Cardiology Lett. 2017;26(4):223–227

Flash update on MitraClip based treatment of mitral regurgitation

Ondrus T[1,2], Penicka M[2], Kotrc M[3], Vanderheyden M[2], Bartunek J[2]

[1]Department of Internal Medicine and Cardiology, Medical Faculty of Masaryk University and University Hospital Brno, Brno, Czech Republic, [2]Cardiovascular Center Aalst, OLV Hospital, Aalst, Belgium and [3]Department of Cardiology, Institute for Clinical and Experimental Medicine (IKEM), Prague, Czech Republic

Ondrus T, Penicka M, Kotrc M, Vanderheyden M, Bartunek J**. Flash update on MitraClip based treatment of mitral regurgitation.** Cardiology Lett. 2017;26(4):223–227

Abstract. Despite the evidence of unfavourable prognosis, around half of patients with severe MR are not referred for surgery due to high per-operative risk. MitraClip (Abbott Vascular-Structural Heart, Menlo Park, California, United States) implantation is an emerging percutaneous technique with edge-to-edge MV repair inspired by the Alfieri surgery. Favourable safety profile together with improvement of functional status and decrease of MR severity in high-surgical-risk patients have been demonstrated in randomized clinical trials and "real-world" registries for both primary and secondary MR. Our own data confirmed its safety and efficacy comparing to minimally invasive MV surgery in treatment of functional MR in population with severe systolic heart failure.

Introduction

The European Society of Cardiology (ESC) guidelines classify this disorder as either primary (organic, degenerative) or secondary (functional, ischaemic). Mitral regurgitation (MR) is the second most prevalent heart valve disease requiring surgery with a prevalence of 1.7% increasing to 10% in older population (1,2). Primary MR is caused by a morphological abnormality of one or more components of a complex mitral valve (MV) apparatus, i.e. leaflets, chordae tendineae, papillary muscles or mitral annulus. In secondary MR, anatomically normal MV fails to coapt adequately because of left ventricular (LV) remodelling, papillary muscle displacement and annular dilatation. Thus, secondary MR is more disease of the LV myocardium than MV itself with implications to therapeutic options: while severe organic MR is a clear indication to MV surgery (class Ia), management of functional MR (without concomitant revascularization therapy) is multifactorial and interventional options remain matter of discussion (3).

Nevertheless, both organic and functional MR are linked with unfavourable prognosis in the absence of intervention (4–6). Surgical treatment is the approach with defined clinical success, providing sustained relief of symptoms or heart failure and valve repair should be the preferred mode of surgical correction (7). However, around half of patients with severe MR (both organic as well as functional) are not referred for surgery because of high per-operative surgical risk mainly due to advanced age, frailty, comorbidities or severe LV dilation and dysfunction (8).

MitraClip

MitraClip (Abbott Vascular-Structural Heart, Menlo Park, CA, United States) therapy is an emerging approach for treating MR in high-surgical-risk patients providing significant reduction of MR severity with favourable safety profile. The principle of this percutaneous technique is based on a tech-

From [1]Department of Internal Medicine and Cardiology, Medical Faculty of Masaryk University and University Hospital Brno, Brno, Czech Republic, [2]Cardiovascular Center Aalst, OLV Hospital, Aalst, Belgium and [3]Department of Cardiology, Institute for Clinical and Experimental Medicine (IKEM), Prague, Czech Republic

In order to extend the information, we publish our work as a secondary publication in the journal Cardiology Letters. The primary publication was published in Cor et Vasa 2017, 59, 85-91

Corresponding author at: Prof. Jozef Bartunek, MD, Cardiovascular Center Aalst, OLV Hospital, Aalst, Belgium

E-mail addresses: ondrus.tomas@fnbrno.cz (T. Ondrus), martin.penicka@olvz-aalst.be (M. Penicka), martin.kotrc@medicon.cz (M. Kotrc), marc.vanderheyden@olvz-aalst.be (M. Vanderheyden), jozef.bartunek@olvz-aalst.be (J. Bartunek).

nically simple surgical method first described by Alfieri in the early 1990s consisting of MV leaflets central suture (9). MitraClip therapy provides mechanical edge-to-edge grasping of the anterior and posterior leaflets using a small clip device and thereby restoring MV coaptation.

