ESC HEART FAILURE
ESC Heart Failure 2021; **8**: 4617–4625
Published online 8 September 2021 in Wiley Online Library (wileyonlinelibrary.com) **DOI:** 10.1002/ehf2.13564

ORIGINAL ARTICLE

Re-do MitraClip in patients with functional mitral valve regurgitation and advanced heart failure

Michael M. Kreusser[1,2]*, Andreas Weber[1], Nicolas A. Geis[1], Leonie Grossekettler[1], Martin J. Volz[1], Sonja Hamed[1], Hugo A. Katus[1,2], Sven T. Pleger[1], Norbert Frey[1,2] and Philip W. Raake[1]

[1]*Department of Internal Medicine III, Division of Cardiology, University of Heidelberg, Im Neuenheimer Feld 410, Heidelberg, 69120, Germany; and* [2]*DZHK (German Center for Cardiovascular Research), Partner Site Heidelberg/Mannheim, Heidelberg, Germany*

Abstract

Aim Percutaneous mitral valve repair (PMVR) via MitraClip implantation is a therapeutic option for severe mitral regurgitation (MR) in advanced stages of heart failure (HF). However, progressive left ventricular dilation in these patients may lead to recurrent MR after PMVR and consequent re-do MitraClip implantation. Here, we describe the characteristics and outcomes of this clinical scenario.

Methods and results Patients with systolic HF and functional MR undergoing a re-do MitraClip procedure were retrospectively analysed. Inclusion criteria were age ≥18 years, technical, device and procedural success at first MitraClip procedure, functional MR and systolic HF with an ejection fraction (EF) of <45%. Seventeen out of 684 patients undergoing PMVR with the MitraClip device at our institution between September 2009 and July 2019 were included. All patients displayed advanced HF with an EF of 20% (±9.9) and highly elevated N-terminal pro-brain natriuretic peptide. Technical success of the re-do MitraClip procedure was 100%, whereas procedural and device success were only achieved in 11 patients (65%). Unsuccessful re-do procedures were related to lower EF and implantation of more than one clip at initial procedure. However, despite reduction in MR grade and no occurrence of significant mitral stenosis after the procedure, the mortality during 12 months follow-up remained high (8 of 17; 47%).

Conclusions In a cohort of patients with advanced HF undergoing PMVR, re-do MitraClip procedure was feasible, but procedural success was unsatisfactory and morbidity and mortality remained high, possibly reflecting the advanced stage of HF in these patients.

Keywords Percutaneous edge-to-edge mitral valve repair; MitraClip; Advanced heart failure; Re-do MitraClip procedure

Received: 11 December 2020; Revised: 8 July 2021; Accepted: 4 August 2021
**Correspondence to: Michael M. Kreusser, Department of Internal Medicine III, University of Heidelberg, Im Neuenheimer Feld 410, 69120 Heidelberg, Germany. Phone: +49 6221 56 8611; Fax: +49 6221 56 5515. Email: michael.kreusser@med.uni-heidelberg.de*

Introduction

Heart failure (HF) is a leading cause of death worldwide with high morbidity and mortality, increasing incidence and prevalence, and a growing economic importance.[1–3] HF often is characterized by progressive dilation of the left ventricle (LV), leading to widening of the mitral anulus with consequent mitral regurgitation (MR).[4] This functional MR significantly contributes to cardiac morbidity and mortality in HF patients, and surgical correction of the MR is at high and often prohibitive risk.[5,6] Thus, patients with multiple co-morbidities and/or advanced stages of HF are thought to be rather eligible for non-surgical techniques, such as edge-to-edge percutaneous mitral valve repair (PMVR) via the MitraClip device (Abbott Vascular, North Chicago, Illinois, USA).[1,7,8] PMVR via MitraClip procedure in HF patients recently has been evaluated in two large randomized trials: the MITRA-FR trial (Multicentre Study of Percutaneous Mitral Valve Repair MitraClip Device in Patients With Severe Secondary Mitral Regurgitation) and the COAPT trial (Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients With Functional Mitral Regurgitation).[9–11] Nevertheless, as correction of MR via MitraClip procedure does not suspend LV dilation, in some

patients, recurrent MR occurs after first MitraClip procedure,[6] and re-do MitraClip procedure may be considered. Data on feasibility and outcomes of re-do MitraClip procedure are very limited and have not been explicitly elaborated for patients with HF.[12,13] Here, we evaluated procedural data and outcomes after re-do PMVR with focus on patients with advanced HF.

Methods

The study was performed in a retrospective approach and conforms with the principles outlined in the Declaration of Helsinki.[14] Medical decision for MitraClip implantation was provided by cardiologists and cardiac surgeons in the heart team.[3,15] All patients were informed about specific risks and alternatives of MitraClip therapy, as well as the options for continued medical treatment and high-risk surgical mitral valve repair and gave informed written consent to the procedure. The study protocol was in accordance with the local ethics committee (reference number S-299/2015).

