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REVIEW

Critical evaluation of the MitraClip system in the management of mitral regurgitation

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Abstract: The MitraClip (MC) system is a device for percutaneous, transseptal edge-to-edge reconstruction of the mitral valve (MV) in patients with severe mitral regurgitation (MR) not eligible for surgery. Recently, a number of studies have underlined the therapeutic benefit of the MC system for patients with extreme and high risk for MV surgery suffering from either degenerative or functional MR. The MC procedure shows negligible intraprocedural mortality, low periprocedural complication rates, and a significant reduction in MR, as well as an improvement in functional capacity and most importantly quality of life. Presently, the MC system has become an additional interventional tool in the concert of surgical methods. It hereby enlarges the spectrum of MV repair for the Heart Team. Lately, many reviews focused on the MC system. The current review describes the developments in the treatment of MR with the MC system.

Keywords: MitraClip, mitral regurgitation, percutaneous mitral valve repair

Introduction

With increasing age, the prevalence of mitral regurgitation (MR) is rapidly growing.[1] Aging of the world's population challenges health care professionals worldwide to develop new and less invasive treatment options for the elderly.

The MitraClip (MC) system is by now an established interventional therapy for severe MR in a very selective group of patients with high or extreme risk for conventional surgery (class IIB, evidence class C, recommendation, European Guidelines)[2] – namely the elderly, patients with multiple comorbidities, and/or patients with severely reduced ejection fraction.

Mitral valve repair (MVR) – despite the absence of randomized trials – is the gold standard for the treatment of severe MR. If repair is not suitable, mitral valve replacement (MVRx) is the only surgical option.[3] In young and low surgical risk patients, results are excellent; the mortality rate for MVR is low with 1.4%, and for MVRx with 1.6%. However, in octogenerians and patients with high surgical risk, 30-day mortality has been shown to be substantially higher with 11.0% for MVR and 18.9% for MVRx. For the latter, there is a great need for a less invasive interventional therapy. The MC device (Abbott Laboratories, Abbott Park, IL, USA) is a transvenous, transseptal, edge-to-edge repair system for patients with high surgical risk for the treatment of severe functional (FMR) and degenerative MR (DMR). In 2005, the first results of the Endovascular Valve Edge-to-Edge Repair Study (EVEREST) I trial were published.[5] At present, over 22,000 patients (as of April 2015, according to the manufacturer Abbott Laboratories) have been treated worldwide (Table 1).

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Table 1 MitraClip clinical trials and commercial use with corresponding number of patients

Study	Population	N*
EVEREST I (feasibility)	Feasibility patients	55
EVEREST II (pivotal)	Pre-randomized patients	60
EVEREST II (pivotal)	Nonrandomized patients (high-risk study)	78
EVEREST II (pivotal)	Randomized patients (2:1 clip-to-surgery ratio)	279 184 clip 95 surgery
REALISM (continued access)	Nonrandomized patients	899
Compassionate/ emergency use	Nonrandomized patients	66
ACCESS Europe Phase I	Nonrandomized patients	567
ACCESS Europe Phase II	Nonrandomized patients	286
Commercial use	Commercial patients	19,946
Total		22,141 + 95 surgery

Notes: *Data given are as of April 30, 2015. Courtesy of Abbott Laboratories.
Abbreviations: EVEREST, the Endovascular Valve Edge-to-Edge Repair Study; REALISM, Real World Expanded Multicenter Study of the MitraClip System study; ACCESS-Europe, A Two-Phase Observational Study of the MitraClip System in Europe.

In the USA, the commercial use of the MC system started in 2014 with a steadily growing number and holds a current market share of 20%–25% (Figure 1). Globally, the etiology of MR is 2/3 FMR and 1/3 DMR (Figure 2).

European guidelines recommend MC treatment for both FMR and DMR,[2] whereas the MC system is approved only for DMR in the USA. After 10 years of clinical experience with percutaneous MVR, this review focuses on the results of recent registries and clinical studies, such as EVEREST II,[6–10] ACCESS-EU,[11,12] GRASP,[13,14] TRAMI,[15–17] and one meta-analysis.[18]

The MitraClip: eligibility criteria and procedure

To guarantee safe positioning of the clip, anatomical eligibility criteria are recommended. A coaptation length of ≥2 mm, a coaptation depth of <11 mm, and in the case of degenerative disease, a flail gap of <10 mm and a flail width of <15 mm are favorable.[19] The MC system consists of a steerable guide catheter that is introduced transfemoral, and through echocardiographic guiding transseptal into the left atrium (Figure 3). The clip delivery system can be introduced through the guide catheter. Once the delivery system is completely introduced into the guide, the operator can move the MC in all dimensions under echocardiographic guidance and fluoroscopic confirmation. In the area of the MR, the clip is guided directly above the leaflets by 3D-echo, and the orientation of the clip arms should be perpendicular to the line of coaptation.

