

Current Status of Percutaneous Mitral Repair Using the MitraClip System

Growing experience with this first-in-class device suggests it will have an important role in treating patients with mitral regurgitation.

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Mitral regurgitation (MR) is usually caused by either primary left ventricular dysfunction or by degenerative valve disease. Significant MR can lead to progressive left ventricular dysfunction, heart failure, and death. Medical management with diuretics can relieve symptoms temporarily, but MR is ultimately a mechanical problem requiring a mechanical solution. Although mitral valve replacement is effective for eliminating MR, it is well accepted that outcomes are superior if the native valve can be successfully repaired. Surgical mitral valve repair is not a single technique but rather encompasses a variety of techniques often used in combination that attempt to address the specific pathology, at least in degenerative valve disease. One of the reasons why a variety of techniques are combined is to minimize the need for reoperation, which carries a substantially higher risk of morbidity and mortality. In addition, the mitral valve is a complex structure, and MR can result from a variety of mechanisms.

The mitral valve is a semilunar structure with a larger anterior leaflet and smaller posterior leaflet (Figure 1). The posterior leaflet is composed of three scallops: P1, P2, and P3. Corresponding segments of the anterior leaflet are referred to as A1, A2, and A3. The leaflets are contiguous with the saddle-shaped annulus at the base, and the free edges are attached to the papillary muscles through chordae tendineae.

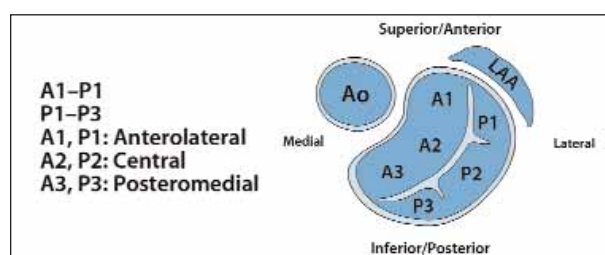


Figure 1. Normal mitral valve anatomy. The mitral valve is a semilunar structure with a larger anterior leaflet and smaller posterior leaflet. The posterior leaflet is composed of three scallops labeled P1, P2, and P3, with corresponding segments of the anterior leaflet labeled A1, A2, and A3. The leaflets are contiguous with the saddle-shaped annulus at the base and the tips are attached to the papillary muscles through chordae tendineae.

degenerate MR involves prolapse or flail of the posterior leaflet most commonly and less commonly the anterior or both leaflets due to myxomatous or fibro-elastic changes of the leaflets and chordae. Surgical techniques for degenerative valve disease continue to evolve. The standard surgical technique for degenerative posterior pathology typically involves resection of the affected P2 segment and placement of a buttressing annular ring. More complex techniques are employed for anterior leaflet

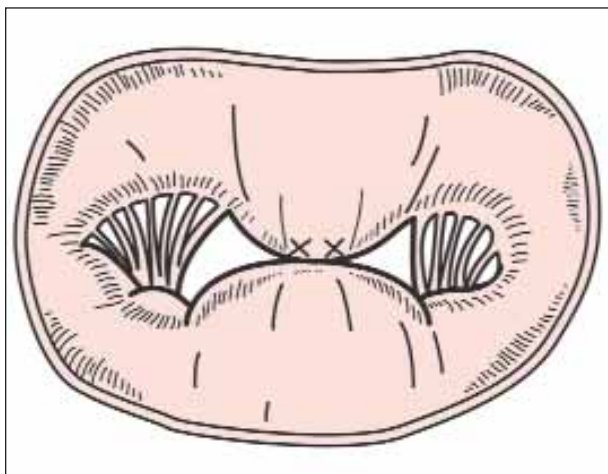


Figure 2. Alfieri edge-to-edge repair. (Reprinted with permission from Kal et al. *Cardiac Interv Today*. 2008;4:39-45.)

pathology, and leaflet-sparing techniques are emerging as a new repair approach. Functional MR results from geometric remodeling of the left ventricle from dilated or ischemic cardiomyopathy. Whereas the leaflets are grossly structurally normal, leaflet tethering and eventual annular dilation lead to mechanical malcoaptation of the leaflets and MR. Surgical repair of functional MR usually consists of an undersized circumferential annular ring to re-establish coaptation. Other pathology (rheumatic and endocarditic changes) is less common and will not be addressed herein.