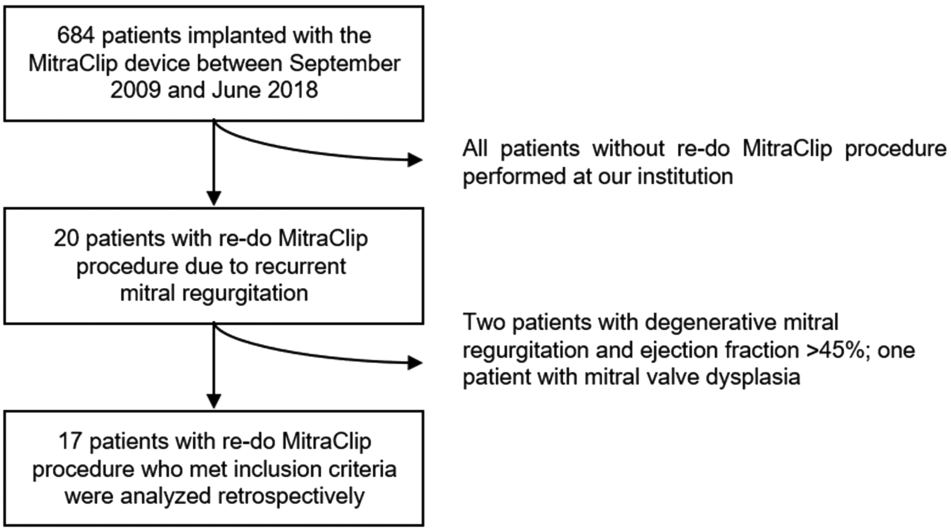
Patient population

From September 2009 to July 2019, 684 consecutive high surgical risk or non-surgical candidates with severe and moderate to severe symptomatic MR were treated with the MitraClip device at our institution. Of these, we retrospectively identified 20 patients in whom MitraClip re-do procedures were performed at our centre. As focus of the study was on HF patients, inclusion criteria were defined as follows: (i) severe or moderate to severe functional MR, (ii) dyspnoea New York Heart Association (NYHA) class II to IV, and (iii) reduced LV function. One patient was excluded because of complex medical history with underlying congenital heart disease and mitral valve dysplasia. This particular case was published by our group previously.[16] Two other patients were excluded because the underlying pathology was degenerative MR and EF was >45%. The inclusion/exclusion pathway for the study is depictured in *Figure 1*. All included patients (n = 17) were on stable (at least 4 months) optimized individual target HF medication according to current guidelines.

Pre-interventional workup

Pre-interventional workup included the patient's medical history, careful clinical assessment, and determining NYHA class as well as 6 min walk test (6-MWT). Further, laboratory workup included high-sensitivity troponin T, N-terminal-pro-brain-natriuretic peptide (NT-proBNP), and serum creatinine. Glomerular filtration rate (GFR) was calculated by using the MDRD (Modification of Diet in Renal Disease) formula. Cardiac function, mitral regurgitation, and mitral valve morphology were determined by transthoracic and transoesophageal echocardiography (TTE and TEE)[17-19] as previously described.[20] To objectify MR for all patients in the present study in a standardized manner, vena contracta was re-evaluated from the original echocardiography sequences retrospectively. Laboratory data were taken from up to 4 days before MitraClip procedure, echocardiography, and 6-MWT

Figure 1 Study protocol. All patients included in the study underwent a re-do MitraClip procedure at our institution between September 2009 and June 2018 and met the following inclusion criteria: (i) severe or moderate to severe functional mitral regurgitation, (ii) dyspnoea New York Heart Association (NYHA) class II to IV, and (iii) reduced left ventricular function. The main exclusion criteria were morphological properties of the mitral valve that would make successful MitraClip implantation unlikely or impossible.



were performed within 2 weeks prior the procedure. NYHA class and medication were reported at hospitalization for the respective procedure (see *Tables 1* and *2*).

MitraClip implantation procedure and follow up

MitraClip procedures were performed under general anaesthesia[21–23] as previously described.[24] Procedural data (see *Table 3*: number of implanted clips, MR before/after, transmitral gradient, and mitral stenosis) were taken in-procedure. For follow-up, patients were seen in our outpatient clinic at 1, 6, and 12 months after PMVR. NYHA class after the procedure (see *Table 2*) was reported at 30 day follow-up. Study endpoint was defined as death from cardiovascular or non-cardiovascular cause. Technical, device, and procedural success were defined according to the Mitral Valve Academic Research Consortium (MVARC)[25]: *Technical success*: successful device deployment. *Device success*: absence of procedural mortality or stroke and proper placement and positioning of the device and freedom from unplanned surgical or interventional procedure related to the device or access procedure and continued intended safety and performance of the device including no evidence of structural or functional failure, no specific device-related technical failure issues and complications and reduction of MR to either optimal (trace or absent residual MR) or acceptable (residual MR reduced by at least one grade from baseline and to no more than moderate in severity) levels without significant mitral stenosis (postprocedural mean transmitral gradient $\leq$5 mmHg) and with no greater than mild paravalvular MR (and without associated haemolysis). *Procedural success*: device success and absence of major device or procedure related serious adverse events.