MitraClip device. The MitraClip device is a 4 mm wide chrome-cobalt clip with 2 mobile, polyester covered arms. On the inner portion of the clip there are 2 "grippers" stabilizing the leaflets from the atrial site. After grasping, the leaflet tissue is secured between the arm and gripper. The MitraClip device is delivered using a 24-Fr steerable catheter guidewire and a sophisticated clip delivery system. The system has knobs that allow the antero-posterior and medio-lateral steering of the catheter tip and control the opening, closure, and detachment of the clip. The clip is magnetic resonance conditional to 3 tesla (T). New modified version MitraClip NT is able to achieve wider angle of motion enhancing the steering and facilitating the grasping and resulting in better precision and more confident clip placement.

Implantation procedure. Implantation procedure is performed under general anaesthesia using fluoroscopy and transesophageal echocardiography (TEE) navigation. Left atrium (LA) is reached via right femoral vein access and transseptal puncture. Maximal postero-superior puncture position should be attempted to allow sufficient clip mobility inside the LA and optimal distance to the line of coaptation. After reaching the mitral orifice, MitraClip perpendicularity has to be set up using 3D TEE navigation. Then, the clip is advanced through the MV into the LV with slightly closed arms. The system is withdrawn until both mitral leaflets have been grasped under continuous TEE guidance. Careful TEE evaluation of the clip position, its stability with sufficient tissue being grasped and residual MR is of the outmost importance. If the result is suboptimal (only one leaflet capture, presence of significant residual MR or stenosis), the clip may be reopened with repeated grasp attempts. In the case of optimal result, the clip is released according to the manufacturer's instructions and presence of residual MR or mitral stenosis is determined. If significant residual MR persists after implanting a first clip, a second or event third clip may be implanted (20).

Several single-centre reports, multicentre registries and randomized clinical trials including a considerable number of patients support clinical use of MitraClip in awaiting the findings of the phase III clinical trial. The MitraClip system has had European Union approval (CE Mark) since 2008 for treatment of both degenerative and functional MR in inoperable and high-risk patients and is supported in the latest ESC guidelines on the management of valvular heart disease (3). More than 30,000 MitraClips have been implanted worldwide so far (10).

EVEREST (Endovascular Valve Edge-to-Edge REpair Study) is a prospective multicentre registry that analyzed the feasibility, safety and efficacy of MitraClip in patients with moderate-to-severe (3+) or severe (4+) both organic (79%) and functional (21%) MR. A total of 107 patients were enrolled, at 1 year follow up, 66% remained free of death, MR greater than 2+ or mitral surgery. Functional class and symptoms improved in 74% of patients and the results were similar in both degenerative and functional MR. In terms of safety, no deaths occurred during the procedure and 10 patients (9.3%) had had an adverse event at 30 days. This first, initial experience of the MitraClip device enabled to establish the feasibility and safety, in carefully selected patients (11).

EVEREST II is a first randomized clinical trial comparing the efficacy and safety of MitraClip with conventional surgery (MV repair or replacement). Patients were randomized 2:1

Table 1

Parameters	Mild	Moderate	Severe
Qualitative			
MV morphology	Normal/abnormal	Normal/abnormal Intermediate	Flail leaflet/ruptured PM
Colour flow MR jet	Small, central jet	Dense/parabolic	Large central/eccentric jet reaching the posterior LA wall
CW signal of MR jet	Faint/parabolic		Dense/triangular
Semi-quantitative		Intermediate	
VC width (cm)	<0.3 cm	Intermediate signs Intermediate	≥0.7 cm (>0.8 cm biplane)
Pulmonary vein flow	Systolic dominant flow	signs	Systolic flow reversal
Mitral inflow	A-wave dominant		E-wave dominant (1.5 m/s)

Parameters	Mild	Mild-moderate	Moderate-severe	Severe
Quantitative				
R Vol (ml)[a]	<30	30–44	45–59	≥60
RF (%)	<30	30–39	40–49	>50
EROA (cm^2)[a]	<0.2	0.2–0.29	0.3–0.39	≥0.4

Adapted from [17].

