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EXPEDITED REVIEWS

Percutaneous Mitral Valve Repair Using the Edge-to-Edge Technique

Six-Month Results of the EVEREST Phase I Clinical Trial

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OBJECTIVES This study sought to evaluate the clinical results of a percutaneous approach to mitral valve repair for mitral regurgitation (MR).

BACKGROUND A surgical technique approximating the middle scallops of the mitral leaflets to create a double orifice with improved leaflet coaptation was introduced in the early 1990s. Recently, a percutaneous method to create the same type of repair was developed. A trans-septal approach was used to deliver a clip device that grasps the mitral leaflet edges to create the double orifice.

METHODS General anesthesia, fluoroscopy, and echocardiographic guidance are used. A 24-F guide is positioned in the left atrium. The clip is centered over the mitral orifice, passed into the left ventricle, and pulled back to grasp the mitral leaflets. After verification that MR is reduced, the clip is released.

RESULTS Twenty-seven patients had six-month follow-up. Clips were implanted in 24 patients. There were no procedural complications and four 30-day major adverse events: partial clip detachment in three patients, who underwent elective valve surgery, and one patient with post-procedure stroke that resolved at one month. Three additional patients had surgery for unresolved MR, leaving 18 patients free from surgery. In 13 of 14 patients with reduction of MR to ≤2+ after one month, the reduction was maintained at six months.

CONCLUSIONS Percutaneous edge-to-edge mitral valve repair can be performed safely and a reduction in MR can be achieved in a significant proportion of patients to six months. Patients who required subsequent surgery had elective mitral valve repair or intended replacement. (J Am Coll Cardiol 2005;46:2134–40) © 2005 by the American College of Cardiology Foundation

Mitral valve repair is the preferred surgical approach for treatment of severe mitral regurgitation (MR). Surgical outcomes show higher risk for replacement compared with repair (1). A variety of surgical approaches for mitral valve repair are in wide use, including annuloplasty, leaflet repair, and chordal reconstruction. Beginning in 1991, a surgical technique involving approximation of the middle scallops of the anterior and posterior mitral leaflets was described (2–5). This approach, initially used for anterior leaflet prolapse, results in a double-orifice mitral valve and re-establishes leaflet coaptation. Creation of a double-orifice mitral valve has subsequently been used as a surgical mitral valve repair technique for patients suffering from MR caused by leaflet prolapse, secondary regurgitation attributable to ischemia, and left ventricular dilatation with heart failure (6). Recently a percutaneous method for creating the same type of double-orifice repair has been developed (7,8). The trans-septal approach is used to deliver a clip device that can grasp the central mitral leaflet edges to create a double orifice. After extensive testing in animals showed persistence of a double orifice for more than six months, a U.S. Food and Drug Administration Investigational Device Exemption-approved phase I safety and feasibility trial (EVEREST: Endovascular Valve Edge-to-Edge Repair Study) was initiated (7,8). The short-term and six-month results of this trial in 27 patients with moderate-to-severe or severe MR are described.

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Abbreviations and Acronyms
MAE = major adverse event
MR = mitral regurgitation

METHODS

Mitral valve repair device. The MitraClip system uses a clip with a tri-axial catheter system (Evalve Inc., Menlo Park, California). The tip of the outer guide catheter is delivered to the left atrium using a standard trans-septal approach over a guidewire and tapered dilator. The guide catheter is 24-F proximally, and tapers to 22-F at the point where it crosses the atrial septum. A steering knob on the proximal end of the guide catheter allows flexion and lateral movement of the distal tip.

A clip delivery system, with a clip attached to its distal end, is passed through the guide catheter. This system is steerable using a two-knob coaxial system that permits medial-lateral and anterior-posterior steering. The clip delivery system is advanced through the guide catheter into the left atrium and is positioned so that the clip is orthogonal to the three planes of the mitral valve and over the origin of the regurgitant jet.

The clip is a polyester-covered mechanical device with two arms that are opened and closed by control mechanisms on the clip delivery system (Fig. 1). The two arms have an opened span of approximately 2 cm when opened in the grasping position. The width of the clip is 4 mm. On the inner portion of the clip is a U-shaped "gripper" that matches up to each arm and helps to stabilize the leaflets from the atrial aspect as they are captured during closure of the clip arms (Fig. 2). Leaflet tissue is secured between the closed arms and each side of the gripper, and the clip is then closed and locked to effect and maintain coaptation of the two leaflets.