The MC is lowered through the valve into the left ventricle to load the leaflets on the clip arms. The grippers fix the leaflets to the clip arms, and then the arms are closed and the MC can be released from the delivery system (Figure 3).

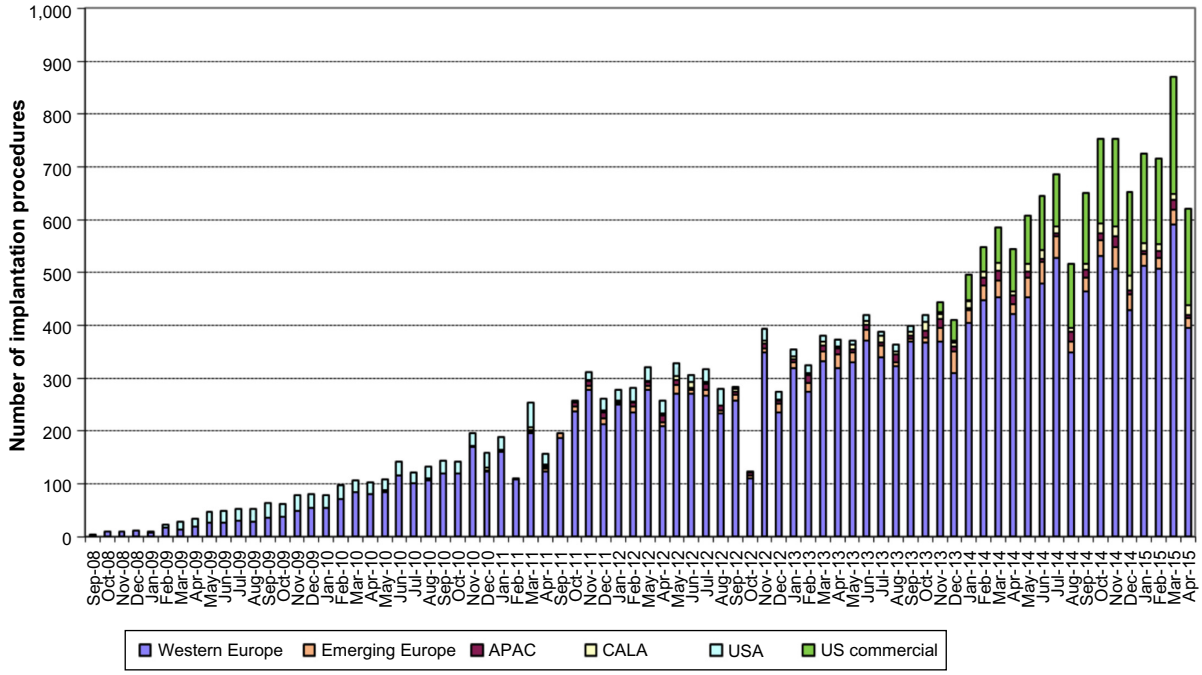

Figure 1 Worldwide experience with the MitraClip procedure from September 2008 until April 2015.
Note: Courtesy of Abbott Laboratories.
Abbreviations: APAC, Asia-Pacific; CALA, Caribbean and Latin America.

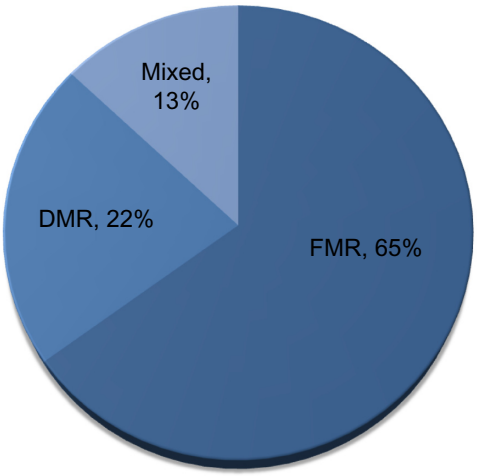

Figure 2 Etiology of mitral regurgitation according to the manufacturer Abbott Laboratories (as of April 30, 2015).
Note: Courtesy of Abbott Laboratories. MitraClip Therapy Worldwide Experience 2015, April 30, 2015. © 2015 Abbott. All rights reserved. AP2939842-OUS Rev. M 9-EH-4-3874-01 05-2015 REV P.
Abbreviations: DMR, degenerative mitral regurgitation; FMR, functional mitral regurgitation.