Although the multitudes of surgical techniques are difficult to reproduce simultaneously percutaneously, an alter-

native repair technique pioneered by Dr. Ottavio R. Alfieri inspired the MitraClip technology. This surgical technique involves the creation of a double-orifice valve by suturing together the central portions of the anterior and posterior leaflets, thereby re-establishing adequate leaflet coaptation and forming a stabilizing tissue bridge (Figure 2).^{1,2} Results with the surgical double-orifice technique appear similar to standard techniques for both short- and long-term outcomes. Although this technique, when used in surgery, typically involves an annular ring, data are available that support similar outcomes without a ring in selected patients.³

DEVICE AND PROCEDURE

The MitraClip system consists of a steerable guiding catheter, a clip delivery system, and the MitraClip device (Figure 3). The MitraClip is composed of a cobalt chromium alloy covered with polyester fabric to promote progressive endothelial encapsulation. The MitraClip has two arms corresponding to each leaflet, and each arm is paired with a gripper with frictional elements. Leaflets are secured between the arm and gripper. Unlike current percutaneous aortic valve replacement programs, the MitraClip procedure is truly percutaneous without need for a cutdown and is performed entirely from femoral venous access. Although fluoroscopy is utilized, the primary imaging modality for guidance is transesophageal echocardiography. General anesthesia is employed for patient comfort. Transseptal access is achieved in the standard fashion but is facilitated and made safe and more precise with transesophageal

echocardiography guidance. Guide position relative to the line of valve closure is important for the procedure, and attention is paid to crossing the septum in a relatively high and posterior position.

The 24-F guiding catheter is advanced from the groin through the septum (22 F at the septum) over a stiff wire, and after the procedure, the septal defect heals in almost all patients. The clip delivery system (along with the MitraClip device) is advanced through the guide into the left atrium and then steered into a position coaxial with the long axis of the ventricle over the MR jet. The open clip arms are aligned perpendicular to the line of valvular coaptation (Figure 4). The clip is then advanced into the ventricle and slowly withdrawn to the level



Figure 3. The MitraClip (top left panel) and clip delivery system (far right panel) (Evalve, Inc., Menlo Park, CA). Mitral leaflets fall onto MitraClip arms (top right panel). Mitral leaflets are secured, and the MitraClip is tightened (bottom left panel). A bio-orifice valve is created, reducing MR, and the MitraClip may be deployed (bottom right panel).

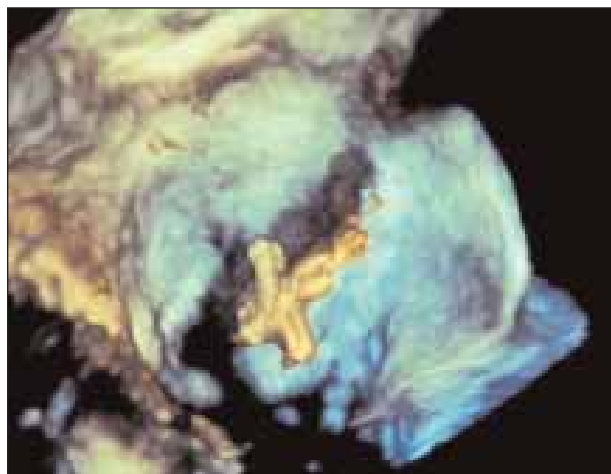


Figure 4. Three-dimensional TEE image of the open MitraClip positioned over the mitral valve.

