 178 underwent an initial MitraClip procedure, of whom 37 underwent a subsequent MV operation within 1 year of their index the MitraClip procedure. A logistic regression model was used to predict MV replacement according to valve pathology, etiology of mitral regurgitation, age, previous cardiac surgery, and treatment group.

Results: The rate of percutaneous or surgical MV repair at 1 year was 89% (158/178) in patients initially receiving the MitraClip device versus 84% (67/80) in the surgical patients ($P = .36$). Surgical repair was performed after the MitraClip procedure in 20 (54%) of 37patients ($P < .001$ vs surgery). In both the MitraClip device and surgery groups, MV replacement was significantly associated with anterior leaflet pathology ($P = .035$). Logistic regression analysis showed that anterior leaflet pathology predicted MV replacement. In 5 (13.5%) of 37 patients undergoing surgery after MitraClip therapy, replacement was performed in part because of MV injury associated with the MitraClip procedure.

Conclusions: These data suggest that anterior leaflet pathology is strongly associated with MV replacement in patients undergoing either de novo MV surgery or surgery after MitraClip therapy. MitraClip therapy has a repair rate similar to surgery through 1 year but also imparts a risk of replacement of a potentially repairable valve. (J Thorac Cardiovasc Surg 2012;143:S60-3)

In patients undergoing surgery for mitral regurgitation (MR), mitral repair has advantages over mitral replacement of improved durability, less anticoagulation, and better preservation of left ventricular function.[1] As mitral repair techniques have improved, some investigators have concluded that nearly all regurgitant mitral valves (MVs) with degenerative disease can and should be repaired.[2] However, large population-based samples have shown MV repair rates of only 50%.[3] Factors proposed to predict MV replacement instead of repair include surgeon factors,[3,4] older patient age,[4] anterior or bileaflet mitral pathology,[4] previous mediastinal radiotherapy,[5] calcification,[4] previous cardiac surgery, and functional etiology of MR.[6] Most of these studies are potentially subject to patient selection bias and problems from retrospective data analysis.

The Endovascular Valve Edge-to-Edge Repair Study (EVEREST II) is a prospective, multicenter, randomized controlled trial comparing the MitraClip system with MV surgery in the treatment of MR.[7,8] Data from the EVEREST II trial were analyzed to meet 4 objectives:

1. To determine whether the overall repair rate is comparable between patients who underwent the MitraClip procedure versus de novo surgery.
2. To determine the specific baseline demographic or valve characteristics that are predictive of MV replacement.
3. To assess the MitraClip procedure effect on the ability to surgically repair the valve.
4. To evaluate the effect of surgeon experience on MV replacement.

From the Duke University Medical Center,[a] Durham, NC; University of Virginia Health System,[b] Charlottesville, Va; Columbia University Medical Center,[c] New York, NY; Baylor University Medical Center,[d] Dallas, Tex; Cedars-Sinai Medical Center,[e] Los Angeles, Calif; Abbott Vascular,[f] Menlo Park, Calif; Evanston Hospital,[g] NorthShore University Health System, Evanston, Ill; University of California,[h] San Francisco, San Francisco, Calif; and Brigham and Women's Hospital,[i] Harvard Clinical Research Institute, Harvard Medical School, Boston, Mass.

Disclosures: Donald Glower, Gorav Ailawadi, Michael Argenziano, Michael Mack, Alfredo Trento, Andrew Wang, D. Scott Lim, William Gray, Paul Grayburn, John Dent, Linda Gillam, Barathi Sethuraman, Ted Feldman, Elyse Foster, Laura Mauri, and Irving Kron have nothing to disclose with regard to commercial support.

Presented at The American Association for Thoracic Surgery Mitral Conclave, New York, New York, May 5-6, 2011.

Received for publication May 15, 2011; revisions received Dec 28, 2011; accepted for publication Jan 16, 2012.

Address for reprints: Donald Glower, MD, Duke University Medical Center, Box 3851, Durham, NC 27710 (E-mail: Glowe001@mc.duke.edu).

0022-5223/$36.00

doi:10.1016/j.jtcvs.2012.01.047

Abbreviations and Acronyms

EVEREST II = Endovascular Valve Edge-to-Edge Repair Study
MV = mitral valve
MR = mitral regurgitation

METHODS

After individual institutional review board approval, 279 patients were enrolled at 37 sites in North America and randomized 2:1 (184 to the MitraClip device and 95 to surgery) in the EVEREST II randomized controlled trial.[9] Patients with functional MR or degenerative MR involving anterior, posterior, or bileaflet disease were eligible for enrollment, and repair and replacement surgery were considered acceptable outcomes of the trial in the surgery group. Before randomization, the surgeons were asked to indicate whether surgical MV repair versus replacement was planned.

