

Original Research

Percutaneous Mitral Valve Repair Using the Edge-to-Edge Technique: First Greek Experience

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Introduction: Mitral valve (MV) repair is the treatment of choice for degenerative mitral regurgitation (MR), but the surgical options for functional MR are limited. Percutaneous edge-to-edge MV repair using the MitraClip system has evolved as a new tool for the treatment of certain anatomical subsets of both functional and degenerative MR. We present the first Greek series of MV repair using the MitraClip.

Methods: Five symptomatic patients (age 75 ± 9 years, logistic EuroSCORE $29 \pm 11\%$) with moderate-to-severe ($n=2$) or severe ($n=3$) MR underwent MV repair using the MitraClip. All patients were treated with one clip and there were no primary adverse events.

Results: Acute MR reduction by 3 grades was achieved in 2 patients and by 2 grades in 3 patients (reduction ≥ 2 grades in 100%). The total procedure time was 2.9 ± 2 hours (median 2 hours), the length of the ICU stay was 1 ± 0 day and the total length of hospital stay was 3.2 ± 0.6 days. All patients reported functional status improvement by 1 month (mean NYHA class improved from 3.0 ± 0.3 to 1.6 ± 0.6).

Conclusion: Our initial experience with percutaneous MV repair using the MitraClip system demonstrated that it can be performed safely, resulting in substantial acute echocardiographic and early clinical improvement.

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Mitral regurgitation (MR) is a common valvular abnormality, accounting for 24% of valvular heart disease cases in adults, while 7% of the population older than 75 years suffer from at least moderate MR.^{1,2} MR is classified into organic (intrinsic alteration of the leaflets, usually secondary to degenerative disease) and functional (normal leaflets with annular dilation or apical displacement of the point of apposition of the leaflets, usually secondary to ischemic or dilated cardiomyopathy).³ Pharmaceutical therapy may temporarily alleviate the related symptoms but cannot correct the often complex anatomical fault. Surgical intervention is recommended for symptomatic severe MR or asymptomatic severe MR with left ventricular dysfunction

or dilatation.^{4,5} The treatment of severe degenerative MR has evolved from mitral valve replacement to mitral valve repair, because repair produces superior clinical outcomes.^{4,9} For functional MR, however, the role of surgical treatment is less clear and it is usually carried out only as an adjunct to coronary bypass grafting. The surgical outcomes in these patients, as well as their prognosis, are usually poorer because of their left ventricular impairment.¹⁰⁻¹⁵

Mitral valve repair can also be achieved through minimally invasive surgical approaches.^{16,17} This desire for less invasive approaches, coupled with the fact that a significant proportion of patients – especially elderly persons, or those with significant comorbidities or severe left ventricular (LV) dysfunction – are never referred for

surgery,¹⁸ has driven the development of percutaneous MV repair devices.

The MitraClip® (Abbott Vascular, Santa Clara CA, USA) was the first percutaneous system for MV repair (CE Mark granted in 2008) and has been used in over 6000 patients since 2003. Recently, the first randomized controlled study in the field of percutaneous MV repair, the EVEREST II trial, compared MitraClip with surgical MV repair and demonstrated the superior safety of the MitraClip repair and similar improvements in clinical symptoms.¹⁹

The performance of the MitraClip transcatheter procedure has been restricted to selected centers that fulfill certain setup and multidisciplinary training requirements. Our hospital was the first to employ this novel procedure in Greece. Herein, we describe our initial experience, focusing on patient selection, set-up requirements and acute clinical outcomes.