of the leaflets. The leaflet-grasping technique has evolved such that the clip is pulled back slowly, allowing the leaflets to fall onto the clip arms. The grippers are then lowered, and the arms are partially closed to capture the leaflets. Once a secure leaflet grasp with adequate leaflet tissue between the arms and the gripper has been confirmed, the clip is fully closed to further coapt the leaflets, and the resulting reduction of MR is assessed. The grasp may be released, and the clip can be repositioned repeatedly for optimal positioning. A second clip may be placed if more leaflet coaptation is required for a broader MR jet origin. Clip deployment is not committed until it is released once adequate MR reduction has been confirmed. The delivery system and guide are then withdrawn, and the femoral venous access site can be sealed with a subcutaneous figure-of-eight suture.

CLINICAL EXPERIENCE

The MitraClip has been evaluated through a series of North American studies. To qualify for treatment, patients had to have a clinical indication for mitral valve surgery with at least grade 3 MR, with symptoms or left ventricular ejection fraction (LVEF) < 60% or LV end-systolic dimensions > 40 mm, according to the 2006 ACC/AHA guidelines.⁴ The MR jet had to arise from the central portion of the valve, and there had to be sufficient leaflet tissue available for mechanical coaptation (Figure 5). Patients could not have rheumatic or endocarditic valve pathology, severe LV dysfunction with LVEF < 20%, or severely dilated left ventricle (> 60 mm).

The EVEREST I study was a phase 1 registry to evaluate safety. EVEREST II is the pivotal study randomizing standard surgical risk patients in a 2:1 fashion to MitraClip or open surgical repair or replacement, respectively. The High-Risk

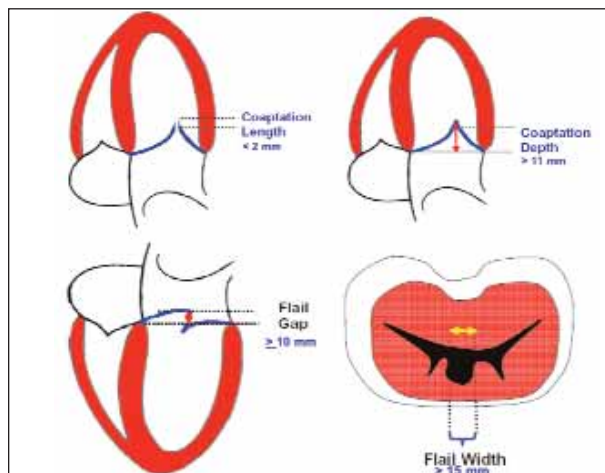


Figure 5. Echocardiographic exclusion criteria for the EVEREST trials.

Registry, an arm of EVEREST II, was a registry of high surgical risk patients. Clinical experience is ongoing in the REALISM continued access registry in the United States and a post-market (CE Mark) observational study in Europe. Results of the EVEREST II randomized trial are expected in 2010. Limited results from EVEREST I and roll-in patients from EVEREST II, as well as 1-year results of the High-Risk Registry, have now been reported at medical conferences and are in the process of publication.

RESULTS REPORTED TO DATE

Results from the initial 107 patients treated in EVEREST I and II (roll in) have been reported.⁵ This initial cohort of patients had a mixture of pathologies, with 79% degenerative and 21% functional etiology. In general, patient characteristics were similar to typical surgical populations, with baseline demographics comparable to that of the STS surgical database (Table 1). Although acute procedural success was defined in the protocol as a reduction of baseline MR grade to $\leq 2+$, the goal of the procedure is to reduce MR to trace to 1+ and to maintain the MR reduction for the long-term, as assessed through an echocardiography independent core lab. Of this initial cohort of 107 patients, 74% had discharge MR grade $\leq 2+$, 10% were aborted without clip implantation due to inability to adequately reduce MR, and 16% had a clip implantation but discharge MR grade was rated > 2+. Of the patients with $\leq 2+$ MR, 77% had < 2+ MR. Although less than perfect, these results are remarkable in that they reflect the early learning curve, with 70% of procedures representing the operator's first to third procedure using the device. Furthermore, early in the protocol, the FDA allowed only a single clip implantation, but, after approval of a second clip, the option to further reduce MR with a second clip was avail-