A comparison of the overall repair rate between the patients who underwent the MitraClip procedure versus de novo surgery was performed using Fisher's exact test.

Specific baseline demographic or valve characteristics were assessed for association with MV repair versus replacement on univariate analyses and in a multivariate logistic regression model, including the following variables: anterior or bileaflet leaflet pathology, functional etiology of MR, previous cardiac surgery, patient age, and treatment group (MitraClip vs surgery). Three MitraClip patients who were not implanted with a MitraClip device and did not undergo subsequent MV surgery were excluded from the present analysis because they received no treatment (repair or replacement) for MR.

MV injury or difficulty removing the MitraClip device was assessed by retrospectively reviewing the operative notes. To assess surgeon experience, surgeons were asked to provide the number of MV repairs and replacements performed in the year before enrolling patients in the EVEREST II randomized controlled trial.

The baseline characteristics between 2 groups were compared using Fisher's exact test for categorical variables and Student *t* test for continuous variables.

RESULTS

Surgical Results Through 1 Year in MitraClip and Surgery Groups

Of the 279 patients, 178 were randomized and treated in the MitraClip group, and 80 were randomized to the surgery group. The planned surgical repair rate before randomization was 92% for treated patients in both the MitraClip and surgery groups. Through 1 year, 37 (21%) of 178 MitraClip patients underwent subsequent MV surgery, of whom 20 (54%) underwent MV repair. The planned repair rate for the 37 patients who underwent surgery after the MitraClip procedure (92%) was significantly greater than the actual repair rate (54%, $P = .005$). The number of MitraClip devices implanted (17 with no clip, 7 with 1 clip, and 13 with 2 clips) was not associated with MV replacement ($P = .12$). The median interval to MV surgery after the MitraClip procedure for these 37 patients was 41 days, with 28 (76%) of 37 performed within 90 days from the index procedure. As previously reported by Feldman and colleagues,[7] the reason for surgery in these 37 patients was no MitraClip device implanted in 17, MR grade 3+ or 4+ after MitraClip implantation before hospital discharge in 5, MR grade 3+ or 4+ after single leaflet device attachment in 9, and MR grade 3+ or 4+ after MitraClip implantation after hospital discharge despite dual leaflet attachment in 3 and symptoms in 3.

In the de novo surgery group, 67 (84%) of 80 patients underwent MV repair surgery ($P < .001$ vs surgery after MitraClip) through 1 year. In this group, the planned surgical repair rate was 92% ($P = .14$, 84% [67/80] vs 92% [60/67]). Two surgery patients underwent MV replacement as a second operation after the initial repair (Figure 1).

Overall Repair (Percutaneous and Surgical) and Replacement Rates Through 1 Year

Among the 178 patients who underwent the MitraClip procedure in the MitraClip group, 158 (89%) underwent repair, either percutaneous (n = 138) or surgery (n = 20) after the MitraClip procedure, and was not significantly different from the repair rate in the surgery group (67/80 [84%], $P = .36$) through 1 year.

Predictors of MV Repair Versus Replacement

The baseline characteristics of the MitraClip (n = 178) and surgery (n = 80) groups, including age, functional etiology of MR, previous cardiac surgery, and anterior anterior/bileaflet pathology were not significantly different ($P = .47$). When all patients were combined (percutaneous and surgical), the only variable that showed a trend toward a difference between groups was anterior/bileaflet pathology on univariate analysis, with the patients undergoing replacement showing a trend toward a greater incidence of anterior/bileaflet pathology (47% vs 28%, $P = .055$).

Age, functional etiology of MR, previous cardiac surgery, incidence of anterior/bileaflet pathology), and treatment group (MitraClip device vs surgery) were included in a logistic regression model to determine whether any of these variables was associated with MV replacement. Anterior/bileaflet pathology was the only variable significantly associated with MV replacement ($P = .037$). In the present small sample size, the association between MitraClip treatment and MV replacement was not significant ($P = .086$).

Effect of MitraClip Procedure on Ability to Surgically Repair the Valve

Of the 37 patients who underwent surgery after the MitraClip procedure, 15 (41%) underwent replacement when repair was planned before randomization, 19 (51%) underwent repair as planned preprocedurally, 2 (5%) underwent replacement as planned preprocedurally, and the remaining patient (3%) underwent MV repair when replacement was planned (n = 1).