

## Percutaneous mitral valve repair with MitraClip

### MitraClip ile perkütan mitral kapak onarımı

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**Summary** – Over the last decade, several technologies have been developed for percutaneous repair of the mitral valve for patients with severe mitral regurgitation (MR) and at high-risk for the traditional open-heart mitral valve repair or replacement. Among them, MitraClip has emerged as the only clinically safe and effective method for percutaneous mitral valve repair. It is adapted from the surgical technique that was initially described by Dr. Alfieri and his group by placement of a suture approximating the edges of the mitral leaflets at the origin of the MR jet, leading to creation of so-called bow-tie or double orifice with significant reduction in the MR jet. Here, we review the details of the technology, its procedural perspective as well as currently available data for its safety and effectiveness on a case-based report.

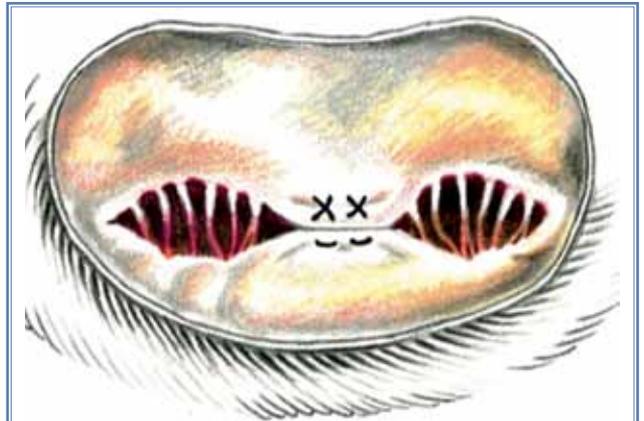
**Özet** – Geçen on yıl içinde, açık kalp ameliyatı ile kapak değişimi veya onarımı yerine, cerrahi riski yüksek olan ve ileri derecede mitral kapak yetersizliği olan hastaların perkütan tedavisi için birçok yöntem geliştirilmiştir. Bu yöntemlerden, MitraClip yöntemi kullanılarak yapılan perkütan mitral kapak onarımı, güvenli ve etkinliği gösterilmiş tek yöntem olarak öne çıkmıştır. Bu yöntem, daha önce Dr. Alfieri ve grubu tarafından, mitral yetersizlik jetinin olduğu yerde mitral kapağın iki kanadının birbirlerine bir dikiş ile birleştirilip çift orifis haline getirilmesinden uyarlanmıştır ve mitral yetersizlik derecesinde belirgin bir azalmaya yol açmaktadır. Bu yazıda, bu yeni teknolojinin ayrıntıları, girişimsel yaklaşımı ve yöntemin uygulanması üzerine güvenilirlik ve etkinlik ile ilgili güncel veriler, olgu sunumları ile birlikte gözden geçirildi.

Percutaneous mitral valve repair using MitraClip (Abbott Laboratories, Abbott Park, Illinois, USA) has emerged as a novel

and successful therapy for treatment of clinically significant mitral regurgitation in a group of so-called high-risk patients for the traditional surgery. Defined by Dr. Alfieri, it was initially developed as a percutaneous variant of the surgical edge-to-edge repair (Fig. 1).<sup>[1-3]</sup> The device has already received CE approval and is increasingly being used for percutaneous repair of both degenerative and functional MR in Europe. Its use has been approved under clinical research registries in the United States of America, but has not received an FDA approval yet.

#### Abbreviations:

CDS Clip delivery system  
MR Mitral regurgitation  
NYHA New York Heart Association  
TEE Transesophageal echocardiography  
TTE Transthoracic echocardiography



**Figure 1.** Double-orifice surgical mitral valve repair with suture. Surgical repair of anterior leaflet prolapse using the edge-to-edge technique by opposing the middle scallops of the anterior and posterior leaflets with a stitch, creating a so-called dual or double orifice. (by courtesy of Bryn Mawr Communications LLC)

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### Device description

The device consists of a 24-Fr steerable guide catheter with a 22-Fr tapering distal end, a separately steerable clip delivery system, and a detachable clip (Fig. 2). Mounted on the distal end of the CDS, the MitraClip is a Dacron-covered mechanical device with two arms that are opened and closed by control mechanisms on the CDS. A steering knob on the proximal end of the guide catheter marked as +/- allows flexion and movement of the distal tip. The two arms of the clip have an opening span of approximately 2 cm when opened in the grasping position (Fig. 3). In the inner portion of the clip are U-shaped “grippers”, which are small, flexible, multipronged friction elements that appose and stabilize tissue from the atrial aspect when captured during closure of the clip arms (Fig. 3). When closed, the clip has an outside diameter of 15 Fr. It is designed to vertically hold up to 8 mm of leaflet height and 4 mm of width. Leaflet tissue is secured between the arms and each side of the grippers, and the clip is then closed and locked to effect and maintain coaptation of the two leaflets (Fig. 3).