Methods

MitraClip device and delivery system

The MitraClip system percutaneously creates a double mitral valve orifice in a way similar to the Alfieri stitch.²⁰ The MitraClip system consists of three parts: the MitraClip implant, the Clip Delivery System (CDS) and the steerable guide catheter (SGC). There is also a stabilizer that keeps the system precisely in position (Figure 1). The clip implant is made

from cobalt-chromium and covered with polyester fabric. It has two arms that are roughly 8 mm long and 4 mm wide. These measurements approximate the surgical Alfieri stitch and allow adequate vertical coaptation of the mitral valve leaflets.²⁰ The arms are opened and closed by a control mechanism on the CDS handle. The system uses two dials that permit medial-lateral and anteroposterior steering. On the inner aspect of the arms are two corresponding “grippers” allowing for secure capture of the mitral leaflets. Each leaflet is grasped between an arm and a gripper. The closed clip can be locked in its final position and then released and deployed in this state. The SGC is 24 F (tapered to 22 F distally at the part that crosses the atrial septum) and is delivered with an echogenic tapered dilator, allowing the introduction of the CDS into the left atrium. The tip of the guide catheter has a radiopaque marker. The steerable properties of both the SGC and the CDS allow precise orientation and positioning of the MitraClip.

Patient selection

Patients were evaluated by our heart team, consisting of three cardiologists, two cardiac surgeons and an anesthesiologist. Patients had a standard diagnostic workup, including physical examination, functional capacity assessment (New York Heart Association, NYHA class), electrocardiogram, blood tests, trans-

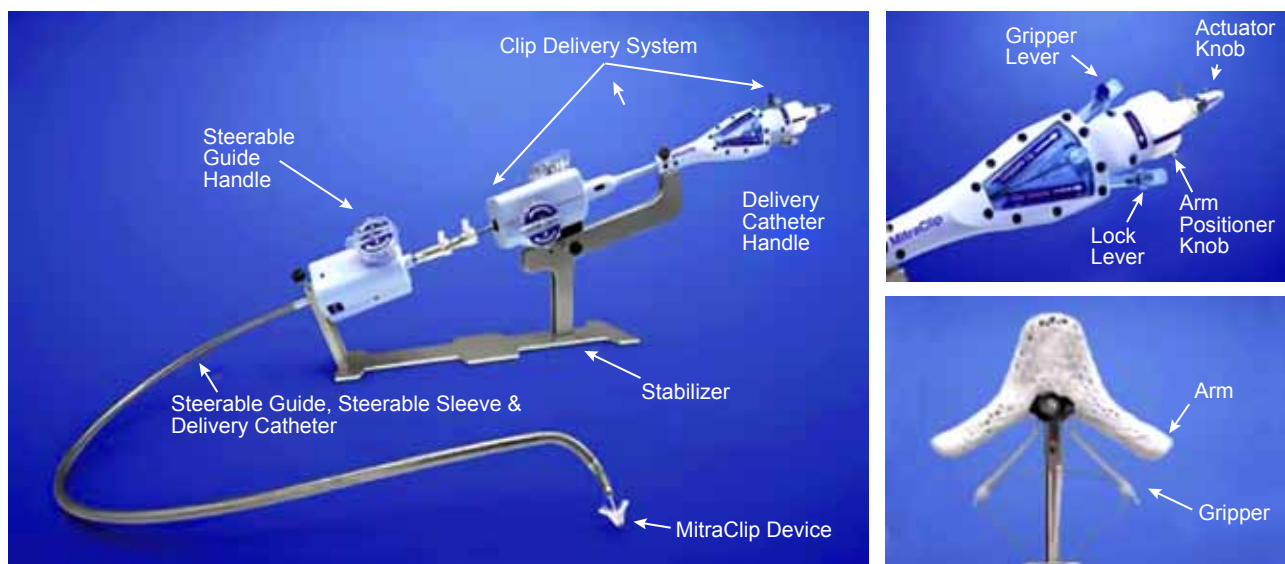


Figure 1. The MitraClip system consists of three major parts: the MitraClip, the clip delivery system (CDS), and the steerable guide catheter (SGC). There is also a stabilizer that keeps the system in position.