Procedure technique. The procedure is performed under general anesthesia using fluoroscopy and both transesophageal and transthoracic echocardiographic guidance. After trans-septal puncture using standard techniques, heparin is administered to achieve an activated clotting time of 250 s or more. A 0.035-inch guidewire is passed into the left atrium, and the trans-septal apparatus is exchanged for the guide catheter. The guide is positioned in the mid left atrium, de-aired, and flushed. The clip delivery system is introduced into the guide catheter, and the clip is advanced into the left atrial chamber. Using echocardiographic and fluoroscopic guidance, the clip is moved in small iterations until it is centered over the mitral orifice. The arms of the clip are opened and oriented perpendicular to the long axis of the leaflet edges, and then the clip is advanced into the left ventricle just below the mitral leaflet edges. The clip is closed to 120° and pulled back until the mitral leaflets are captured in the arms of the clip. The gripper is then lowered onto the atrial aspect of the leaflets. The clip is partially closed. At this point, achievement of a double-orifice mitral valve, leaflet insertion into the closed clip arms, and the degree of MR can be assessed using Doppler echocardiography. Next, the clip is closed incrementally under real-time echocardiography to optimize the reduction of MR. For the first 10 patients enrolled in the trial, only one clip could be used. Beginning with the 11th patient, a protocol change allowed a second clip to be placed if only partial improvement was achieved with a single clip. If necessary, the clip can be opened, the mitral leaflets released, and the clip repositioned. In the event that the clip must be withdrawn back into the left atrium, the clip arms are everted so that they may be retracted through the mitral apparatus into the left atrium without entangling the chordae tendinea. After adequate reduction of MR is achieved, the clip is released from the clip delivery system and the delivery system and guide catheter are withdrawn. Repeat hemodynamic, angiographic, and echocardiographic assessments are performed. After a clip was placed, patients were treated with aspirin 325 mg daily for 6 months and clopidogrel 75 mg daily for 30 days.

Figure 1. Photograph of the clip attached to the delivery system. The clip is covered with polyester fabric. The two arms are opened and closed by control mechanisms on the clip delivery system. The two arms have an opened span of approximately 2 cm and a width of 4 mm.

Patient selection. Patients were selected for therapy if they met basic criteria for intervention from the American College of Cardiology/American Heart Association Joint Task Force recommendations regarding therapy for valvular heart disease (9). Patients with moderate-to-severe or severe MR who were symptomatic or asymptomatic patients with moderate-to-severe or severe MR with compromised left ventricular function (left ventricular ejection fraction <60% or left ventricular end-systolic dimension >45 mm) were selected (Table 1). A screening echocardiogram was reviewed by a core laboratory (University of California at San Francisco). Mitral regurgitation was graded according to the criteria of the American Society of Echocardiography (10). On the basis of the screening echocardiogram, a minimum of three of six criteria for moderate to severe (3+) or severe (4+) MR were required for entry; at least one of the three had to be quantitative (Table 1). The inclusion criteria included flail segment width <1.5 cm and a regurgitant jet

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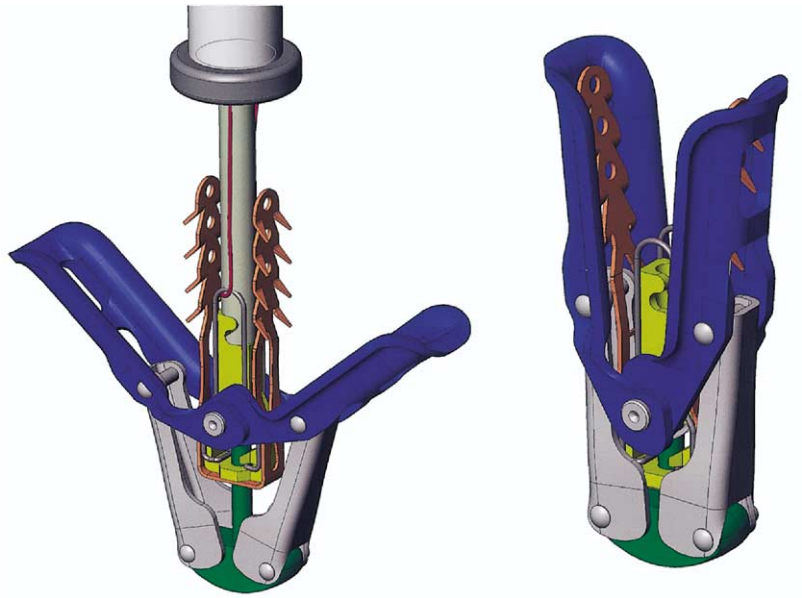