Extensive animal experiments using chronic porcine models during the device development showed safety and effectiveness of this therapy by creating



**Figure 3.** Schematic drawing of the components of the clip. In the inner portion of the clip, there 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 arms and each side of the gripper, and the clip is then closed and locked to effect and maintain coaptation of the two leaflets. (by courtesy of Bryn Mawr Communications LLC)



**Figure 2.** MitraClip system components. The valve repair system uses a detachable clip and a triaxial catheter system with a steerable guide catheter and a clip delivery system. (by courtesy of Bryn Mawr Communications LLC)

a double orifice with formation of tissue growth and subsequently tissue bridging over the clip, leading to control of annular dilatation, as well (Fig. 4).<sup>[4,5]</sup>

### Optimal patient selection for MitraClip therapy

Specific morphological features for proper patient selection for this therapy have been previously described (Fig. 5).<sup>[6,7]</sup> It is critically important to evaluate transthoracic echocardiographic parasternal short-axis images with color Doppler interrogation of the MR jet, which is the single most commonly missed part of conventional echo exams that is necessary for evaluation of patients for this therapy. Adequate evaluation includes assessment of the leaflet coaptation length, the flail width, the flail gap, and the absence of leaflet calcification at the potential point of clip attachment, along with careful scanning of the mitral funnel with color Doppler interrogation in the parasternal short-axis view to be sure that the origin of the MR jet is central, and ideally, relatively discrete, originating from within the central two-thirds of the line of leaflet coaptation (Fig. 6). It is also very important to exclude any possible rheumatic valvular disease during this examination to avoid iatrogenic creation of mitral valve stenosis.

### Procedural technique

The procedure requires a dedicated team of physicians, including an interventional physician, a skilled echocardiographer, and an anesthesiologist all working together during the procedure. To achieve an opti-



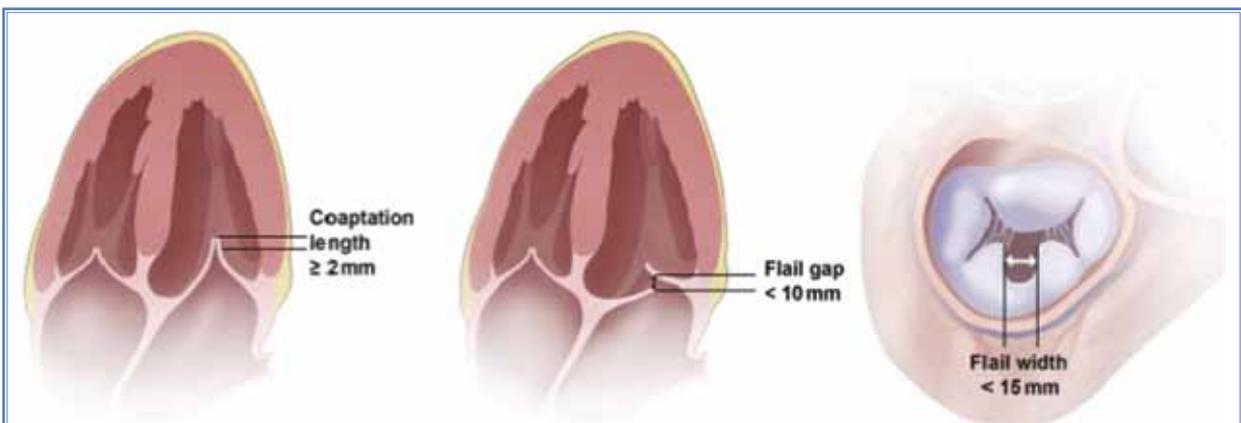
**Figure 4.** Edge-to-edge repair with suture apposing the anterior and posterior leaflets. Mitral valve is viewed from the left atrial side. The middle scallops of the anterior and posterior leaflets are approximated with the MitraClip, which creates a double orifice, edge-to-edge or bow-tie repair.

mal result, clear communication is critical between the interventionalist and the echocardiographer providing the transesophageal echocardiographic guidance.