**TABLE 1. EVEREST PRELIMINARY COHORT
BASELINE CLINICAL CHARACTERISTICS (N = 107)**

	EVEREST Registry	STS Database 2007 Repair
Median age	71 (26–88)	59
≥ age 65	62%	37%
Male gender	62%	59%
Diabetes mellitus	21%	11%
Hypertension	69%	56%
COPD	12%	16%
History CHF	53%	34%
Atrial fibrillation	29%	N/A
Median EF	62%	58%
NYHA III or IV	46%	41%
Previous CABG	19%	9% (previous surgery)

Abbreviations: COPD, chronic obstructive pulmonary disease; CHF, congestive heart failure; EF, ejection fraction; CABG, coronary artery bypass graft surgery; NYHA, New York Heart Association.

able. As with any new technology, results will continue to improve as techniques evolve and the technology expands. Procedural outcomes were acceptable giving the learning curve of the operators, with a 30-day freedom from major adverse events rate of 91% (Table 2). The majority of patients with adequate MR reduction at 30 days have sustained MR reduction through 12 months, regardless of etiology. Mean length of stay was low at 3.2

**TABLE 2. EVEREST PRELIMINARY COHORT
(N = 107) 30-DAY MAJOR ADVERSE EVENTS**

Freedom From Major Adverse Events 91%	
Event	No. of Patients
Death (unrelated to clip)	1
Stroke (> 72 hours)	1
Myocardial infarction	0
Reoperation for failed surgery	1
Nonelective cardiac surgery (transseptal comp.)	2
Renal failure	0
Deep wound infection and septicemia	0
Ventilation > 48 hours	1
Gastrointestinal complication requiring surgery	0
Bleeding requiring transfusion ≥ 2 units	4
Total	10/107 (9%)

days. Clinical benefit was evident through sustained improvement in NYHA class at 1 year for patients with adequate procedural MR reduction (Figure 6).

Midterm follow-up is now available for these patients with survival of 92.8% and freedom from mitral valve surgery of 81.3% at 2 years, similar to that reported with open surgical repair (Figure 7). Partial clip detachment and clip embolization are potential concerns. With

growing experience, partial clip detachment occurs now in < 4% of cases and can be addressed with elective surgical conversion or through stabilization with a second clip. Complete clip embolization has thus far not occurred in > 750 MitraClip devices implanted. Another potential concern involves clip-induced valve scarring, which could prevent successful repair should surgical conversion be required in the long-term. Of patients in this initial cohort who have required surgery after clip implantation, 68% were able to undergo successful repair, with a median follow-up of 2.9 years.⁶