Abbreviations: MV, mitral valve; PM, papillary muscle; MR, mitral regurgitation; LA, left atrium; CW, continuous wave; VC, vena contracta; R Vol, regurgitant volume; RF, regurgitant fraction; EROA, effective regurgitant orifice area.

[a]In functional MR, thresholds of severity (0.2 cm^2 for EROA and 30 ml for R Vol).

to percutaneous therapy versus surgery. Some 258 patients with MR 3+ or 4+ (27% functional and 73% organic) were enrolled. This trial demonstrated less periprocedural complications as compared to surgery; however its efficacy in MR reduction was inferior. Yet, there was no difference in clinical end-points, in particular mortality. In the subgroup analysis, the best results in the MitraClip group were obtained in patients with older age (≥70 years), functional MR, and low ejection fraction (12).

ACCESS-EUROPE is a multicentre, non-randomized European observational registry showing data from the "real life", without predefined inclusion or exclusion criteria, enrolling 567 patients with significant MR (77% functional MR) from 14 centres in 4 European countries. In this real-world, post-approval experience in Europe, patients undergoing the MitraClip therapy were high-risk, elderly and mainly affected by functional MR. At 12-month follow-up, MR grade 2+ or less was maintained in 79% of the patients, functional class had improved significantly (72% with NYHA ≤2 at 1-year follow-up), as had quality of life and the distance covered in the 6-min walking test. In addition, the MitraClip procedure was associated with low rates of hospital mortality and adverse events (13).

TRAMI (TRAnscatheter Mitral Interventions) registry aimed to assess the safety and efficacy of percutaneous mitral valve therapy in Germany. Patients were mainly elderly with significant comorbidities and high or inacceptable risk valve of surgery. One-year outcomes, now available in 828 patients, showed significant clinical benefits: 63% of patients pertained to NYHA functional classes I or II compared with 11% at baseline, with significant proportion of patients regained the complete independence in self-care (14).

COAPT (Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy) trial is a US based randomized study to determine the safety and effectiveness of the MitraClip for treatment of significant functional MR in heart failure subjects compared to standard-of-care therapy. It includes patients who have been determined by the site's local heart team as not appropriate for mitral valve surgery. The trial is still ongoing, first results are awaited in 2017.

MITRA-FR is a French national, multicentre, investigator-initiated, open-label, randomized trial to evaluate the benefits and safety of percutaneous MV repair using the MitraClip system plus optimal medical therapy (OMT) compared with OMT alone in patients with severe symptomatic secondary MR contraindicated to surgical repair. The trial is still ongoing, first results are awaited in 2017.

Patient selection

Identification of a MitraClip candidate is a multidisciplinary, stepwise process taking into account patient's clinical characteristics (i.e. surgical risk evaluation) and thorough echocardiography MR assessment (aetiology, severity of MR and MV anatomy eligibility). The role of a 'heart team' (cardiologist, cardiovascular surgeon, imaging specialist, cardio-anaesthetist, and also geriatrician where available) with a particular expertise in valvular heart disease is crucial in the decision making process.

Surgical risk evaluation. According to the guidelines, percutaneous edge-to-edge procedure may be considered in patients with symptomatic severe *primary* MR who fulfil the echo criteria of eligibility, are judged inoperable or at high surgical risk by a heart team and have a life expectancy greater than 1 year (IIb, C). In *secondary* MR, the procedure may be considered in patients with symptomatic severe regurgitation despite OMT, including cardiac resynchronization therapy (CRT) if indicated, who fulfil the echo criteria of eligibility, are judged inoperable or at high surgical risk by a heart team, and who have a life expectancy greater than 1 year (IIb, C) (3).

However, definition of a high-surgical risk patient is controversial and often subjective. Evaluation should always be based on individual characteristics and patient tailored approach is necessary. The role of a heart team is crucial and goes beyond the conventional calculation of the risk scores. This should also include the assessment of frailty, implementation and response to standard of heart failure care including CRT. Risk calculators could be helpful for identification of a very high-risk patient (logistic EuroSCORE ≥20%, STS score >10%). As MV repair mortality in general population is approximately 2%, indication to MitraClip therapy can be considered if individual's risk of mortality is either >5% or twice the risk of the population undergoing that procedure (15,16).