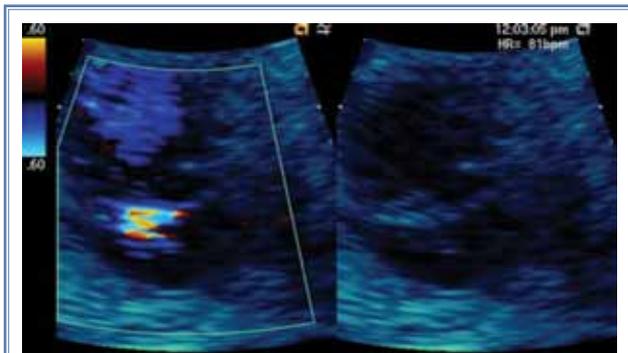
We previously described the procedural steps in detail.<sup>[8]</sup> In summary, the procedure is performed under general anesthesia using fluoroscopy and TEE guidance. Transesophageal echocardiography-guided transeptal puncture is performed in a specific location, ideally in superior and posterior part of the interatrial septum with the aim of an adequate working space and distance above the mitral leaflets (ideal height from the annulus should be 3.5-4 cm) for delivery catheter manipulations, clip opening, and clip retraction during

grasping. Afterwards, the CDS is advanced into the mitral annular plane in specific TEE views and clip arms are opened and advanced into the LV perpendicular to the plane of coaptation (*see* supplementary video file 1)\*. Origin of the MR jet is identified using TEE guidance with color Doppler and grasping of the leaflets at the MR jet origin is performed (video file 2). Following grasping of the leaflets (video file 3) and release of tension of the CDS system, using color Doppler, reduction in MR jet and mitral valve area are reevaluated along with hemodynamic reassessment.

If necessary, the clip can be reopened, the leaflets released, and the clip can then be repositioned by us-



**Figure 5.** Specific morphologic features of the mitral valve are required for the MitraClip to have a good probability of success. There must be adequate coaptation length for the clip to be grasped. A flail gap greater than 10 mm makes success of adequate reduction in MR unlikely, as does a flail width of more than 15 mm.



**Figure 6.** The mitral regurgitation jet must arise from the central two-thirds of the line of coaptation as seen on the short-axis color Doppler examination.

ing real-time echocardiographic assessment to attain the best possible result before final deployment.

### Case examples

#### Percutaneous MitraClip repair in degenerative MR

A 90-year-old female was referred for severe degenerative MR and congestive heart failure associated with recurrent hospital admissions and primary symptom of dyspnea at rest (NYHA class IV). She had a prior history of aortic mechanical valve replacement, congestive heart failure with a preserved left ventricular systolic function (ejection fraction 75%), diabetes, hypertension, and hypothyroidism. She had been hospitalized several times in the past year and, during her most recent hospitalization, IV dopamine, nifedipine and IV diuretics were started. Her estimated STS (Society of Thoracic Surgery) score was 40. The chest X-ray showed bilateral pulmonary edema and TEE showed ruptured chords in the A2 scallop of the anterior mitral leaflet, resulting in acute wide-open (severe) MR (video file 4). Superior displacement of the flail A2 scallop was less than 1 cm with a normal LV systolic function (video file 5). She had mild-to-moderate left atrial enlargement and normally functioning mechanical aortic valve. The patient was enrolled in the EVEREST I high-risk arm. Baseline hemodynamic assessment revealed a systolic pulmonary artery pressure of 80 mmHg with large V waves (Fig. 7). After placement of two clips, the patient had a significant drop in pulmonary artery systolic pressure from 80 mmHg to 40 mmHg with normalization of V waves as well as a significant increase in cardiac output (Fig. 7). After two-clip placement, TEE images showed significant reduction in MR (video file 6), which sustained during her 2-year follow-up. She was discharged from hospital in a couple of days and was able to resume her daily activities including driving,

climbing two stairs, and playing bowling. Her 2-year TTE follow-up showed a sustained improvement in MR with a residual 1+ MR (video file 7).