thoracic (TTE) and transesophageal (TEE) echocardiography, and coronary angiography. According to the scale of the European Association of Echocardiography, MR severity was classified as: (1⁺) mild, (2⁺) mild-to-moderate, (3⁺) moderate-to-severe, or (4⁺) severe MR.²³ Patients were considered to be eligible for the percutaneous approach, based on the anatomic criteria set by the EVEREST-II trial¹⁹ and according to the collaborative European experience,^{21,22} when they: 1) were not candidates for conventional surgical repair due to excessive risk as assessed by the logistic EuroSCORE and our Surgeon's consultation; 2) had symptomatic moderate-to-severe (3⁺) or severe (4⁺) MR; and 3) had a reasonable life expectancy (above 1 year). Anatomical inclusion criteria for the MitraClip device were: 1) MR originating from the A₂-P₂ area; 2) coaptation length >2 mm; 3) coaptation depth <11 mm; 4) flail gap <10 mm; 5) flail width <15 mm; 6) mitral valve orifice area >4 cm²; 7) mobile leaflet length >1 cm; and 8) absence of leaflet or excessive annular calcification.

We screened 14 patients with significant symptomatic MR for MitraClip treatment suitability. Of those, 4 patients were excluded for the following reasons: 1 due to a heavily calcified mitral annulus, 1 due to previous valve repair with Alfieri stitch, 1 due to hypertrophic cardiomyopathy, 1 refused further assessment, and 1 patient died before the start of our program. Five patients were treated and 4 are on the waiting list to undergo the procedure.

Procedure

All procedures were performed in the catheterization laboratory with specific sterile precautions. General sterile cleaning of the room was carried out the night before the procedure and access to it was restricted to those immediately involved in the procedure. The personnel in the room consisted of two interventional cardiologists, one echocardiographer, one cardiac surgeon, one cardiac anesthesiologist, two nurses and two technicians.

The procedures were performed under general anesthesia. During the procedure, invasive arterial pressure was monitored through the radial artery and a central venous catheter was placed in the internal jugular vein. Prophylactic antibiotics were given before the procedures and all patients were pretreated with aspirin and clopidogrel. The right femoral vein was cannulated with a 7 F introducer sheath and a baseline right heart catheterization was

performed. Subsequently, the 7 F introducer sheath was exchanged for an 8 F SLO sheath (St. Jude Medical, St Paul MN, USA) over a 0.32" guidewire, and a transseptal puncture 35-40 mm above the line of coaptation of the mitral valve leaflets was performed using a Brockenbrough needle under TEE guidance. Following successful transseptal puncture, intravenous heparin was administered and activated clotting time (ACT) was monitored throughout the procedure to maintain a level of approximately 250-300 seconds. A 0.035" Amplatz Extra-Stiff exchange length guidewire was advanced through the SLO catheter to the left upper pulmonary vein. The transseptal catheter was then removed and exchanged for the SGD. Then the 22 F tapered SGC was introduced into the left atrium, and the dilator and Extra-Stiff wire were slowly and carefully retrieved under continuous saline infusion to avoid vacuum air bubbles. The MitraClip attached to the CDS was then advanced through the guide catheter into the left atrium. With the help of 2- and 3-dimensional TEE, the MitraClip was orientated appropriately over the mitral valve. The clip was then opened and the arms were positioned perpendicularly to the leaflets. Once properly oriented, the clip was advanced to the left ventricle, and the CDS was then slowly pulled back until both leaflets sat on its arms. The leaflets were then grasped by dropping the grippers (Figure 2). After adequate grasping of the leaflets had been confirmed, the arms were closed and the reduction in MR was assessed (Figure 3). If there was no significant change in MR, the

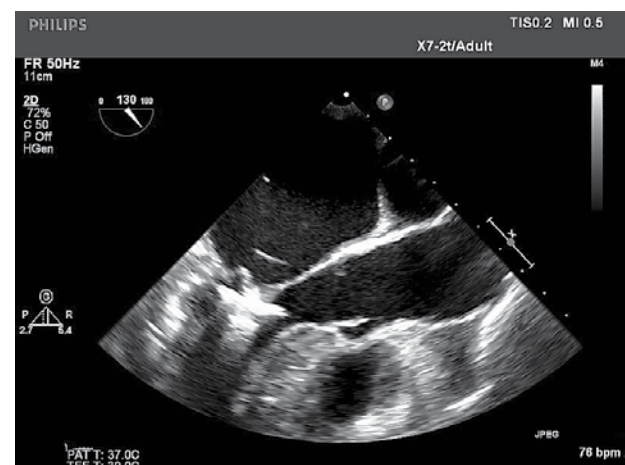


Figure 2. Successful grasping of mitral valve leaflets on the MitraClip arms.