Figure 2. Schematic drawing of the components of the clip. On the inner portion of the clip is a U-shaped gripper that matches up to each arm and helps to stabilize the leaflets from the atrial aspect as they are captured during closure of the clip arms. Leaflet tissue is secured between the closed arms and each side of the gripper, and the clip is then closed and locked to effect and maintain coaptation of the two leaflets.

origin from within the central two-thirds of the line of leaflet coaptation. Specific anatomic measurements were made according to the protocol.

All patients were candidates for mitral valve surgery in the event that it was required for managing potential complications. Patients were excluded if they had recent myocardial infarction within 14 days of the intended percutaneous mitral repair, if any interventional or surgical procedure was performed within 30 days of the index procedure, if they had prior median sternotomy, or if the etiology of MR was rheumatic or infectious. Left ventricular dysfunction with an ejection fraction <30%, left ventricular end-systolic dimension >55 mm, and mitral valve orifice area <4 cm^2 were also exclusion criteria. The protocol was approved by the institutional review boards of the participating centers (Appendix).

Study end points. The primary end point of the study was acute safety at 30 days defined as freedom from death, myocardial infarction, cardiac tamponade, cardiac surgery for failed clip, clip detachment, stroke, or septicemia. The end point was met if the major adverse event (MAE) rate was ≤34.4%, which was based on the event rate in the Society of Thoracic Surgeons cardiac surgical database of 17.0% for mitral valve surgery, with a large margin of error for a relatively small sample size (11).

Table 1. Criteria for Moderate-Severe or Severe MR

Mitral regurgitant severity of moderate-to-severe or severe grade as defined by a minimum of three of the following criteria, one of which must be quantitative (i.e., 4, 5, or 6):

1. Color flow jet may be central and large (>6 cm^2 or >30% of left atrial area) or smaller if eccentric, encircling the left atrium
2. Pulmonary vein flow may show systolic blunting or systolic flow reversal
3. Vena contracta width >0.3 cm measured in the parasternal long-axis view
4. Regurgitant volume of >45 ml/beat
5. Regurgitant fraction >40%
6. Regurgitant orifice area >0.30 cm^2

Secondary safety end points included in-hospital major vascular complications, 30-day and 6-month major bleeding, endocarditis, clip thrombosis, hemolysis, and mitral valve injury. At the six-month time point, cardiac surgery for a failed clip or device was also a secondary safety end point.

Echocardiograms were performed according to a prespecified protocol at baseline, pre-discharge, and at one and six months (Fig. 3). The efficacy goal was defined as MR severity of ≤2+ after clip placement. On the baseline and follow-up (pre-discharge, 30-day, 6-month) echocardiograms, MR was graded based on four of the six criteria used at screening. The vena contracta width and the regurgitant orifice area have not been validated for the double-orifice valve, and thus were eliminated from this analysis. A four-point score was based on the average of four variables graded on a scale of 1 to 4. An overall "expert" grade was also assigned based on integrated core laboratory analysis that considered regurgitant volume, regurgitant fraction, color jet penetration, pulmonary venous flow pattern, and continuous-wave Doppler characteristics of the regurgitant jet, pulmonary artery pressure, and left atrial size using a previously validated approach (12). To evaluate for the potential development of mitral valve stenosis, mitral valve area was measured by planimetry, pressure half-time, and mean gradient. After the procedure, each of the two orifices underwent planimetry at the level of the clip and was summed for the mitral valve area.