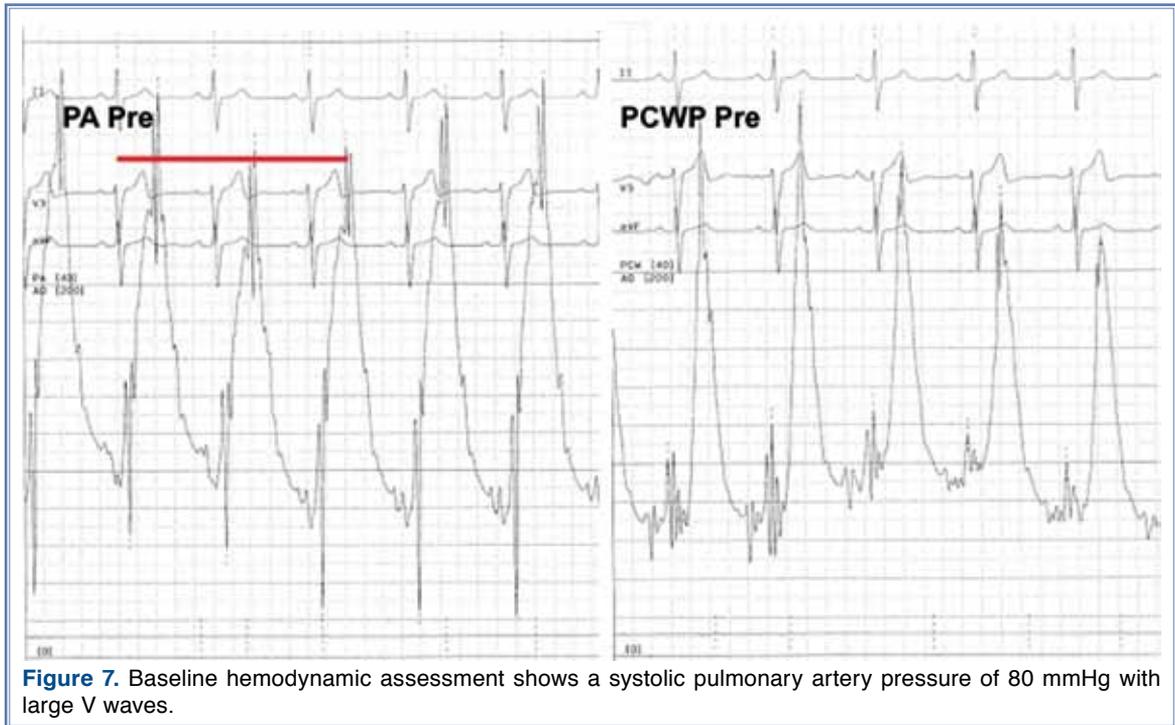
#### Percutaneous MitraClip repair in functional MR

A 53-year-old diabetic male was referred for moderately severe MR (3+, regurgitant fraction 44%, effective regurgitant orifice 38 cm<sup>2</sup>) and ischemic cardiomyopathy (ejection fraction 35%) with dyspnea on mild exertion (NYHA class III) and recurrent hospital admissions for congestive heart failure (video file 8). He suffered from inferolateral ST-segment elevation myocardial infarction a year before and underwent staged percutaneous coronary intervention with drug-eluting stent implantation for lesions in the left anterior descending artery, right coronary artery, and circumflex artery, respectively. His creatinine was 1.4 mg/dl. Estimated STS score was 1% and he was enrolled in the REALISM Registry, the continued access arm of the EVEREST II study. After two-clip placement, significant reduction in the MR jet was noted (video file 9). Following the procedure, he was very active, working on his garden. He complained of occasional exertional dyspnea on lifting heavy objects, with NYHA class I. He had no murmur. Findings of 1-month TTE were as follows: mitral valve area 4.4 cm<sup>2</sup> (planimetry), mitral valve gradient 2 mmHg, MR 1+ (regurgitant fraction 20%, effective regurgitant orifice 9 cm<sup>2</sup>), and ejection fraction 30%. He also had a mild secundum atrial septal defect with minimal R-L shunt (Qp/Qs 1.26).

### Clinical trials

The safety and efficacy of MitraClip therapy have been evaluated in the EVEREST I and EVEREST II clinical trials in the USA. Perlowski and Feldman<sup>[9]</sup> have recently reported a detailed analysis of all the clinical trials with this technology.