Table 1 Patients characteristics

Number of patients	17
Age at first procedure (a)	69 (±8.5)
Male sex	16 (94%)
Functional mitral regurgitation	17 (100%)
Ejection fraction at re-do procedure (%)	20 (±9.9)
EF < 35% at re-do procedure	16 (94%)
Time between 1st and 2nd procedure (d)	589 (±790)
Follow-up after re-do procedure (d)	291 (±294)
Patients died during follow-up	8 (47%)
Heart failure aetiology	
DCMP	8 (47%)
ICMP	9 (53%)
Previous CABG surgery	6 (35%)
Medical therapy at re-do procedure	
Beta-blocker	16 (94%)
ACE-I/ARB	16 (94%)
Aldosterone antagonist	9 (53%)
Device therapy at re-do procedure	
Pacemaker	1 (6%)
ICD	6 (35%)
CRT-D	6 (35%)
Cardiovascular risk factors	
Arterial hypertension	14 (82%)
Diabetes mellitus	6 (35%)
Dyslipoproteinaemia	13 (76%)
(Previous) smoking	11 (65%)
Family history of cardiac disease	4 (24%)
Co-morbidities	
Previous stroke	1 (6%)
Peripheral artery disease	4 (24%)
Obstructive lung disease	5 (29%)
CKD > Stage II at re-do procedure	13 (76%)
Atrial fibrillation	11 (65%)

ACE-I, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; CABG, coronary artery bypass graft; CKD, chronic kidney disease (stages I–V according to KDIGO (Kidney Disease Improving Global Outcomes); CRT-D, cardiac resynchronization therapy with defibrillator; DCMP, dilated cardiomyopathy; EF, ejection fraction; ICD, implantable cardioverter/defibrillator; ICMP, ischaemic cardiomyopathy.
All data were taken from before the initial MitraClip implantation, if not stated otherwise. Data are given as mean (±standard deviation) or absolute number (%).

Statistical methods

Quantitative data are presented as mean (±standard deviation) and median and interquartile ranges [25; 75], depending on the distribution of the data. For qualitative parameters absolute and relative frequencies are presented. Parameters were compared by using the Mann–Whitney *U*-test, Wilcoxon signed-rank test, or Fisher–Yates test, as appropriate. Survival data were summarized by Kaplan–Meier survival curves. A $P < 0.05$ was considered statistically significant. Statistical analyses were performed using GraphPad Prism (GraphPad Software, La Jolla, CA).

Results

Patient population

Of a total of 684 MitraClip patients during the study period, 17 re-do PMVR patients fulfilled inclusion criteria. All patients displayed marks of advanced HF already at first MitraClip procedure, including an EF of 25% (±8.8), NYHA class of 3 ([3.0;3.5]; NYHA class I or II: 0%, NYHA class III: 71%; NYHA class IV: 29%), impaired functional capacity (6-MWT; 327 m (±111)) and elevated NT pro-BNP (7958 ng/L (±9542)), with further advancement at second procedure (see *Tables 1 and 2*). In all patients, secondary functional MR was the underlying disease mechanism, and ischaemic (ICMP) and dilated cardiomyopathy (DCMP) were evenly distributed (*Table 1*).

Therapy with implantable cardioverter/defibrillator (ICD) and/or cardiac resynchronization with defibrillator (CRT-D) therapy was realized in 70% of patients (n = 12). In two patients, EF was 40%, and there was no history of ventricular arrhythmias, consequently decision was made against primary prevention. Three patients refused ICD therapy (no indication for CRT-D). Included patients display a high-risk population,

Table 2 Heart failure related data at implantation

	First procedure	Re-do procedure	*P*-value
6-MWT before the procedure (m)	364 (±129)	327 (±111)	0.493
NYHA class before procedure	3.0 [3.0; 3.5]	3.0 [3.0; 3.5]	0.692
NYHA class after procedure	2.5 [2.0; 3.0]	3.0 [2.5; 3.0]	**0.006**
Delta NYHA class	−0.5 [−1.0; −0.5]	0 [−0.5; 0]	**0.005**
Cardiac biomarkers			
NT-pro BNP (ng/L)	7958 (±9542)	10 196 (±9736)	0.510
High-sensitivity troponin T (pg/mL)	38 (±26)	39(±24)	0.907
Echocardiography data			
Ejection fraction (%)	25 (±8.8)	20 (±9.9)	**0.043**
LA diameter (mm)	53 (±6.9)	54 (±5.3)	0.644
LVED diameter (mm)	63 (±8.7)	68 (±11.7)	0.084
RV diameter (mm)	34 (±5.8)	37 (±5.2)	0.097
Tricuspid valve regurgitation	1.5 [0; 2.0]	1.5 [1.0; 2.0]	0.741
Systolic PA pressure (mmHg)	53 (±4)	51 (±2)	0.765

6-MWT, 6-min walk test; LA, left atrium; LVED, left ventricular end-diastolic; NT pro-BNP, N-terminal pro-brain natriuretic peptide; NYHA, New York Heart Association; PA, pulmonary artery; RV, right ventricle.
Data are compared between first MitraClip implantation and re-do MitraClip procedure. Data are given as mean (±standard deviation) or median and interquartile ranges [25; 75]. Comparison was performed by using the Wilcoxon signed-rank test. Values in bold represent *P*-values <0.05.