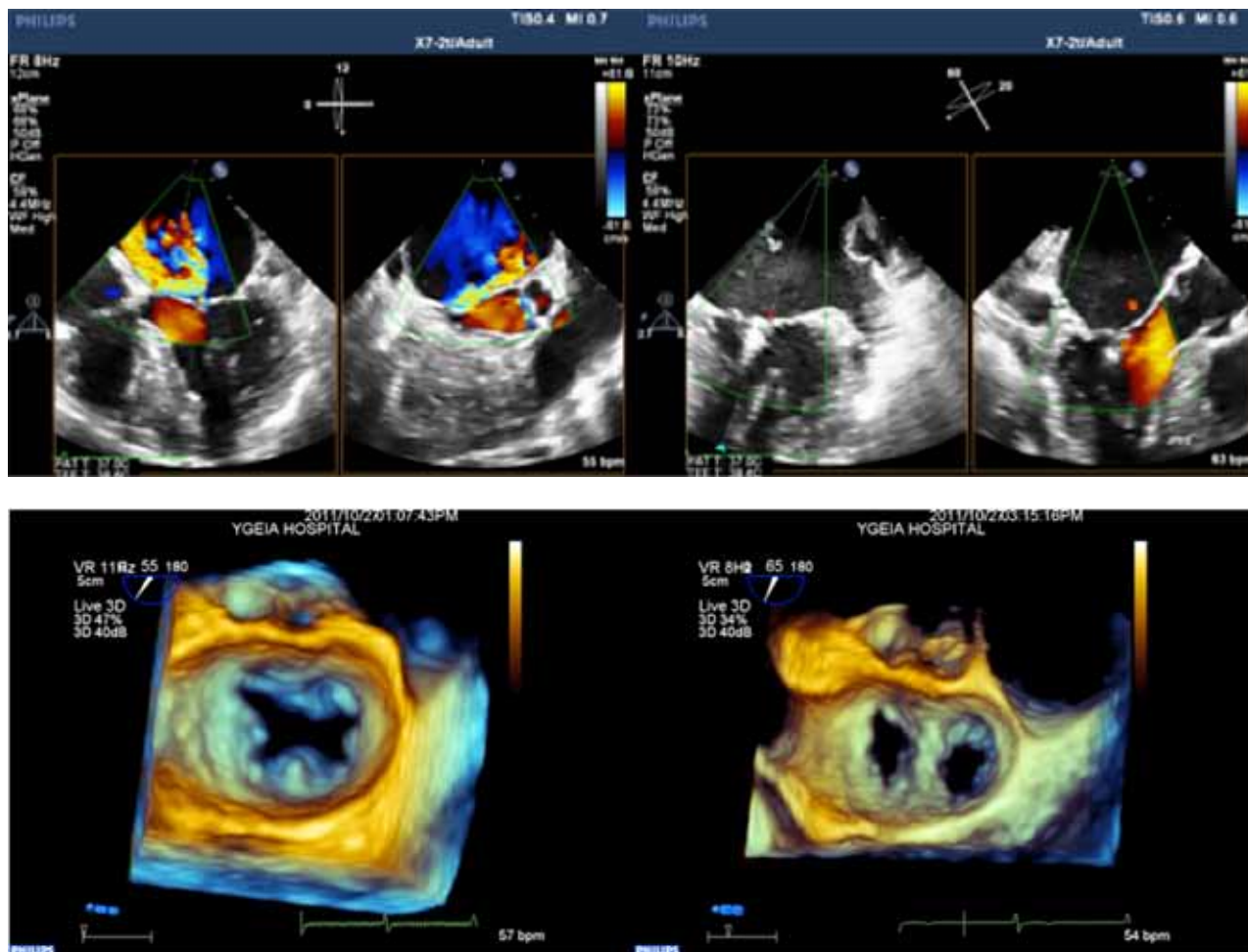


Figure 3. The mitral valve before (right) and after (left) the MitraClip deployment. The elimination of the regurgitation can be appreciated in the 2D color images (top row) and the change in the mitral valve from single to double orifice is seen with 3D imaging (bottom row).

clip was repositioned. If the reduction in MR was adequate, the clip was deployed. In addition to assessment of the MR, valve gradients were checked before deployment to ensure that there was no iatrogenic mitral stenosis.