Echocardiography is the most important guiding modality for all steps of the procedure, especially during clip positioning, whereas fluoroscopy is only essential for wiring, transseptal puncture, and control of coaxial alignment of the clip to the line of coaptation during transvalvular maneuvering. Further use of fluoroscopy as a second tool of visualization is optional and operator-dependent. Fluoroscopy duration is approximately 25 minutes. Contrast agents are not needed.[12]

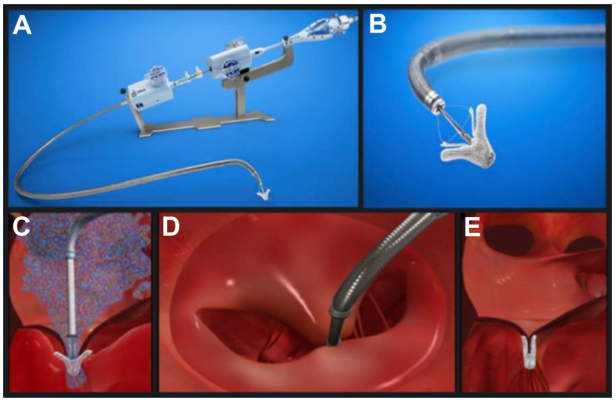

Figure 3 The MitraClip system.
Notes: (**A**) The MitraClip system with the steerable guide catheter, the clip delivery system, and the MitraClip positioned in the stabilizer. (**B**) The MitraClip is attached to the delivery system. The two arms are open, and the grippers are almost touching the arms. (**C**) The MitraClip is being positioned directly below the mitral valve with each leaflet on one side between the clip arms and the grippers in the region of mitral regurgitation. (**D**) Surgical view from the left atrium onto the valve: the grippers fix the leaflets to the clip arms, and the clip arms are closed, resulting in a dual orifice during diastole. The clip is still attached to the delivery system. (**E**) The clip is released from the delivery system after grasping the anterior and posterior mitral leaflet (pictures and graphics courtesy of Abbott Laboratories).

Conventional management of MR in comparison to the MC system

Standard of care for severe MR is surgical treatment, preferably mitral valve (MV) reconstruction before MVRx.[20] So far, the EVEREST II trial is the only randomized controlled trial comparing MV surgery (MVS) and MC.[10] Of note, patients in this study were eligible for surgery in contrast to the majority of MC studies. In this study, MC shows a clear inferiority regarding acute efficacy in MR reduction as well as an inferiority in the composite end point of primary efficacy (freedom of death, MVS or reoperation, and MR grade 3+ or 4+) at 1-year follow-up in the intent-to-treat analysis (73% for MVS vs 55% for MC, P=0.007). Following MC, 20% of the patients had to be reoperated compared to 2.2% after MVS (4-year follow-up: 24.8% and 5.5%, respectively). More patients had MR grade 2+ after MC therapy. However, patients showed less symptomatic heart failure according to the New York Heart Association (NYHA) class when compared to those who underwent MVS. Interestingly, at 4-year follow-up the composite end point of freedom from death, surgery, or MR ≥ grade 3+ showed a rate of 39.8% in the MC group and 53.4% after MVS, a difference that was no longer statistically significant (P=0.07). The interventional and surgical long-term results proved to be stable at 4 years with 25% vs 5.5% (MC vs MVS) of the patients requiring surgery for MV dysfunction. Remarkably, if a good result after 6 months was found with the MC, the likelihood of recurrent MR was low, and there was no evidence of late device-related complications.[10]