Table 3 Procedural results at first and re-do MitraClip procedure

	First procedure	Re-do procedure	*P*-value
Number of clips			0.698
Patients with 1 clip	13 (76%)	12 (71%)	
Patients with 2 clips	4 (24%)	5 (29%)	
Mitral regurgitation			
MR before procedure	4.0 [3.0; 4.0]	3.5 [3.0; 4.0]	0.227
MR after procedure	1.0 [1.0; 1.5]	2.0 [1.0; 2.5]	**0.043**
Transmitral gradient (mmHg)	2.8 (±0.8)	2.8 (±1.4)	0.686
Mitral stenosis (>5 mmHg)	0	0	0.999
Success rates			
Technical success	17 (100%)	17 (100%)	0.999
Device success	17 (100%)	11 (65%)	**0.007**
Procedural success	17 (100%)	11 (65%)	**0.007**
30-day mortality	0	2 (12%)	0.145
Intraprocedural mortality	0	0	0.999
Intraprocedural complications	0	0	0.999

MR, mitral regurgitation.
Data are compared between first MitraClip implantation and re-do MitraClip procedure. Data are given as mean (±standard deviation), median and interquartile ranges [25; 75] or absolute number (%). Comparison was performed by using Wilcoxon signed-rank test or Fisher's exact test. Values in bold represent *P*-values <0.05. Technical, device and procedural success were defined according to the Mitral Valve Academic Research Consortium (MVARC)[25]: *Technical success*: successful device deployment. *Device success*: absence of procedural mortality or stroke and proper placement and positioning of the device and freedom from unplanned surgical or interventional procedure related to the device or access procedure and continued intended safety and performance of the device including no evidence of structural or functional failure, no specific device-related technical failure issues and complications and reduction of MR to either optimal (trace or absent residual MR) or acceptable (residual MR reduced by at least one grade from baseline and to no more than moderate in severity) levels without significant mitral stenosis (postprocedural mean transmitral gradient ≤5 mmHg) and with no greater than mild paravalvular MR (and without associated haemolysis). *Procedural success*: device success and absence of major device or procedure related serious adverse events.

indicated by high incidence of previous coronary artery bypass graft (CABG) surgery (6/9 ICMP patients; 67%), and a high burden of cardiovascular risk factors and co-morbidities, in particular concomitant chronic kidney disease (*Table 1*), the latter resulting in a rather low rate of aldosterone antagonist treatment in only 59% of patients. However, all patients were on stable optimized individual target HF medication (*Table 1*), as far as was tolerated.

Re-do MitraClip procedure

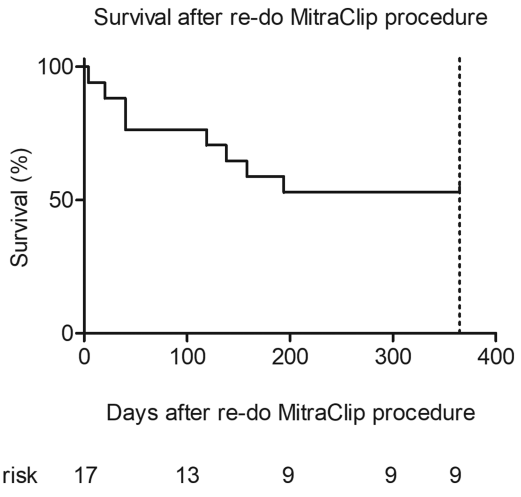
In all 17 patients, re-do PMVR via MitraClip was performed due to severe or moderate-to-severe recurrent MR (median MR 3.0 [3.0; 4.0]), which was concomitant with distinct symptomatic HF (NYHA class 3.0 [3.0;3.5]; 6-MWT 327 m (±111); NT pro-BNP 10196 ng/L (±9736)). Mean interval between first and second PMVR procedure was 589 days (±790), with the

earliest re-interventions performed in two patients both at 28 days after first implantation. Intriguingly, in all patients, the deployment of the clip was successful (n = 17; technical success 100%). Moreover, transmitral gradients were in an acceptable range (2.8 mmHg (±1.4)), and in none of the patients, significant mitral stenosis occurred (*Table 3*). And in all patients, the re-do MitraClip procedure was safe, without intraprocedural complications and without intraprocedural mortality (*Table 3*). However, device success and procedural success were only 65% according to MVARC,[25] and symptomatic HF was not improved by the second MitraClip procedure (delta NYHA class 0 [0; −0.5]). Moreover, outcome after re-do MitraClip was unsatisfactory: eight patients (47%) died within 1 year after the re-do MitraClip implantation. Short-term mortality at 30 days after PMVR was 12% (two patients) (*Figure 2*).

Comparison of first and re-do procedure

Severity of MR was graded comparably at first and second procedure (vena contracta 0.80 mm (±0.04) vs. 0.79 (±0.06); P = 0.413)). Although re-do MitraClip procedure was performed with high technical success rate and without producing further increased transmitral gradients nor procedural complications compared with the first procedure, the improvements in NYHA class (*Table 2*) and MR (*Table 3*) were significantly lower, indicating that patients did not benefit much from the re-do intervention. However, pre-interventional evaluation revealed a further decreased cardiac function at the time of re-do PMVR (EF 25% vs. 20%; P = 0.043), as well as further deteriorated ventricular geometry, indicated by larger left ventricular end-diastolic (LVED) and right ventricular (RV) diameters (*Table 2*).

Figure 2 One year survival after re-do MitraClip procedure. Kaplan–Meier estimated curve for patients who underwent a re-do MitraClip procedure due to recurrent severe or moderate-to-severe mitral regurgitation.



Comparison between successful and non-successful re-do interventions

To identify potential risk factors for failure, we stratified re-do MitraClip procedures for device and procedural success. In the cases without device/procedural success after MVARC,[25] MR grade was decreased by less than one grade or residual MR was between grade II and III after the intervention, leading to classification as 'no device/procedural success achieved' (6/17; 35%). Partial clip detachments or complete loss of leaflet insertions were not observed; however, in one patient, a partial loss of leaflet insertion was interrelated to insufficient MR reduction, leading to re-do procedure 28 days later. When re-do patients were stratified for device/procedural success (*Table 4*), we found no significant differences in parameters such as age at intervention, time interval between first and re-do procedure, and outcome (30 day mortality). But, in the patient group with device/procedural success, one single clip was deployed in all cases during the first procedure, whereas two clips were necessary in four of six of the non-successful cases (66.6%) during the first procedure. Further, we found systolic PA pressure and LVED diameters numerically higher in the non-successful cases at the time of the second procedure, as well as a significantly impaired LV ejection fraction (*Table 4*).