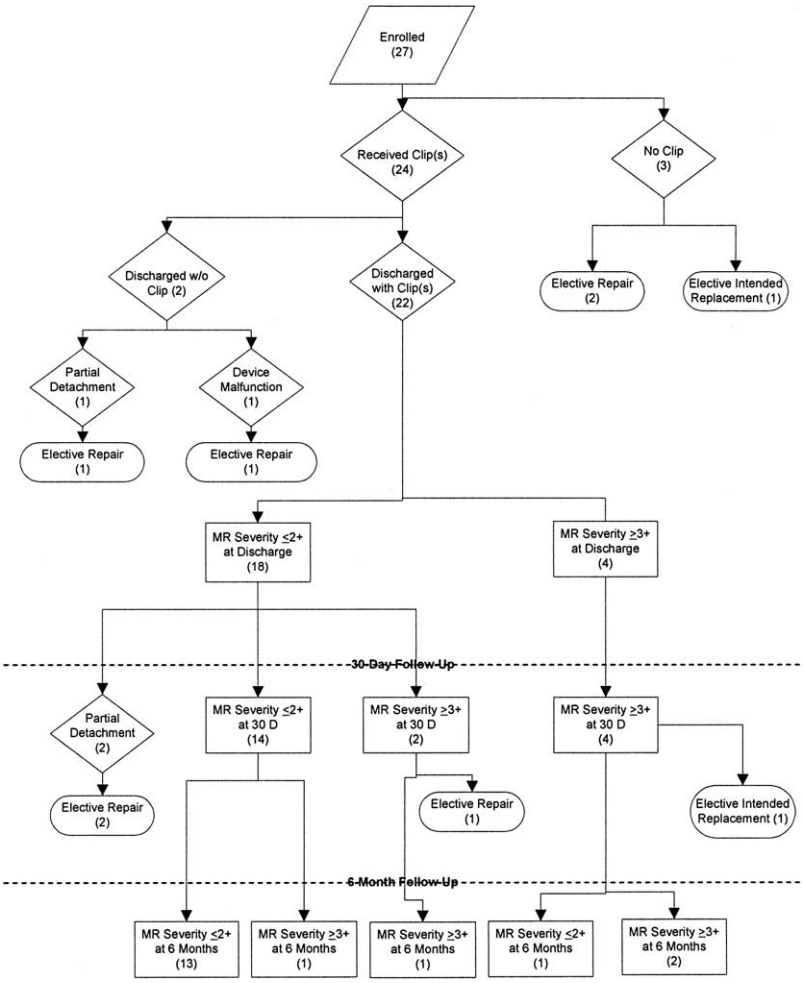

Figure 3. Flow chart showing overall results for the 27 study patients.

RESULTS

Patient characteristics. Clinical features of 27 patients (mean age, 69 ± 12 years) who underwent a percutaneous mitral repair procedure are shown in Table 2: 59% were men, 59% had a history of congestive heart failure, 41% had atrial fibrillation, and 44% were New York Heart Association functional class III or IV. The etiology of MR is shown in Table 3: 93% of patients had degenerative MR and 7% of patients had ischemic MR. Six-month follow-up was available for the 24 patients who received clips.

Table 2. Clinical Features

	%	n
Age (mean), yrs	68.6 ± 12.5	27
Male gender	59%	16
Diabetes mellitus	15%	4
Hypertension	63%	17
COPD	18%	5
History of CHF	59%	16
Atrial fibrillation	41%	11
NYHA functional class III/IV	44%	12

CHF = congestive heart failure; COPD = chronic obstructive pulmonary disease; NYHA = New York Heart Association.

Procedure and hospital results. Figure 3 shows the overall procedure results for all 27 patients. A clip was successfully implanted in 24 of 27 patients. There was one clip implanted in 20 patients, and 4 patients were treated with two clips. The protocol was amended after the first 10 patients to allow placement of two clips if needed. A clip was not implanted in three of the first seven patients treated for inadequate reduction of the degree of MR. The clip and delivery system were uneventfully removed at the time of the attempted percutaneous repair from all three of these patients without any MAE. All three underwent their pre-procedure indicated elective surgery, with valve repair in two and intended valve replacement in one. One of these patients was found to have a cleft between P1 and P2 at surgery. The use of two clips was not an option when these patients were treated. In a fourth patient, the clip was placed

Table 3. Mitral Regurgitation Etiology

Degenerative	25 (93%)
P2 prolapse/flail	14 (56%)
Bi-leaflet prolapse/flail	10 (40%)
A2 prolapse/flail	1 (4%)
Ischemic	2 (7%)