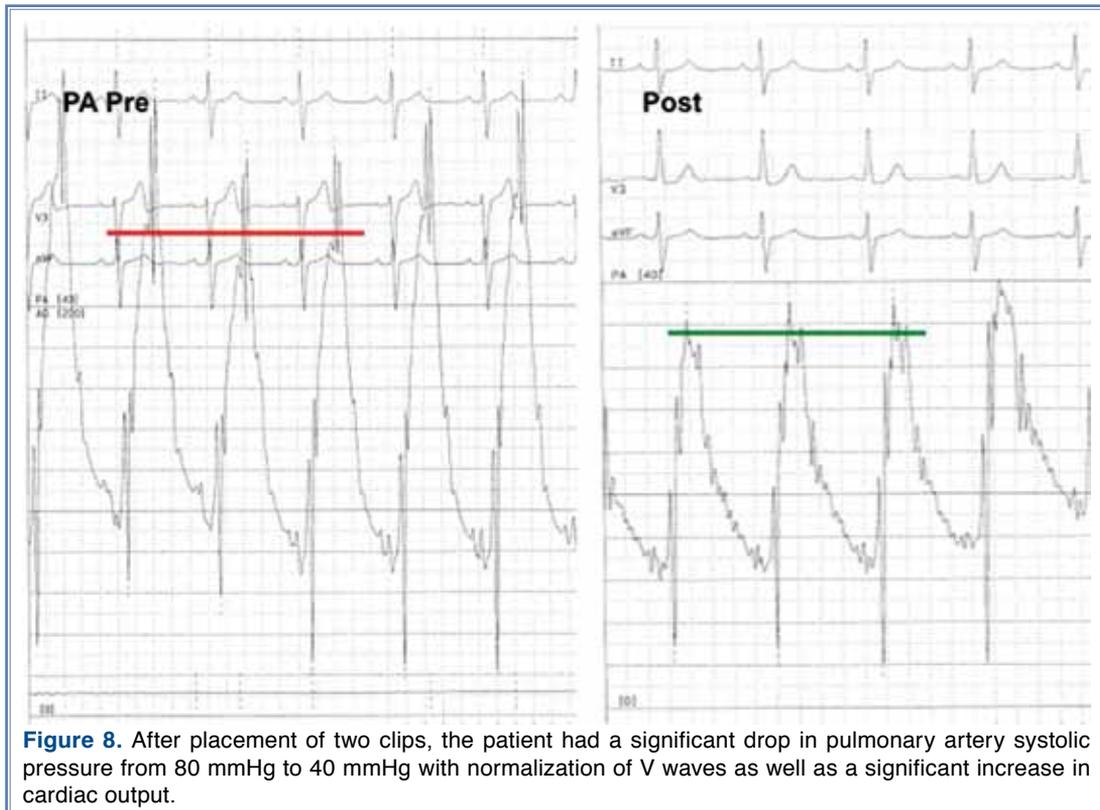
Concisely, the MitraClip system was initially evaluated in a U.S. phase I clinical trial (Endovascular Valve Edge-to-edge REpair Study; EVEREST I) for its safety.<sup>[6,7]</sup> The study population consisted of surgical candidates with moderate-to-severe or severe MR and clinical symptoms. Asymptomatic patients were eligible if echocardiographic evidence for LV dysfunction was present. The criteria of the ACC/AHA (American College of Cardiology/American Heart Association) guidelines for surgical intervention were followed and patients were closely screened using the quantitative methods for assessment of MR severity of the American Society of Echocardiography.<sup>[10,11]</sup> All



**Figure 7.** Baseline hemodynamic assessment shows a systolic pulmonary artery pressure of 80 mmHg with large V waves.

echocardiographic exams were reviewed in a core laboratory. A phase I trial was completed in a cohort of 55 patients. Registry data from a nonrandomized group of 107 patients<sup>[7]</sup> as well as outcomes in

a high-risk cohort of 78 patients were reported. The primary endpoint of the EVEREST I trial was safety at 30 days, which was defined as freedom from the following: death, myocardial infarction, cardiac tam-



**Figure 8.** After placement of two clips, the patient had a significant drop in pulmonary artery systolic pressure from 80 mmHg to 40 mmHg with normalization of V waves as well as a significant increase in cardiac output.

ponade, cardiac surgery for failed clip or device, clip detachment, or permanent stroke or septicemia. The clip was placed successfully in about 90% of the cases. Of those who achieved acute procedural success, defined as adequate reduction in MR without a procedural complication, two-thirds were alive and had no need for repeat procedures after 2-year follow-up. In a high-risk group of 78 patients, in addition to improvement in NYHA functional class, favorable ventricular remodeling with decreases in LV systolic and diastolic dimensions and reduction in the need for hospitalizations were demonstrated. Compared to matched controls who were also considered to be at high risk for surgery, there was improved 1-year survival.