A meta-analysis of 21 studies with 6,463 patients compared the outcome of MVS (n=3,265) and MC (n=3,198) demonstrating similar high rates of procedural success (MVS 98% vs MC 96%).[21] However, while MVS was superior with respect to 30-day technical failure rate (0.6% vs 3.2%, P=0.002), outcome for MC was superior to MVS in the pooled key safety analysis at 30 days (mortality: 3.3%, 95% confidence interval [CI] 2.6–4.2 vs 16.2%, 95% CI 13.0–20.0; stroke: 1.1%, 95% CI 0.6–1.6 vs 4.5%, 95% CI 3.6–5.3; bleeding: 4.2%, 95% CI 3.0–7.0 vs 59.0%, 95% CI 50.0–67.0; prolonged mechanical ventilation: 1.7%, 95% CI 1.1–2.2 vs 36.3%, 95% CI 33.1–40.0). These results were shown despite a higher surgical risk profile in the patient group treated with MC (eg, mean left ventricular ejection fraction [LVEF] of 38% vs 52% [MC vs MVS]).[21] One-year mortality of MC patients was 13%. Since there is no long-term data available for MVS, results are not comparable. A further limitation of this meta-analysis is the fact that most of these studies on MC therapy were derived from registries or retrospectively analyzed case

series; they are not randomized or controlled, especially for the patient population characteristics.

MC therapy has to be compared to the best medical therapy in heart failure patients with severe MR. This group of patients have a 1-year mortality of 20%, a 5-year mortality of 50%, and a high rate of recurrent hospitalization for heart failure.[22] Trials prospectively comparing best medical treatment with interventional therapy are ongoing. The currently enrolling studies COAPT (ClinicalTrials.gov registration number: NCT01626079) and RESHAPE-HF (ClinicalTrials.gov registration number: NCT01772108) will address this important question in the near future.

Mortality and safety

The largest meta-analysis comprising 2,980 patients from 16 studies (12 European and four North American) demonstrated a very low intra-procedural mortality of only 0.1%. Nevertheless, 30-day mortality increased to 4.2%, and all-cause mortality during a mean follow-up of 310 days was 15.8%.[18] Thirty-day mortality ranged between 0.9%[14] and 4.7%[12] in most clinical trials. Recent trials report a high 1-year mortality ranging between 12% and 18.2%.[12,14,20] Significant comorbidities expressed by a high logistic European System for Cardiac Operative Risk Evaluation (EuroSCORE) I of 23.4%±1.5% most likely accounts for the high mortality rate during the first year.[18] In the GRASP registry, 55% of deaths during the first year were attributed to noncardiac reasons.[14]

Complications

In the meta-analysis, the most relevant procedure-associated complication was major bleeding (requiring transfusion) with 9.7% followed by stroke/transient ischemic attack (1.3%), chordal rupture (0.8%), pericardial tamponade (0.7%), and myocardial infarction (0.4%).[18] The ACCESS registry reports even lower rates of stroke (0.7%) and bleeding complications (3.8%).[12] In summary, complication rates associated with MC are low (Table 2), particularly when compared to those associated with transcatheter aortic valve replacement. Here, arterial puncture and calcification of vessels and the aortic annulus increase the risk of transient ischemic attack as well as stroke, ranging from 4.0% to 6.7%,[23] and of major vascular complications, ranging from 8.2%[24] to 16.2%.[23]

Heart failure and MC

MR in combination with congestive heart failure has a very poor prognosis.[22,25] Reverse left ventricular (LV) remodeling and improvements of symptoms after MVS in patients with advanced LV dysfunction have been reported in several studies.[26,27] Thirty-day mortality ranges between 8% and

Table 2 Complications of percutaneous mitral valve repair

	EVEREST II (30-day FU)[7]	TRAMI[15] (EuroSCORE ≥20%/ EuroSCORE <20%), data for in-hospital events	ACCESS-EU[1]	Meta-analysis[18]
Procedural death	0.0%	–	0.0%	0.1%
30-Day mortality	7.7%	4.3%/1.1% (in hospital)	3.4%	4.2%
All-cause mortality during FU	24.4%	13.4%/9.6% (mean FU of 72 days)	17.3% (12-month FU)	15.8% (mean FU of 310 days)
Vascular complications needing intervention	–	–	–	1.0%
Major bleeding requiring transfusion	17.9%	13.7%/8.7%	–	9.7%
Bleeding complications	–	–	3.9%	–
Tamponade or significant pericardial effusion	–	1.1%/1.6%	1.1%	0.7%
Emergent cardiac surgery	0.0%	–	0.4%	0.7%
Nonfatal myocardial infarction	2.6%	0.0%/0.2%	0.7%	0.4%
Chordal rupture	–	–	–	0.8%
Single leaflet clip detachment	–	–	4.8% (diagnosed within 6 months)	2.3%
Clip embolism	–	–	0.0%	0.04%
Hemorrhagic or ischemic stroke/TIA	2.6%	0.7%/0.0%	0.7%	1.3%
Acute renal failure	3.8%	1.8%/0.2% (dialysis at discharge)	4.8%	4.2%
Need for repeat MitraClip	0.0%	1.8%/1.6%	3.4%	1.6%