Discussion

Interventional edge-to-edge mitral valve repair is a feasible therapy in patients with severe degenerative or functional MR, who are at high surgical risk. Worldwide more than 100 000 interventions have been performed up to date,[26–28] making PMVR an already established therapeutic option for MR by now. In some cases, severe MR after MitraClip procedure re-occurs and, in this situation, the clinical management remains unclear. Due to prohibitive surgical risk, mitral valve surgery in these cases usually is not an option and data regarding re-do PMVR are sparse.

General considerations for re-do MitraClip procedure

Our data demonstrate that a re-do MitraClip procedure after recurrent MR is not a commonly conducted procedure: it was performed in 20 (3%) of 684 MitraClip patients, which is comparable with the rate reported in other series.[5,6,29–31] Correspondingly to this rare realization, only

Table 4 Stratification for device/procedural success

	D/P success	No D/P success	*P*-value
Age at second procedure (a)	70.7 (±10.7)	71.7 (±5.7)	0.687
Time between 1st and 2nd proc. (a)	778 (±917)	241 (±301)	0.145
Patient died during follow-up	5/11 (45.5%)	3/6 (50%)	0.793
30 day mortality	1/11 (9.1%)	1/6 (16.7%)	0.631
Number of clips at 1st procedure			**0.002**
Patients with 1 clip	11	2	
Patients with 2 clips	0	4	
MR after 1st procedure	1.0 [1.0; 1.5]	1.5 [1.0; 1.6]	0.253
Cardiac parameters at 2nd procedure			
Ejection fraction (%)	22.6 (±6.6)	15.8 (±4.9)	**0.031**
LVED diameter (mm)	66 (±8.9)	71.4 (±12.5)	0.391
Systolic PA pressure (mmHg)	47.1 (±7.8)	53.4 (±10.5)	0.181

LVED, left ventricular end-diastolic; MR, mitral regurgitation; PA, pulmonary artery.
Data are compared between patients with achieved device/procedural (D/P) success and patients without. Data are given as mean (±standard deviation), median and interquartile ranges [25; 75] or absolute number (%). Comparison was performed by using Mann–Whitney *U*-test or Fisher's exact test. Values in bold represent *P*-values <0.05. Device and procedural success were defined according to the Mitral Valve Academic Research Consortium (MVARC).[25]

two case series of 16 and 21 patients, respectively, with mixed aetiology of MR, functional (71% and 53%, respectively), and degenerative (29% and 47%, respectively) at first intervention have been published so far on this subject.[12,29] Although cardiac function was superior to our study and LV diameters were smaller, in the other two series, the overall procedural success rates were only 62% and 73%, respectively, for the re-do MitraClip intervention.[12,29] In our study, the success rate was comparable with this (65%). Reasons for lack of success were unsatisfying reduction of MR grade in all cases (35%), without underlying partial clip detachments or other procedure-related pathologies. Thus, the stark contrast to the success rate of 100% at index intervention may be explained by the further advanced HF status documented by LV diameter, PA pressure, and LVEF. This may then result in less favourable leaflet geometry for grasping at second attempt. And as a majority of the patients (66.7%) already had two clips implanted in the first procedure, result optimization during the re-do case by just implanting another (fourth) clip was limited, giving a potential explanation for the inferior results. Nevertheless, the exact underlying mechanism for recurrence of MR could not be explored in detail in our study due to its retrospective nature. However, as no partial clip detachment was observed, and partial loss of leaflet insertion only in one single patient, we speculate that one relevant mechanism was progressive LV dilation with resulting functional MR, at least in some of the patients.

Re-do percutaneous mitral valve repair in advanced heart failure

All three studies on the topic of re-do PMVR, including the present, demonstrate that this procedure is rather a bailout strategy or must at least be seen as an *ultima ratio* for high-risk patients: for instance, in the series of Kreidel, an elderly population, but not a severe HF cohort, 62% of patients died within 3 months after re-do attempt, including three (with functional MR) of five patients who were sent to surgery. Likewise, in our study, only 53% of patients were alive at 12 months after re-do procedure. The patients with failed intervention were treated conservatively and not send to surgery, as surgical risk was deemed too high. Taken together, these data reflect the vulnerability of patients with recurrence of MR after successful index intervention. And, among those, patients with advanced HF and recurrence of moderate-to-severe or severe MR after a primary successful MitraClip procedure are an especially challenging patient cohort.[32,33]