Mitral regurgitation severity. Echocardiography-based evaluation of MR severity is the key point in the selection process. Although a thorough algorithm grading MR severity have been developed by the European Association of Echocardiography **(Table 1)**; differentiating moderate from severe MR can be sometimes difficult (17). Severe MR is usually associated with a LA and LV enlargement due to chronic volume overload; however this hint might be missing in the settings of acute MR onset. Note, cut-off values defining severe MR are different for organic and functional regurgitation (EROA 0.4 cm^2, R Vol 60 ml versus EROA 0.2 cm^2, R Vol 30 ml, respectively) (17,18).

Mitral valve anatomy. The EVEREST trial has defined anatomic eligibility criteria for both functional and organic MR (11). Key MV anatomic inclusion criteria included central origin of a regurgitant jet (A2-P2 MV segments), mitral valve orifice area >4 cm^2 and, for patients with functional MR, a coaptation length of ≥2 mm and a coaptation depth of <11 mm, and for patients with leaflet flail, a flail gap <10 mm and a flail width <15 mm. Caution should be taken

in the case of short posterior leaflet (<8 mm) or calcification in the grasping area. Perforated mitral leaflets or clefts, lack of chordal support, rheumatic or endocarditic MV are contraindications to the procedure. Nevertheless, these criteria are of relative importance as experience has shown that the MitraClip device can be successfully implanted in patients with more complex MV anatomy and local expertise should always be considered.

Early experience compared to minimal invasive MV repair

In our retrospective study, we evaluated efficacy and safety of MitraClip therapy versus minimally invasive surgical MV repair using the videothoracoscopic technique (Heartport) in high-risk patients with significant functional MR and severe systolic heart failure (19). Heartport technique is a state-of--the-art minimal invasive technique superior to conventional surgery as regards the safety profile that can be considered as a gold standard when comparing the safety and efficacy profile of the percutaneous mitral valve interventions. The MitraClip population consisted of the first consecutive 24 high-surgical--risk patients (age 75 ± 9 years, 75% males, NYHA III/IV 88%, LV ejection fraction 31 ± 9%, EuroSCORE II 18 ± 14%), while the surgical group consisted of 48 patients matched for age, NYHA class and LV ejection fraction. The median follow-up was 1028 days (IQR: 272–1564 days) in the MitraClip group and 890 days (IQR: 436–1381 days) in the surgical group (p = 0.95). Both the MitraClip and the surgical group had similar 30-day mortality rates (4% vs. 13%, p = 0.41) and prevalence of serious adverse events (25% vs. 38%, p = 0.43). Total all--cause mortality (54% vs. 60%, log-rank p = 0.64) and rates of rehospitalizations for heart failure (42% vs. 29%, log-rank p = 0.68) did not differ significantly between groups. Both techniques were associated with significant decrease in NYHA class and severity of functional MR (p < 0.001 for all).

Conclusion

MitraClip catheter-based technique has recently emerged as a new option for MV repair in patients with high risk for cardiac surgery. Results from several trials and registries demonstrate its favourable safety profile and significant improvement in the degree of MR and symptomatology. Though the efficacy in the MR reduction is lower as compared to surgery, cumulative experience across the trials, registry and real world practice provide with the encouraging signals of the clinical benefit. Ongoing pivotal trials will determine the clinical impact of MitraClip intervention in high risk patients with advanced heart failure and functional MR as compared to standard of care.