Post-procedure care

A “figure-of-eight” suture was used to obtain hemostasis at the 24 F access site and was removed 24 hours later. Electrocardiography and laboratory testing were performed within 24 hours. All patients were prescribed aspirin 100 mg daily lifelong and clopidogrel 75 mg daily for three months. Before discharge, all patients underwent TTE to assess the position of the clip and residual MR as described previously, and endocarditis prophylaxis was advised.

Results

Tables 1 and 2 summarize the clinical and echocardiographic data of the first 5 patients who underwent the MitraClip procedure in our centre. The mean age was 75 ± 9 years and the average functional status was 3.0 ± 0.3 . The mean logistic EuroSCORE was $29 \pm 11\%$. Two patients had functional MR, 2 patients had degenerative MR with P₂ prolapse, and one patient had mixed MR.

Procedural, in-hospital and 1-month outcomes

The procedure time for 4 patients was in the range of 120-140 minutes, but it reached 390 minutes in 1 patient. The mean procedure time was 171 minutes, the mean fluoroscopy time was 42 minutes, and the dose-

Table 1. Demographics and risk factors.

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
Age	66	73	72	83	82
Gender	M	M	M	F	F
Comorbidities:					
Heart failure	+	+	+	+	+
NYHA class	II-III	III-IV	III	III	III
LVEF (%)	29	45	30	65	60
CAD	+	+	+	+	+
Previous MI	+	-	+	-	-
Previous CABG	-	+	+	-	-
Previous PCI	+	-	-	-	-
Atrial Fibrillation	-	-	-	+	+
Diabetes	-	+	+	-	-
CRD (Stage)	+(III)	+(IV)	-	-	-
EuroSCORE (%)	21.2	39.8	38.9	18.5	24.4
STS score (%)	2.6	5.5	3.2	3.3	2.9
STS m&m (%)	23.7	38.8	20.9	20.5	16.8

M – male; F – female; NYHA – New York Heart Association; LVEF – left ventricular ejection fraction; CAD – coronary artery disease; MI – myocardial infarction; CABG – coronary artery bypass grafting; PCI – percutaneous coronary intervention; CRD – chronic renal dysfunction; m&m – mortality and morbidity; STS – Society of Thoracic Surgeons.

Table 2. Mitral regurgitation characteristics at baseline and post-MitraClip.

	Type of MR	Baseline ERO (cm ²)	Baseline MR severity	Post MitraClip MR severity
Patient 1	F	31	3+	1+
Patient 2	M	41	4+	2+
Patient 3	F	37	3+	1+
Patient 4	D	52	4+	1+
Patient 5	D	56	4+	1+
Average	-	43 ± 10	3.6 ± 0.5	1.2 ± 0.4

MR – mitral regurgitation; ERO – effective regurgitant orifice; F – functional; M – mixed; D – degenerative.

area product (DAP) was 219.512 cGy.cm². The procedure success rate (defined as correct positioning of the MitraClip with MR reduction of at least 2 grades on extubation of the patient) was 100%. No clip detachment occurred. The procedural and in-hospital mortality was 0%. The mean length of hospital stay was 3.2 ± 0.6 days and the mean intensive care unit (ICU) stay was 1 ± 0 day.

One patient required blood transfusion (one unit) because of gastrointestinal bleeding. He had a past history of multiple gastrointestinal bleedings and we believe that the periprocedural heparin administration and the double antiplatelet treatment contributed to this event. This same patient developed self-limited contrast-induced nephropathy with no further sequel. No other in-hospital complications occurred.