Our data show that in patients with severe HF and functional MR, re-do MitraClip is feasible, but symptomatic and procedural results are lower compared with the index intervention and outcomes remain unsatisfactory as HF further advances in these patients. PMVR in HF patients is a complex treatment option, as demonstrated in the MITRA-FR and COAPT trials.[9-11] Certainly, the procedure is more successful under optimized circumstances, and successful PMVR in advanced HF patient cohorts has been reported from many centres.[17,18,34] This has to be even more taken into account when alternative treatment options such as permanent mechanical circulatory support are available, and patients with end-stage HF may rather benefit from early implantation of a ventricular assist device, and prior PMVR may only delay this often unavoidable therapy.[35] In patients with advanced HF, PMVR certainly is a potential therapeutic option, but therapeutic strategies must be carefully evaluated. We believe that this is only possible in a specialized heart failure team, including heart failure cardiologists, interventional cardiologists, cardiac surgeons experienced in heart failure surgery, and colleagues from other disciplines such as anaesthesiology and nephrology.[3]

Potential predictors for re-do success

What can we extract now from our data to potentially predict re-do success of future procedures? First, in patients without successful re-do procedures, the ejection fraction was lower, pointing to a more advanced HF in the group with device/procedural failure. Second, in the device/procedural failure group significantly, more clips were implanted during the first procedure. Thus, less space was left for further clip placement, and as such, proper treatment of MR was hampered. A maximum of three clips were placed in our patients. For reasons of space or transmittal pressure gradients, a fourth clip could not be deployed in any case. No partial clip detachments occurred in the re-do cases (data not shown). So, far advanced stages of heart failure as well as space limitations due to multiple clips implanted may be the most relevant limiting factors for re-do MitraClip procedures.

Limitations

The present study bears many limitations, most of them derived by the small number of patients included. Further, the data were retrieved from a single centre in a retrospective approach, and data calculation was not realized by a core lab. Further, grading of MR was not performed in a standardized manner at the time of PMVR procedure, but retrospectively. However, our study comprises the first series of patients with advanced HF undergoing re-do MitraClip implantation and therefore may add to current discussions.

Conclusions

Data regarding the management of recurrent MR after initial successful index MitraClip procedure are limited. Still this is a rare event, but these patients with recurrence of MR in need of treatment are at high risk. We could demonstrate that re-do MitraClip is feasible even in advanced HF, but procedural success rate is much lower compared with the index interventions. In this regard, individual decisions have to be made reflecting surgical or interventional risks, the individual prognosis and the patient's will. Furthermore, re-do interventions are far more complex and should only be carried out in experienced centres.[3]

Acknowledgements

We thank the colleagues from the Institute for Medical Biometry and Medical informatics, University of Heidelberg, Heidelberg, Germany, for statistical advice and review. Open Access funding enabled and organized by Projekt DEAL.

Conflict of interest

S.T.P. and P.W.R. received speaker honoraria from Abbott Vascular. M.M.K. and S.T.P. received research grants from Abbott Vascular. M.M.K., N.A.G., and P.W.R. are investigators in the RESHAPE-HF (*A Randomized Study of the MitraClip Device in Heart Failure Patients with Clinically Significant Functional Mitral Regurgitation*) study. All other authors have no conflicts of interest to disclose.

References

1. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JGF, Coats AJS, Falk V, González-Juanatey JR, Harjola VP, Jankowska EA, Jessup M, Linde C, Nihoyannopoulos P, Parissis JT, Pieske B, Riley JP, Rosano GMC, Ruilope LM, Ruschitzka F, Rutten FH, van der Meer P, ESC Scientific Document Group. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC) developed with the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur Heart J* 2016; **37**: 2129–2200.
2. Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE Jr, Drazner MH, Fonarow GC, Geraci SA, Horwich T, Januzzi JL, Johnson MR, Kasper EK, Levy WC, Masoudi FA, McBride PE, McMurray JJV, Mitchell JE, Peterson PN, Riegel B, Sam F, Stevenson LW, Tang WHW, Tsai EJ, Wilkoff BL. 2013 ACCF/AHA guideline for the management of heart failure: executive summary: a report of the American College of Cardiology Foundation/American Heart Association Task Force on practice guidelines. *Circulation* 2013; **128**: 1810–1852.
3. Kreusser MM, Tschierschke R, Beckendorf J, Baxmann T, Frankenstein L, Dosch AO, Schultz JH, Giannitsis E, Pleger ST, Ruhparwar A, Karck M. The need for dedicated advanced heart failure units to optimize heart failure care: impact of optimized advanced heart failure unit care on heart transplant outcome in high-risk patients. *ESC Heart Fail* 2018; **5**: 1108–1117.
4. Patel JB, Borgeson DD, Barnes ME, Rihal CS, Daly RC, Redfield MM. Mitral regurgitation in patients with advanced systolic heart failure. *J Card Fail* 2004; **10**: 285–291.
5. Feldman T, Foster E, Glower DD, Kar S, Rinaldi MJ, Fail PS, Smalling RW, Siegel R, Rose GA, Engeron E, Loghin C, Trento A, Skipper ER, Fudge T, Letsou GV, Massaro JM, Mauri L. Percutaneous repair or surgery for mitral regurgitation. *N Engl J Med* 2011; **364**: 1395–1406.
6. Feldman T, Kar S, Elmariah S, Smart SC, Trento A, Siegel RJ, Apruzzese P, Fail P, Rinaldi MJ, Smalling RW, Hermiller JB, Heimansohn D, Gray WA, Grayburn PA, Mack MJ, Lim DS, Ailawadi G, Herrmann HC, Acker MA, Silvestry FE, Foster E, Wang A, Glower DD, Mauri L, EVEREST II Investigators. Randomized comparison of percutaneous repair and surgery for mitral regurgitation: 5-year results of EVEREST II. *J Am Coll Cardiol* 2015; **66**: 2844–2854.