References

1. B. Iung, G. Baron, E.G. Butchart, et al., A prospective survey of patients with valvular heart disease in Europe: The Euro Heart Survey on Valvular Heart Disease, European Heart Journal 24 (2003) 1231–1243.
2. N.M. Van Mieghem, N. Piazza, R.H. Anderson, et al., Anatomy of the mitral valvular complex and its implications for transcatheter interventions for mitral regurgitation, Journal of the American College of Cardiology 56 (2010) 617–626.
3. A.F. Members, A. Vahanian, O. Alfieri, et al., Guidelines on the management of valvular heart disease (version 2012). The Joint Task Force on the Management of Valvular Heart Disease of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS), European Journal of Cardio-Thoracic Surgery 42 (2012) S1–S44.
4. L.H. Ling, M. Enriquez-Sarano, J.B. Seward, et al., Clinical outcome of mitral regurgitation due to flail leaflet, New England Journal of Medicine 335 (1996) 1417–1423.
5. B.H. Trichon, G.M. Felker, L.K. Shaw, et al., Relation of frequency and severity of mitral regurgitation to survival among patients with left ventricular systolic dysfunction and heart failure, American Journal of Cardiology 91 (2003) 538–543.
6. T.M. Koelling, K.D. Aaronson, R.J. Cody, et al., Prognostic significance of mitral regurgitation and tricuspid regurgitation in patients with left ventricular systolic dysfunction, American Heart Journal 144 (2002) 524–529.
7. M. Enriquez-Sarano, H.V. Schaff, T.A. Orszulak, et al., Valve repair improves the outcome of surgery for mitral regurgitation. A multivariate analysis, Circulation 91 (1995) 1022–1028.
8. M. Mirabel, B. Iung, G. Baron, et al., What are the characteristics of patients with severe, symptomatic, mitral regurgitation who are denied surgery? European Heart Journal 28 (2007) 1358–1365.
9. O. Alfieri, F. Maisano, M. De Bonis, et al., The double-orifice technique in mitral valve repair: a simple solution for complex problems, Journal of Thoracic and Cardiovascular Surgery 122 (2001) 674–681.
10. MitraClip Therapy for Transcatheter Mitral Valve Repair, n.d. http://www.mitraclip.com/hcp (accessed 03.10.16).
11. T. Feldman, S. Kar, M. Rinaldi, 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, Journal of the American College of Cardiology 54 (2009) 686–694.
12. T. Feldman, E. Foster, D.D. Glower, et al., Percutaneous repair or surgery for mitral regurgitation, New England Journal of Medicine 364 (2011) 1395–1406.
13. F. Maisano, O. Franzen, S. Baldus, et al., Percutaneous mitral valve interventions in the real world: early and 1-year results from the ACCESS-EU, a prospective, multicenter, nonrandomized post-approval study of the MitraClip therapy in Europe, Journal of the American College of Cardiology 62 (2013) 1052–1061.
14. M. Puls, E. Lubos, P. Boekstegers, et al., One-year outcomes and predictors of mortality after MitraClip therapy in contemporary clinical practice: results from the German transcatheter mitral

valve interventions registry, European Heart Journal 37 (2016) 703–712.
15. O. Boyd, N. Jackson, How is risk defined in high-risk surgical patient management? Critical Care 9 (2005) 390–396.
16. B. Bridgewater, R. Kinsman, P. Walton, et al., The 4th European Association for Cardio-Thoracic Surgery adult cardiac surgery database report, Interactive Cardiovascular and Thoracic Surgery 12 (2011) 4–5.
17. P. Lancellotti, C. Tribouilloy, A. Hagendorff, et al., Recommendations for the echocardiographic assessment of native valvular regurgitation: an executive summary from the European Association of Cardiovascular Imaging, European Heart Journal Cardiovascular Imaging 14 (2013) 611–644.
18. P. Lancellotti, P. Troisfontaines, A.-C. Toussaint, L.A. Pierard, Prognostic importance of exercise-induced changes in mitral regurgitation in patients with chronic ischemic left ventricular dysfunction, Circulation 108 (2003) 1713–1717.
19. T. Ondrus, J. Bartunek, M. Vanderheyden, et al., Minimally invasive mitral valve repair for functional mitral regurgitation in severe heart failure: MitraClip versus minimally invasive surgical approach, Interactive Cardiovascular and Thoracic Surgery 23 (2016) 784–789.
20. D. Cacela, A. Fiarresga, L. Branco, et al., Percutaneous treatment of mitral valve regurgitation: initial experience with the MitraClip device, Revista Portuguesa de Cardiologia 34 (2015) 515–524.