Table 4. In-Hospital Outcomes

ICU/CCU time (h)	48 (0–417)
Mechanical ventilation >24 h	0
New onset of AF	0
Blood product use	1
Access site complications requiring surgery	0
Renal failure or dialysis	0
Post-procedural hospital stay (days)*	2.5 (0.75–16)
Discharged home (without home health care)	27

*2.5 days includes 3 patients who remained in the hospital for elective surgery. For 24 patients who did not undergo surgery during the same admission, post-procedural hospital stay was 1.7 days.
AF = atrial fibrillation; ICU/CCU = intensive care unit/cardiac care unit.

on the leaflets and control of MR was not adequate. It was not possible to re-open the clip. It was thus deployed, and the patient went for elective uneventful surgical mitral valve repair.

Nine procedures were done at one site, eight procedures at one site, three at two sites, and two each at two sites. The average device time defined as the time from guide insertion until clip delivery system removal diminished with experience. For all 27 procedures, the mean device time was 204 ± 116 min. First procedures (six patients) had a mean device time of 227 min, second procedures (six patients) had a mean device time of 363 min (one of these was the first time two clips were placed, with a procedure time of 530 min), and third procedures (four patients) had mean device time of 196 min. For procedures in which one clip was placed, the mean device time was 168 ± 73 min. Two clip cases had a mean device time of 396 ± 145 min. Cases in which no clip was ultimately implanted had a mean device time of 198 ± 19 min. Because clip placement was guided primarily by echocardiography, fluoroscopy was not used continuously during the procedure.

In-hospital outcomes are shown in Table 4. The length-of-stay time includes three patients who went on to have surgery during the initial hospitalization.

Primary end point. The primary end point results are shown in Table 5: 85% of patients were free from 30-day MAEs (95% confidence limits, 71% to 98%). There were no deaths. One patient had a non-embolic stroke associated with post-procedure hypotension, defined as a persistent neurologic deficit of more than 72 h. The symptoms had resolved by the one-month follow-up evaluation. No patient underwent emergency cardiac surgery for a failed clip. Clip detachment from one of the two mitral leaflets occurred in three patients. One of these was detected on the 24-h follow-up echocardiogram and the other two at the 30-day echocardiogram. Clip embolization did not occur in any patient. There were no occurrences of myocardial infarction, cardiac tamponade, or septicemia. As previously described, in one patient after the clip was initially placed, it was determined that MR reduction was not adequate. It was not possible to open the clip, and it was thus deployed. The patient was scheduled for and underwent uneventful mitral valve repair the following day.

Table 5. Primary End Point: 30-Day Major Adverse Events

Freedom from 30-day MAE	85%
Death	0
Permanent stroke	1
Cardiac surgery for failed clip	0
Clip detachment from 1 leaflet	3
Clip embolization	0
Myocardial infarction	0
Cardiac tamponade	0
Septicemia	0
	4/27 (15%)

MAE = major adverse events.

Twenty-two of the 27 patients (82%) were discharged from the hospital with a clip in place (Fig. 4). Four patients with baseline MR severity of 4+ were improved to 3+ at discharge but did not have their MR severity reduced to 2+ or less in the short term per core laboratory assessment. Two patients experienced a recurrence of MR at 30 days, and two patients had partial clip detachment. Thus, at the one-month time point, 14 patients had MR ≤2+, and 13 of 14 maintained this improvement at six months. The mitral valve area by planimetry was 6.4 ± 1.6 cm (2) at baseline and 3.4 ± 1.7 cm (2) at six months, and by pressure half-time was 4.4 ± 0.80 cm (2) at baseline and 2.9 ± 0.83 cm (2) after six months.

Six patients with MR after percutaneous repair underwent surgery (13). The time interval between percutaneous clip deployment and surgical revision ranged from 1 to 133 days. During open surgical revision, the clips were uneventfully removed in all five cases in which the intention was to repair the valve with no limitation in surgical options. One of these patients had been treated with two clips. In the remaining case of surgical revision, there was no attempt to remove the clip from the valve leaflets during intended mitral valve replacement.

Among patients having six-month follow-up transthoracic echocardiograms, color Doppler evidence of atrial septal shunting was present in four, absent in seven, and indeterminate in eight patients.