Abbreviations: EuroSCORE, European System for Cardiac Operative Risk Evaluation; FU, follow-up; TIA, transient ischemic attack.

9%.[26,28] In this regard, MC is a promising, minimally invasive percutaneous treatment technique.[29] In a study, 108 patients with predominantly FMR and LV dysfunction (mean LVEF 28%±11% with LVEF <40% in 88% of patients) demonstrated an impressively low 30-day mortality of only 1.8%.[30] Most importantly, there are accumulating data that the MC appears to be not only safe but also efficacious in patients with FMR.[30] In this regard, the ACCESS-EU registry showed a similar clinical improvement in patients with an LVEF ≤30% vs >30%. In addition, there is some evidence of reverse remodeling after successful treatment with the MC.[31]

There is an ongoing discussion whether a severely depressed LV function might be susceptible to further acute reduction in an LVEF induced by surgical correction of MR. Interestingly, the occurrence of the so-called afterload mismatch was frequently found (26%) in a study comprising 73 patients with FMR and severely reduced LVEF (27%±9%).[32] Comparison of patients with vs without afterload mismatch after MC revealed that LV end-diastolic diameter (71±8 mm vs 67±7 mm, *P*=0.02) and LV end-systolic diameter (57±9 mm vs 53±7 mm, *P*=0.04) were larger, pulmonary pressure was higher (49±10 mmHg vs 40±10 mmHg, *P*=0.04), and right ventricular dysfunction was more prevalent (68% vs 31%, *P*=0.049). The authors suggested that afterload mismatch was the consequence of an abrupt increase in LV end-systolic wall stress after MR correction on a preexisting status of absent or reduced contractile reserve. Fortunately, the observed hemodynamic deterioration in patients was a transient phenomenon and did not translate into an adverse outcome at 12 months (1-year survival: 81.2% vs 75.2%, *P*=0.44). This study observed no difference in the need for inotropes between patients with and without afterload mismatch in the early postoperative time period.[32]

The previously mentioned study comprising only patients with FMR and reduced LVEF reported that 57.7% of patients required inotropic support on the intensive care unit and 13% of patients were transiently bridged with intra-aortic balloon counter pulsation (IABP) underlining the incidence of a transient window of aggravated heart failure immediately after intervention.[30]

Procedural success, long-term outcome, and predictors of procedural success

Acute procedural success is defined as a reduction in MR to ≤grade 2+. A recent meta-analysis showed acute procedural success in 91.4% of the patients. Persistent MR reduction was found in 85.3% of the patients at 30-days follow-up and in 86.9% at a mean follow-up of 310 days (ranging from 80 days to 4 years).[18] In only 3% of the patients, the therapy failed, and no clip could be implanted. A single-center study in 108 patients with predominantly FMR and LV dysfunction (mean LVEF 28%±11% with 88% having an LVEF <40%) showed a procedural success rate of 99%.[30]

The MC procedure is associated with a low mortality rate. However, it is of great importance to better define predictors of adverse clinical outcome. Only few studies have addressed this topic. In a study of selected FMR patients with severe LV dysfunction, univariate analysis demonstrated an adverse outcome for pre-interventional logistic EuroSCORE I ≥20% (hazards ratio [HR] 4.4, 95% CI 1.8–9.5, *P*=0.01) and pre-interventional proBNP >1,600 pg/mL (HR 21.2, 95% CI 2.5–38, *P*=0.01), a need for post-interventional IABP treatment (HR 3.8, 95% CI 1.2–13.5, *P*=0.02), and peri-interventional occurrence of acute kidney injury (HR 4.1, 95% CI 2–16, *P*=0.01).[30] These findings are in line with results of a single-center study (65% FMR, 35% DMR) analyzing predictors of midterm clinical and survival outcome (all-cause mortality or hospitalization): NYHA IV at baseline (HR 2.4, 95% CI 1.4–4.3, *P*=0.002) and glomerular filtration rate <60 mL/min/1.73 m^2 (HR 2.05, 95% CI 1.1–4.0, *P*=0.03), Sociey of Thoracic Surgeons score >12% (HR 2.20, 95% CI 1.3–3.8, *P*=0.004), and failure of procedural success (HR 2.66, 95% CI 1.4–5.0, *P*=0.002).[33]