7. Baumgartner H, Falk V, Bax JJ, De Bonis M, Hamm C, Holm PJ, Iung B, Lancellotti P, Lansac E, Munoz DR, Rosenhek R. 2017 ESC/EACTS guidelines for the management of valvular heart disease. *Eur Heart J* 2017; **38**: 2739–2791.
8. Wallenborn J, Stork S, Herrmann S, Kukuy O, Fette G, Puppe F, Gorski A, Hu K, Voelker W, Ertl G, Weidemann F. Prevalence of severe mitral regurgitation eligible for edge-to-edge mitral valve repair (MitraClip). *Clin Res Cardiol* 2016; **105**: 699–709.
9. Obadia JF, Messika-Zeitoun D, Leurent G, Iung B, Bonnet G, Piriou N, Lefèvre T, Piot C, Rouleau F, Carrié D, Nejjari M, Ohlmann P, Leclercq F, Saint Etienne C, Teiger E, Leroux L, Karam N, Michel N, Gilard M, Donal E, Trochu JN, Cormier B, Armoiry X, Boutitie F, Maucort-Boulch D, Barnel C, Samson G, Guerin P, Vahanian A, Mewton N. Percutaneous repair or medical treatment for secondary mitral regurgitation. *N Engl J Med* 2018; **379**: 2297–2306.
10. Pfister R, Hausleiter J, Boekstegers P, Mollmann H, Nef H, Rudolph V. Role of percutaneous edge-to-edge repair in secondary mitral regurgitation after MITRA-FR and COAPT: a comment by the section of AV-valve treatment of the Working Group of Interventional Cardiology (AGIK) of the German Society of Cardiology (DGK). *Clin Res Cardiol* 2019; **108**: 969–973.
11. Stone GW, Lindenfeld J, Abraham WT, Kar S, Lim DS, Mishell JM, Whisenant B, Grayburn PA, Rinaldi M, Kapadia SR, Rajagopal V, Sarembock IJ, Brieke A, Marx SO, Cohen DJ, Weissman NJ, Mack MJ. Transcatheter mitral-valve repair in patients with heart failure. *N Engl J Med* 2018; **379**: 2307–2318.
12. Curio J, Reinthaler M, Kasner M, Al-Hindwan HSA, Baeckemo-Johansson J, Neumann T, Jacobs S, Lauten A, Landmesser U. Repeated MitraClip procedure in patients with recurrent MR after a successful first procedure: limitations and outcome. *J Interv Cardiol* 2018; **31**: 83–90.
13. Kreidel F, Alessandrini H, Wohlmuth P, Schmoeckel M, Geidel S. Is surgical or catheter-based interventions an option after an unsuccessful mitral clip? *Semin Thorac Cardiovasc Surg* 2018; **30**: 152–157.
14. World Medical A. World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. *JAMA* 2013; **310**: 2191–2194.
15. O'Gara PT, Grayburn PA, Badhwar V, Afonso LC, Carroll JD, Elmariah S, Kithcart AP, Nishimura RA, Ryan TJ, Schwartz A, Stevenson LW. 2017 ACC Expert Consensus Decision Pathway on the Management of Mitral Regurgitation: a report of the American College of Cardiology Task Force on Expert Consensus Decision Pathways. *J Am Coll Cardiol* 2017; **70**: 2421–2449.
16. Gorenflo M, Katus HA, Bekeredjian R. Successful MitraClipTM implantation in a 15-year-old patient with multiple prior cardiac surgeries. *Cardiol Young* 2013; **23**: 620–622.
17. Geis N, Raake P, Lewening M, Mereles D, Chorianopoulos E, Frankenstein L, Katus HA, Bekeredjian R, Pleger ST. Percutaneous repair of mitral valve regurgitation in patients with severe heart failure: comparison with optimal medical treatment. *Acta Cardiol* 2017; **73**: 1–9.
18. Pleger ST, Schulz-Schonhagen M, Geis N, Mereles D, Chorianopoulos E, Antaredja M, Lewening M, Katus HA, Bekeredjian R. One year clinical efficacy and reverse cardiac remodelling in patients with severe mitral regurgitation and reduced ejection fraction after MitraClip implantation. *Eur J Heart Fail* 2013; **15**: 919–927.
19. Zoghbi WA, Enriquez-Sarano M, Foster E, Grayburn PA, Kraft CD, Levine RA, Nihoyannopoulos P, Otto CM, Quinones MA, Rakowski H, Stewart WJ, Waggoner A, Weissman NJ, American Society of Echocardiography. Recommendations for evaluation of the severity of native valvular regurgitation with two-dimensional and Doppler echocardiography. *J Am Soc Echocardiogr* 2003; **16**: 777–802.
20. Kreusser MM, Geis NA, Berlin N, Greiner S, Pleger ST, Bekeredjian R, Katus HA, Raake PW. Invasive hemodynamics and cardiac biomarkers to predict outcomes after percutaneous edge-to-edge mitral valve repair in patients with severe heart failure. *Clin Res Cardiol* 2019; **108**: 375–387.
21. Ledwoch J, Matic P, Franke J, Gafoor S, Bertog S, Reinartz M, Vaskelyte L, Hofmann I, Sievert H. Transcatheter mitral valve repair with the MitraClip((R)) can be performed without general anesthesia and without conscious sedation. *Clin Res Cardiol* 2016; **105**: 297–306.
22. de Waha S, Seeburger J, Ender J, Desch S, Eitel I, Reinhardt A, Pöss J, Fuernau G, Noack T, Merk DR, Schuler G, Sievers HH, Mohr FW, Thiele H. Deep sedation versus general anesthesia in percutaneous edge-to-edge mitral valve reconstruction using the MitraClip system. *Clin Res Cardiol* 2016; **105**: 535–543.
23. Wiesner G, Tassani-Prell P, Mayr NP. Comment to: De Waha S, Seeburger J et al. (2016): Deep sedation versus general anaesthesia in percutaneous edge-to edge mitral valve reconstruction using the MitraClip system. Clin Res Cardiol 105(6):535-43. *Clin Res Cardiol* 2017; **106**: 160–161.
24. Pleger ST, Mereles D, Schulz-Schonhagen M, Krumsdorf U, Chorianopoulos E, Rottbauer W, Katus HA, Bekeredjian R. Acute safety and 30-day outcome after percutaneous edge-to-edge repair of mitral regurgitation in very high-risk patients. *Am J Cardiol* 2011; **108**: 1478–1482.
25. Stone GW, Adams DH, Abraham WT, Kappetein AP, Genereux P, Vranckx P, Mehran R, Kuck K-H, Leon MB, Piazza N, Head SJ, Filippatos G, Vahanian AS, Mitral Valve Academic Research Consortium (MVARC). Clinical trial design principles and endpoint definitions for transcatheter mitral valve repair and replacement: Part 2: Endpoint definitions: A consensus document from the mitral valve academic research consortium. *J Am Coll Cardiol* 2015; **66**: 308–321.
26. Baldus S, Schillinger W, Franzen O, Bekeredjian R, Sievert H, Schofer J, Kuck KH, Konorza T, Möllmann H, Hehrlein C, Ouarrak T, Senges J, Meinertz T, for the German Transcatheter Mitral Valve Interventions (TRAMI) investigators. MitraClip therapy in daily clinical practice: initial results from the German transcatheter mitral valve interventions (TRAMI) registry. *Eur J Heart Fail* 2012; **14**: 1050–1055.
27. Maisano F, Franzen O, Baldus S, Schafer U, Hausleiter J, Butter C, Ussia GP, Sievert H, Richardt G, Widder JD, Moccetti T. 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. *J Am Coll Cardiol* 2013; **62**: 1052–1061.
28. Scandura S, Capranzano P, Caggegi A, Grasso C, Ronsivalle G, Mangiafico S, Ohno Y, Attizzani GF, Cannata S, Giaquinta S, Farruggio S, Ministeri M, Dipasqua F, Pistritto AM, Immè S, Capodanno D, di Salvo ME, Tamburino C. Percutaneous mitral valve repair with the MitraClip system in the elderly: one-year outcomes from the GRASP registry. *Int J Cardiol* 2016; **224**: 440–446.
29. Kreidel F, Frerker C, Schluter M, Alessandrini H, Thielsen T, Geidel S, Schäfer U, Kuck KH. Repeat MitraClip therapy for significant recurrent mitral regurgitation in high surgical risk patients. *Jacc-Cardiovasc Int* 2015; **8**: 1480–1489.
30. Tay ELW, Lim DS, Yip J. Redo MitraClip mitral valve repair after a late single leaflet detachment. *Catheter Cardiovasc Interv* 2014; **84**: 160–163.
31. De Bonis M, Lapenna E, Buzzatti N, La Canna G, Denti P, Pappalardo F, Schiavi D, Pozzoli A, Cioni M, Di Giannuario G, Alfieri O. Optimal results immediately after MitraClip therapy or surgical edge-to-edge repair for functional mitral regurgitation: are they really stable at 4 years? *Eur J Cardiothorac Surg* 2016; **50**: 488–494.
32. Buccheri S, Barbanti M, Capodanno D, Popolo Rubbio A, Capranzano P, Scaglione U, Giuliano G, Scandura S, Mangiafico S, Immé S, Farruggio S, Giaquinta S, Grasso C, Tamburino C. Procedural management of patients with advanced heart failure undergoing