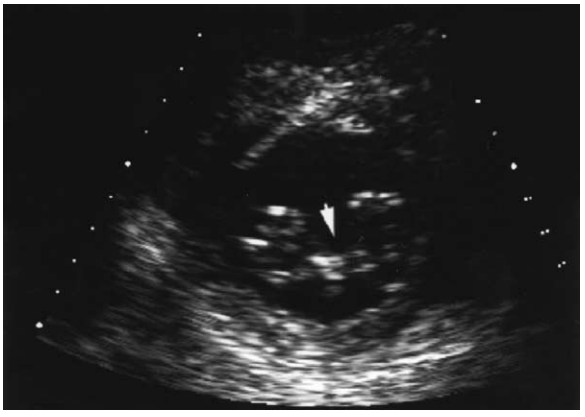

Figure 4. Short axis transthoracic echocardiogram showing a double-orifice mitral valve. The clip can be seen plainly in the center of the double orifice **(arrow)**. The image was obtained from the first patient enrolled in the EVEREST I trial at the 30-day echocardiogram follow-up time point.

Among patients discharged from the hospital with a clip in place, the overall freedom from valve surgery at six months was 18 of 22 (82%).

DISCUSSION

Efficacy. This initial human clinical experience shows that percutaneous edge-to-edge mitral valve repair can be performed safely, that the degree of MR can be reduced significantly, and that the reduction in MR can be sustained at six months.

The clip is deliverable using the trans-septal approach. Coaptation of the anterior and posterior leaflets produces a double-orifice mitral valve and can reduce MR. Combined fluoroscopic and echocardiographic guidance is adequate to orient the device properly in multiple planes so that it can be positioned over the center of the mitral valve orifice and the origin of the MR jet. An echo short-axis view, either transthoracic or transesophageal, is needed to orient the clip perpendicular to the line of leaflet coaptation before grasping. The grasping and capturing mechanisms of the clip were both used successfully. It is possible to grasp and safely release mitral leaflets repeatedly and to reposition the device to achieve optimal control of MR. The gripping mechanism results in stability of the clip on the mitral leaflets both before and after detachment in most patients. It has been established that a tissue bridge forms across the clip in animal models (7). This healing response reproduces the existing surgical approach and has not resulted in significant inflow obstruction in any patient. The surgical approach for edge-to-edge repair has been in use for over a decade, with excellent results in many patients.

Reductions in MR were achieved in most of our patients. In some, the acute result was almost complete resolution of regurgitation, whereas in others it has resulted in a significant improvement in MR: 64% of patients discharged with a clip had MR $\leq$2+ after one month, which increased to 82% when each investigator's first and second procedures were excluded. Although the sample size is small, this finding may support the presence of a learning curve. Importantly, 93% of patients with MR $\leq$2+ at one month had a stable result after six months.

The mean device time from guide catheter insertion until clip delivery system withdrawal ranged from over 200 min for first procedures to a minimum of 70 min in a ninth procedure. One case that involved placement of two clips lasted over 500 min. Despite the duration of the procedures, manipulation of this relatively large system of catheters in the left atrium, mitral orifice, and left ventricle was tolerated remarkably well. Patients were hemodynamically stable throughout the procedure in all cases. No patient required inotropic support for completion of the procedure, and none developed atrial fibrillation, ventricular tachycardia, or acute or delayed pericardial tamponade. The hemodynamic stability observed during this procedure is in marked contrast to the instability of patients undergoing other percutaneous catheter valve procedures such as balloon aortic and balloon mitral valvuloplasty or percutaneous aortic valve replacement. The hemodynamic stability of these patients allows the interventional team to remain focused on steering the clip to the optimal location over the mitral orifice, grasping the leaflets, and ensuring a good result rather than being preoccupied with the management of an unstable patient.

The ability to grasp and remove the clip both during the initial procedure and also during subsequent surgery is an important aspect of the technology. In three patients, multiple grasps were made without adequate control of MR and the device was removed. This did not preclude conventional valve surgical therapy including valve repair in any of these patients. The reversibility of the grasping mechanism of the clip is also critically important. It has been possible to grasp leaflets and assess the degree of improvement in MR, and then reposition the clip if necessary to optimize control of MR. The clip has also been removed during subsequent open surgical procedures. Six patients with MR after percutaneous repair have undergone re-intervention with a time interval between clip deployment and surgery from 1 to 133 days (13). During surgery, the clips were uneventfully removed in all five cases in which the intention was to repair the valve with no limitation in surgical options, including one patient treated with two clips.