All patients reported significant clinical improvement at 1-month follow up. Their average

functional status improved from NYHA class 3.0 ± 0.3 to 1.6 ± 0.6.

Acute effect on MR

There was an improvement in the severity of MR in all patients as assessed acutely (Table 2). Acute MR reduction by 3 grades was achieved in 2 patients and by 2 grades in 3 patients (reduction ≥2 grades in 100%). No significant iatrogenic mitral stenosis was detected after the procedure (mean mitral valve gradient <4 mmHg in all patients).

Discussion

This report describes the first series of MitraClip implantations performed in Greece. We were able to perform the procedures safely in all 5 patients where they were attempted and significant acute MR reduc-

tions were achieved in all of them, and were promptly translated into meaningful clinical improvement. Our initial experience with the MitraClip procedure reproduces the excellent results reported by other centers. Indeed, all first 5 patients experienced an acute improvement of MR by at least 2 grades and they were all left with residual MR of $\leq 2^+$ and without major complications.

Mitral valve repair can be accomplished with a procedure that involves the percutaneous implantation of a clip (MitraClip) that grasps and approximates the edges of the mitral leaflets at the origin of the regurgitant jet. This technology was developed in an attempt to replicate the surgical approach for mitral valve repair, which involves approximation of the mitral leaflets with a suture to create a double orifice.²⁰ This surgical procedure has been described for the treatment of degenerative MR and is usually performed together with an annuloplasty ring. Selected patients who have been treated with this technique as a standalone procedure have had successful results lasting up to 12 years.^{20,24}

The first MitraClip procedure was performed in 2003 and mitral repair with this device in 107 selected patients showed a significant reduction in the severity of MR.²⁵ The MitraClip percutaneous system received the CE Mark in 2008 and it has been implanted in more than 6000 patients to date.

The Endovascular Valve Edge-to-Edge Repair Study (EVEREST II) was a randomized comparison of percutaneous mitral repair and mitral valve surgery that evaluated the efficacy and safety of percutaneous mitral valve repair, as compared with conventional surgical repair or replacement.¹⁹ The majority of the 279 patients enrolled (73%) had degenerative MR, and they were all surgical candidates so that they could be randomized in a 2:1 fashion to MitraClip or surgery (repair in 86% and replacement in the remaining 16%). The study demonstrated that, although percutaneous repair was less effective than surgery in reducing MR before hospital discharge, the rates of reduction in MR were similar at 12 and 24 months, and percutaneous treatment was associated with increased safety, improved left ventricular dimensions, and superior clinical improvements in NYHA class and quality of life.

In most cases of degenerative MR, valve repair is the operation of choice when the valve is suitable and appropriate surgical skill and expertise are available.⁴ This procedure preserves the patient's native valve without a prosthesis and therefore avoids the risk of

chronic anticoagulation (except for patients in atrial fibrillation) or prosthetic valve failure late after surgery. Additionally, preservation of the mitral apparatus leads to better postoperative LV function and survival than in cases in which the apparatus is disrupted.^{4,9} Postoperative function is improved with repair because the mitral apparatus is an integral part of the left ventricle that is essential for the maintenance of the normal shape, volume, and function of the left ventricle.²⁶

The Adult Cardiac Surgery Database of the Society of Thoracic Surgeons indicates that the rate of mitral valve repair for patients with isolated mitral regurgitation increased from 51% in 2000 to 69% in 2007.²⁷ The operative mortality for mitral valve replacement was consistently higher than that for repair (3.8% versus 1.4%), a finding that persisted after risk adjustment (adjusted odds ratio 0.52, 95% confidence interval: 0.45–0.59; $p < 0.0001$). Among patients undergoing elective isolated mitral valve repair, the average operative mortality was 1.2%, and the preoperative functional status was its principal predictor. For asymptomatic (NYHA class I) patients, the operative mortality was 0.6%. The reoperation rate after mitral valve repair is similar to the reoperation rate after replacement.²⁸ There is a 7% to 10% reoperation rate at 10 years in patients undergoing mitral valve repair, usually for severe recurrent MR.^{4,9,28} Percutaneous repair with the MitraClip system should thus be shown to match the corresponding results of surgical MV repair. Until then, it should be reserved for high risk patients with comorbidities that leave them inoperable by consensus.