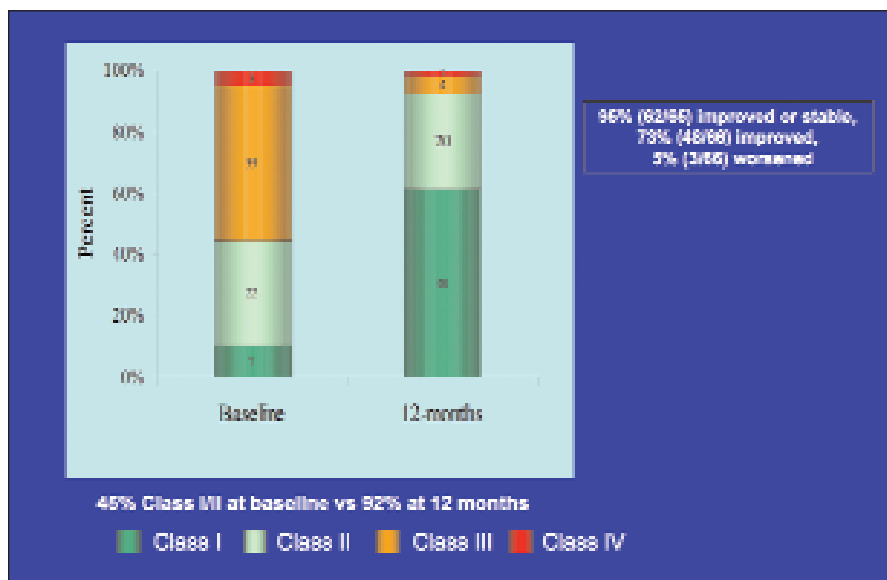


Figure 6. EVEREST preliminary cohort clinical improvement after acute procedural success (APS) (12-months vs baseline; matched data, n = 53). Per protocol-matched pair analysis.

EVIDENCE SUPPORTING PHYSIOLOGIC BENEFIT

In addition to the MR reduction and symptomatic improvement, evidence is now available that MitraClip therapy improves physiologic function through reverse left ventricular (LV) remodeling.⁷ The EVEREST trials were the first studies of any mitral repair technique to include independent core lab echocardiography review,⁸ which affords a unique opportunity to sequentially and objectively track LV functional improvement after percutaneous repair. Compared with preprocedural measurements, LV systolic and diastolic dimensions and volume improved significantly in successfully treated patients (Figure 8). Although symptom improvement is subject to training and reporting bias, objective measures such as LV dimensions strongly suggest a physiologic mechanism facilitating clinical improvement.

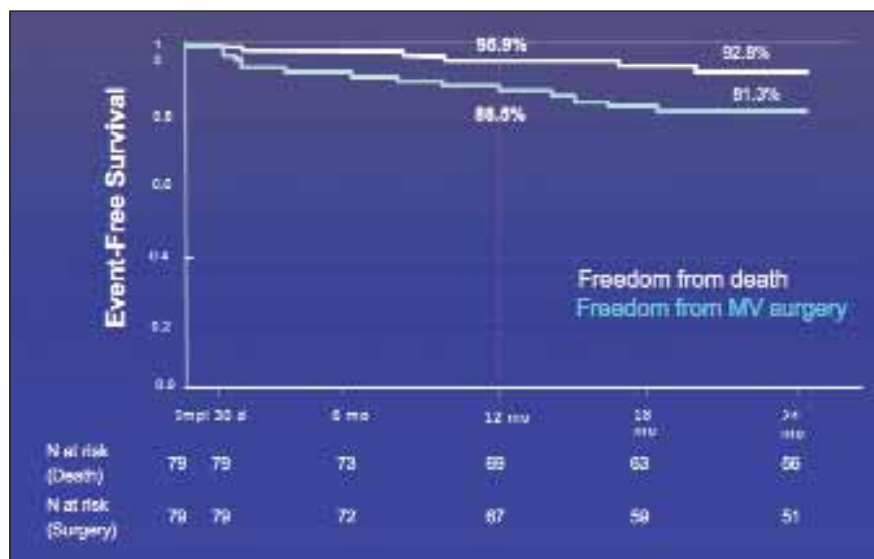


Figure 7. EVEREST preliminary cohort Kaplan-Meier freedom from death and mitral valve surgery. Per protocol analysis.