MitraClip implantation (from the GRASP registry). *J Cardiothorac Vasc Anesth* 2017; **31**: e6–e8.
33. Benito-Gonzalez T, Estevez-Loureiro R, Villablanca PA, Armeni P, Iglesias-Garriz I, Minguito C, Garrote C, de Prado AP, Tundidor-Sanz E, Gualis J, Fernández-Vázquez F. Percutaneous mitral valve repair vs. stand-alone medical therapy in patients with functional mitral regurgitation and heart failure. *Cardiovasc Revasc Med* 2020; **21**: 52–60.
34. Geis NA, Pleger ST, Bekeredjian R, Chorianopoulos E, Kreusser MM, Frankenstein L, Ruhparwar A, Katus HA, Raake PWJ. Haemodynamic effects of percutaneous mitral valve edge-to-edge repair in patients with end-stage heart failure awaiting heart transplantation. *ESC Heart Fail* 2018; **5**: 892–901.
35. Kreusser MM, Hamed S, Weber A, Schmack B, Volz MJ, Geis NA, Grossekettler L, Pleger ST, Ruhparwar A, Katus HA, Raake PW. MitraClip implantation followed by insertion of a left ventricular assist device in patients with advanced heart failure. *ESC Heart Fail* 2020; **7**: 3891–3900.