Functional MR is an important pathology in end-stage ischemic or dilated cardiomyopathy, caused by the expansion of the mitral annulus and/or papillary muscle dysfunction. Mitral insufficiency leads to a vicious circle, with increasing volume overload of the dilated left ventricle thus leading to progression of annular dilatation, worsening of MR and volume overload.²⁹ The resulting mitral valve insufficiency is often refractory to medical therapy and predicts poor survival in this patient group.³⁰

Data on the effect of surgical therapy for pure functional MR are scant, limited and complex to interpret. Restrictive mitral valve annuloplasty in addition to coronary artery bypass grafting is currently the most frequently used technique for the surgical management of patients with severe ischemic MR.³¹ However, this procedure is associated with 10-20% rates of persistent significant MR early after operation

and with 50-70% rates of recurrent MR at 5 years.³¹ Furthermore, the presence of persistent or recurrent MR is associated with a higher incidence of cardiac events³² and reduced survival.³³ Isolated surgical mitral valve annuloplasty (versus medical treatment alone) in patients with significant functional MR and impaired left ventricular function did not alter their long-term outcome in the single study of its kind.³⁴ In patients with ischemic MR and indications for revascularization, coronary revascularization alone (either surgical or percutaneous) has been shown to reduce the degree of MR (ranging from 11% for ≥ 2 grades to 65% for ≥ 1 grade), apparently in those who demonstrate positive LV remodeling.³⁵⁻³⁸ In patients without functional recovery, MV repair by ring annuloplasty is more likely to reduce MR than revascularization alone. However, there are no data to suggest that the addition of restrictive annuloplasty to surgical revascularization improves long term mortality in such patients.^{12-14,38-40} In contrast, many studies have shown that the joint procedure increases the operative mortality, as higher-risk patients are being treated.^{14,36,38}

The perioperative mortality of mitral valve repair alone (usually ring annuloplasty) in patients with reduced LV function has been reported to range between 2.1% and 12.9%,^{34,41,42} while the combination of ring annuloplasty with coronary artery bypass grafting appears to increase the mortality risk (4% to 17.8%).^{14,36,38,43,44} Age, LV ejection fraction and functional status were strongly associated with worse procedural outcomes, with mortality as high as 42.9% in patients with an ejection fraction below 30% being noted in one study.^{42,45,46} Finally, mitral valve repair for ischemic MR is associated with better short-term and long-term survival compared to mitral valve replacement.⁴⁷⁻⁴⁹

In comparison, the 30-day mortality in the 177 patients with functional MR treated with the MitraClip in the EU ACCESS registry was 2.8%, while in the 149 functional MR patients treated with the MitraClip in the EVEREST II high-surgical risk cohort it was 4.7% (1.1% in the 50 patients with functional MR randomized to MitraClip in the EVEREST II trial).⁵⁰⁻⁵¹

The MitraClip is the only percutaneous technology effective for both functional and degenerative MR. The procedure is performed via a venous route and the device is removable and repositionable. These important attributes contribute to the safety of this procedure. Notably, in spite of the fact that the degree of reduction in MR is lower than that of surgery, the

clinical benefits with respect to LV remodeling were observed to be similar to the surgical group.¹⁹

Conclusion

The first Greek series of MitraClip implantations in 5 high surgical risk patients with a mixture of both functional and degenerative MR demonstrates that excellent results with no complications can be obtained from the outset in a start-up program. A universal finding with the MitraClip therapy, which we also encountered in our initial experience, is that MR is significantly reduced but rarely eliminated. However, when treating high-risk patients a suboptimal repair obtained with low risk can be an acceptable outcome. For successful implementation of a patient-centered mitral valve program, integration of surgical and interventional treatment modalities within a heart center is of paramount importance. This is best accomplished by an interdisciplinary dedicated heart team consisting of cardiologists and cardiac surgeons.

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