APPLICATION TO PATIENT SUBGROUPS

Functional MR Population

Functional MR can be defined as MR in the absence of leaflet pathology. This is generally related to leaflet

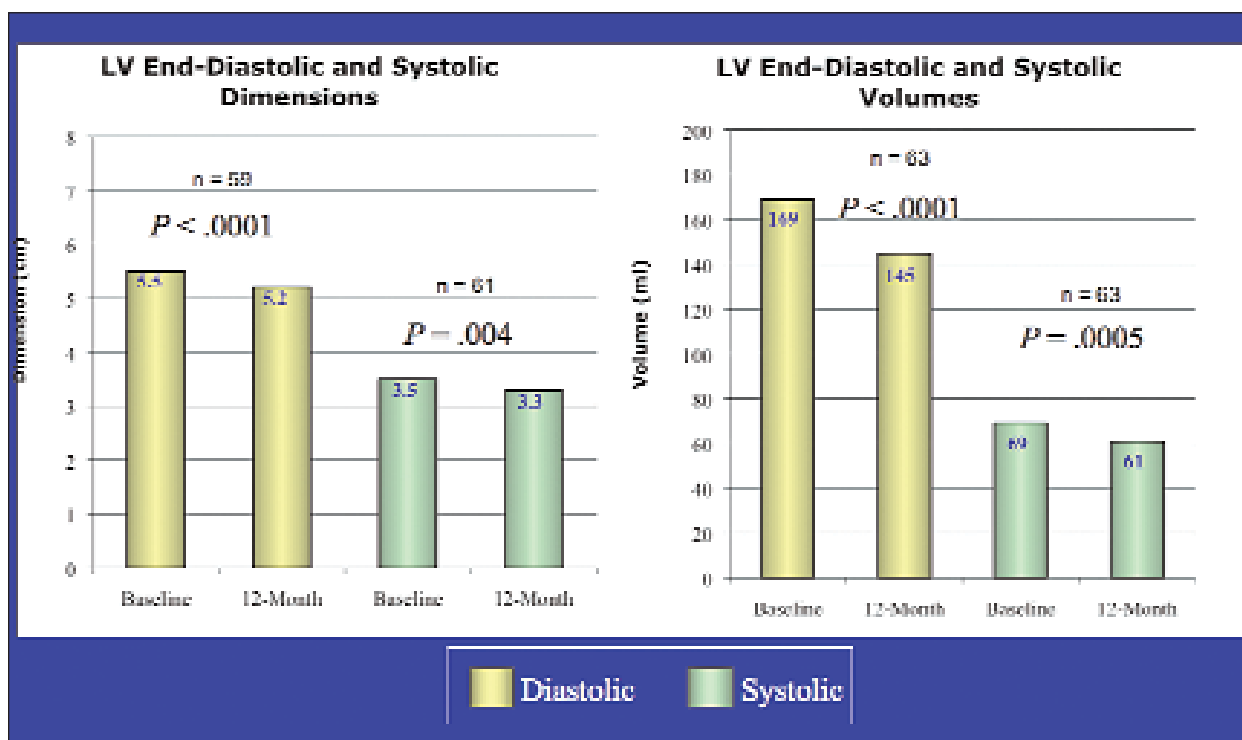


Figure 8. EVEREST preliminary cohort reverse LV remodeling (matched data, APS patients n = 54). All APS patients excluding those who went to mitral valve surgery after clip implantation before 12 months or who have not reached 12-month follow-up. Per protocol-matched pair analysis.

tethering in ischemic disease from previous inferoposterior infarction or papillary muscle displacement and annular enlargement with poor leaflet coaptation in nonischemic dilated cardiomyopathy. Surgical results for functional MR have generally been less favorable compared to those with degenerative disease, mostly related to residual or recurrent MR within the first year.⁹ Thus, the functional MR patient population is an important subgroup, in which new technologies such as the MitraClip are potentially clinically very important. Evidence from the functional cohort of the High-Risk Registry provides intriguing insight (data presented at ACC-i2 2009). Forty-six High-Risk Registry patients had functional MR. Although LV function was relatively preserved, suggesting a select population primarily with ischemic functional MR, this cohort represented a fairly sick population, with > 90% having $\geq$ NYHA functional class III, a high prevalence of major comorbidities, and a high predicted surgical mortality rate. The clip implantation rate was high (98%), and $\leq$ 2+ MR was achieved in 82% at 30 days and maintained in 79% at 1 year. Functional class improved in 80% at 1 year, and the number of hospitalizations for congestive heart failure compared to the previous year was reduced as well. MitraClip therapy appears to be particularly promising for selected patients with functional MR in whom surgical results have been less successful and multiple comorbidities are ubiquitous, making less-invasive therapy even more important.