In a study of 300 MC patients (68% FMR, 32% DMR), regurgitant orifice area ≥70.8 mm^2 and trans-mitral pressure gradient ≥4 mmHg in combination with an MV orifice area ≤3.0 cm^2 (assessed by echocardiography) were defined as predictors of increased risk for procedural failure.[34]

Quality of life

Functional capacity according to the NYHA class showed a relief of symptoms (86% in the NYHA class I and II) 1 year after treatment.[30] The meta-analysis showed an improved functional capacity according to the NYHA (class I and II) in 76.6% of the patients.[18] Moreover, the analysis demonstrated an improvement in LVEF, 6-minute walk distance, and quality of life.[18] The gain in 6-minute walk distance (260.6±13.6 m at baseline vs 359.8±24.9 m at follow-up) was larger than the gain being described after cardiac resynchronization therapy.[23] Similar data were reported for FMR patients with severe LV dysfunction (328.7±80.1 m; mean improvement 108 m). Most interestingly, there were clear signs of LV reverse remodeling with an increase in LVEF (27%±9.8% to 34.7%±10.4%, *P*=0.02 at 1-year follow-up) and with a decrease in LV end-diastolic volume as well as in LV end-systolic volume.[30]

Conclusion

For patients with severe MR and high surgical risk, the treatment with the MC has meanwhile evolved as the therapy of choice in Europe (FMR and DMR) and North America (DMR). There is a class IIb (level of evidence C) recommendation in the European guidelines for interventional mitral device therapy in severe symptomatic FMR as well as DMR in all patients with high surgical risk. Additionally, life expectancy has to exceed 1 year, and the Heart Team (cardiologist, cardiac surgeon) should mutually agree that patients are ineligible for surgery.[2] Additionally, MR pathology has to meet special criteria for intervention by defined echocardiographic parameters.[6,35] North American 2014 guidelines for the management of valvular heart disease[20] strictly follow the results of the EVEREST I and II trials and recommend interventional mitral device therapy only for DMR.[6,7,10] In conclusion, the MC system has evolved as the most important transcatheter MVR therapy till date. Intraprocedural mortality is low, adverse events are seldom, and short- as well as long-term results are satisfactory.

The number of case reports and smaller case series, where the MC device was used as a bailout strategy apart from current guideline recommendations, is rapidly growing. These reports show that with increasing device experience, the anatomical criteria for the applicability of MC implantation broaden. Current guideline-based indications might therefore underestimate the potential of MC therapy.

- In the case of severe coaptation failure, two MCs were implanted via a double-guide approach with two simultaneously introduced clip delivery systems. The first clip was initially used to improve coaptation between the posterior and anterior leaflet for the second clip to be positioned for principal MR treatment. Once a successful grasp was performed with the second clip, the first clip was reopened and optimized ("mitral titration technique").[36]
- The MC was used after MVR to reduce residual severe MR.[37,38]
- The MC was implanted in a series of patients with left ventricular outflow tract (LVOT) obstruction with subsequent MR due to systolic anterior movement of the anterior leaflet in hypertropic obstructive cardiomyopathy patients. Not only MR but also subvalvular LVOT gradient was successfully reduced.[39,40]
- The MC was used as primary rescue therapy for patients with severe MR in cardiogenic shock and/or critically ill.[41–43]
- The MC was implanted in a trileaflet MV.[44]

These cases demonstrate the potential of the device and might inspire reconsideration of the use of MC in future trials. Due to the remarkably low peri-interventional risk, the MC might be considered as a bailout therapy for treatment of severe MR even in critically ill patients.

However, new devices for the therapy of MR are entering the market, ultimately broadening the spectrum of patients being treated by catheter-based techniques in the near future. In line with surgical reconstruction, a combined use of different interventional devices, for example, MC and annuloplasty device, may be the future of interventional MV therapy.

Disclosure

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