Safety. The safety of the device has been clearly shown. The large caliber of the trans-septal puncture has not caused any specific problems. Trans-septal access using devices of this size has been accomplished previously without long-term sequelae with double-balloon mitral valvuloplasty, and more recently with trans-septally delivered percutaneous bypass procedures.

The 24-F femoral venous puncture has been manageable in all of these patients without any special techniques. Manual compression or pneumatic compression using the FemoStop device has been used without any late bleeding. Atrial septal shunting from the trans-septal puncture has not been clinically important in any patients. Most seem to be healed by six months.

Partial clip detachment from one leaflet without embolization occurred in three patients. One of these was detected at the 24-h post-procedure echocardiogram, and the other two were noted at the planned protocol-driven one-month echocardiographic examination. None of these patients had a change in symptoms or a clinical event related to clip detachment from one leaflet. Careful retrospective review of the intraprocedural echocardiograms in these three patients suggests that the angle between the open clip arms and the long axis of the line of mitral coaptation was not perpendicular at the time the leaflets were grasped. Depending on the extent of misalignment, this may result in less leaflet capture on one or both sides of the two clip arms. Based on this experience, it is apparent that careful assessment to confirm a perpendicular orientation of the open clip arms to the long axis of the mitral leaflet line of coaptation is a critical step before grasping the leaflets and closing the

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clip. In addition, proper leaflet insertion into the closed clip arms should be systematically assessed before final clip deployment.

Study limitations. The major limitation of this technique has been the inability to completely obliterate MR in all patients. This article characterizes early experience with a first-in-class device therapy for MR. As seen in Figure 3, 14 of 27 patients had MR reduced to ≤2+ at six months. In four patients, the use of two clips was needed to achieve an adequate reduction in MR. It is clear that the geometry of the regurgitant orifice and the origin of the MR jet are highly variable in position and dimension. The need to increase the width of the apposed segments of coaptation with two-clip devices can be assessed after a single clip has been placed, if the residual jet origin can be clearly seen adjacent to the deployed clip. Similar to surgical edge-to-edge repair, it is possible that creation of a triple-orifice valve will be effective in some patients as well (14). The experience with functional MR in this trial is limited, although initially positive. Additional experience will be required to determine an optimal strategy for the use of multiple clips. The potential to create mitral stenosis must also carefully be evaluated as multiple clips are used. It is notable that mitral stenosis was not created in any of these patients, including the four who received two clips. Experience is limited to 25 patients with degenerative MR and 14 patients with flail leaflets, so the specific features of this etiology that may limit the utility of this first-generation device will also require further experience to define. The experience with functional MR in this trial is limited, although initially positive. The primary reason that experience with functional patients is limited is the protocol mandated exclusion of patients with previous mediastinal surgery. Longer-term follow-up will be required to determine clinical value in different patient populations.

The surgical approach to MR may involve a combination of edge-to-edge repair and annuloplasty. Satisfactory four-year freedom from reoperation rates have been described among patients having edge-to-edge repair without annuloplasty, as well as in patients in whom edge-to-edge repair was used to supplement annuloplasty (15). Some cases of MR will require more than isolated edge-to-edge repair for adequate therapy. This strategy may be modified in patients who are poor candidates for surgery, in whom no mechanical alternatives for mitral repair are available, and the use of a clip repair without annuloplasty may be the patient's only reasonable alternative.

CONCLUSIONS

The safety and feasibility of the technique of percutaneous edge-to-edge mitral valve repair has been shown in this phase I study. Based on an existing surgical approach, the use of the clip seems to accomplish a similar anatomic mitral leaflet repair. Additional follow-up will help clarify the durability and efficacy of this technique. The potential to treat patients who are otherwise surgical candidates, some who may be too high-risk for conventional surgical approaches, and possibly those who are at an earlier point in the natural history of MR, will also require further definition. The risk-benefit profile of this technique in comparison with surgery will be evaluated in an ongoing phase II randomized trial.

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APPENDIX

For a list of the study centers, please see the online version of this article.

Percutaneous Mitral Valve Repair Using the Edge-to-Edge Technique: Six-Month Results of the EVEREST Phase I Clinical Trial

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