High-Surgical-Risk Groups

One particularly important application for the MitraClip repair is in the high-risk surgical patient population. The EVEREST High-Risk Registry subgroup included patients with a predicted surgical mortality rate of $\geq$ 12% based on the Society of Thoracic Surgeons (STS) risk calculation or on the study surgeon's judgment if one or more of a number of established high-risk comorbidities were present. Preliminary data on 78 patients from the High-Risk Registry were presented at EuroPCR 2009, but final presentation of the data is awaiting publication. Generally, patients in the High-Risk Registry fared well with clip therapy, showing similar improvement in functional class, a significant reduction in congestive heart failure hospitalizations, and improvement in LV dimensions similar to that of the initial EVEREST cohort. Furthermore, treated patients had lower 30-day mortality than predicted by their STS risk scores.

CONCLUSIONS

The MitraClip system is a first-in-class technology for the percutaneous treatment of MR. It is applicable to

degenerative and functional causes of MR. Early studies have shown adequate procedural success with significant improvement in symptoms and reverse LV remodeling. In high-surgical-risk populations, it appears to be significantly safer than traditional surgery, improves symptoms, and reduces the need for hospitalizations for congestive heart failure. Results of the landmark EVEREST II randomized trial are anticipated in 2010. Worldwide experience continues to grow through enrollment in the ongoing US EVEREST II REALISM Registry and the commercial European experience. ■

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1. Alfieri O, Maisano F, DeBonis M, et al. The edge-to-edge technique in mitral valve repair: a simple solution for complex problems. *J Thorac Cardiovasc Surg.* 2001;122:674-681.
2. Maisano F, Schreuder JJ, Oppizzi M, et al. The double orifice technique as a standardized approach to treat mitral regurgitation due to severe myxomatous disease: surgical technique. *Eur J Cardiothorac Surg.* 2000;17:201-215.
3. Maisano F, Viganò G, Blasio A, et al. Surgical isolated edge-to-edge mitral valve repair without annuloplasty: clinical proof of the principle for an endovascular approach. *EuroInterv.* 2006;2:181-186.
4. Bonow RO, Carabello BA, Chatterjee K, et al. ACC/AHA 2006 guidelines for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on practice guidelines. *Circulation.* 2006;114:450-457.
5. Feldman T, Kar S, Rinaldi M, et al. Percutaneous mitral repair with the MitraClip system: safety and midterm durability in the Initial EVEREST (Endovascular Valve Edge-to-Edge Repair Study) Cohort. *J Am Coll Cardiol.* 2009;54:686-694.
6. Dang NC, Aboudi MS, Sakaguchi T, et al. Surgical revision after percutaneous mitral valve repair with a clip: initial multicenter experience. *Ann Thorac Surg.* 2005;80:2338-2342.
7. Kar S, Hermiller J, Smalling RW, et al. Significant reverse remodeling of the left ventricle one year after percutaneous mitral repair with the MitraClip device. Oral abstract presented at Transcatheter Cardiovascular Therapeutics; October 2007; Washington, DC.
8. Foster E, Wasserman HS, Gray W, et al. Quantitative assessment of severity of mitral regurgitation by serial echocardiography in a multi-center clinical trial of percutaneous mitral valve repair. *Am J Cardiol.* 2007;100:1577-1583.
9. McGee EC, Gillinov AM, Blackstone EH, et al. Recurrent mitral regurgitation after annuloplasty for functional ischemic mitral regurgitation. *J Thorac Cardiovasc Surg.* 2004;128:916-924.