EVEREST II was the first multicenter trial designed to evaluate the safety and efficacy of percutaneous mitral valve repair with MitraClip versus conventional surgical repair or replacement for MR with 2:1 randomization.<sup>[12]</sup> The primary composite end point for efficacy was freedom from death, surgery for mitral-valve dysfunction, 3+ or 4+ MR, and death at 12 months. The primary safety end point was defined as a composite of major adverse events within 30 days including death, myocardial infarction, reoperation for failed mitral valve surgery, non-elective cardiovascular surgery for adverse events, stroke, renal failure, deep wound infection, prolonged mechanical ventilation, gastrointestinal complication requiring surgery, septicemia, new onset permanent atrial fibrillation, and blood transfusion of  $\geq 2$  units.

At 12 months, the primary end point for efficacy was 55% in the device group as compared to 73% in the surgical group ( $p=0.007$ ). In the intention-to-treat analysis, the rates of death and grade 3+ to 4+ MR were similar between the two groups. The difference in the composite end point was primarily driven by the increased surgical referral rate after MitraClip therapy (20% in the device group as compared to 2.2% in the surgical group).

At 2 years, the primary efficacy end point was 52% in the percutaneous repair group versus 66% in the surgery group ( $p=0.04$ ), with surgery being superior for better reduction in MR grade.<sup>[13]</sup> The difference in the composite end point was again driven by the increased need for surgery for valve dysfunction in the percutaneous group (22% vs. 4%). Although surgical repair had an efficacy advantage over percutaneous repair in the EVEREST II trial, the intent-to-treat analysis showed that this was at the expense of safety with an increased rate of major adverse events at 30 days

in the surgical repair group (48% vs. 15%,  $p=0.001$ ). The difference was primarily driven by the increased need for blood transfusions, which was 45% in the surgical group compared to 13% in the percutaneous repair group. The association between the number of blood transfusions during surgery and increased mortality has been clearly demonstrated in the surgical literature.<sup>[14-17]</sup> Thus, percutaneous repair with MitraClip was a much safer treatment as compared to surgical approach.

The improved safety profile of the percutaneous approach was accompanied by clinically significant improvements (improved NYHA class, and improved quality of life compared to baseline), which were sustained at 2 years.

As compared to US clinical trials, where patients treated with this technology had degenerative MR in majority and functional MR in minority, Franzen et al.<sup>[18,19]</sup> assessed the results of patients treated in the EU. They reported successful outcomes and short-term durability in patients with functional MR, with significant reduction in MR severity as well as significant clinical and symptomatic improvement. Indeed, the majority of patients treated in the EU had functional MR and most of these patients were not only at high-surgical risk but also presented with well-known pitfalls of lack of improvement following surgery. This finding is probably not surprising as functional MR patients usually have structurally normal thickness of their leaflets, etc., which makes it easier to grab the leaflets as compared to some of the degenerative MR patients where it may be challenging.

## Conclusion

MitraClip therapy has emerged as a novel and promising percutaneous treatment option for certain group of selected patients who are considered to be at high-risk for traditional open-heart surgery. In the US-based phase I and phase II EVEREST clinical trials, it has clearly been shown to be a safe and effective mode of therapy for high-risk patients with both degenerative and functional MR. While this technology is being increasingly used in Europe and awaiting completion of ongoing clinical trials in the US, it is quite clear that percutaneous valve therapy offers a promising future for certain group of our patients in addition to the evolving minimally invasive surgical techniques.

**Conflict-of-interest issues regarding the authorship or article: None declared**

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**Key words:** Echocardiography, Doppler, color; heart catheterization; mitral valve insufficiency/therapy; surgical procedures, minimally invasive.

**Anahtar sözcükler:** Ekokardiyografi, Doppler, renkli; kalp kateterizasyonu; mitral kapağı yetersizliği/tedavi; cerrahi işlem, minimal invaziv.