Prognostic Impact of Left Atrial Function Following Transcatheter Mitral Valve Repair

Jakob Ledwoch, MD; Katharina Leidgschwendner; Carmen Fellner; Felix Poch; Ida Olbrich; Ruth Thalmann, MD; Hans Kossmann, MD; Michael Dommasch, MD; Ralf Dirschinger, MD; Anja Stundl, MD; Karl-Ludwig Laugwitz, MD; Christian Kupatt, MD; Petra Hoppmann, MD

***Background*—**Left atrial (LA) function predicts clinical outcome in a variety of cardiovascular diseases. However, limited data are available in the setting of mitral regurgitation. The aim of the present study was to assess potential changes in LA ejection fraction (LAEF) and its prognostic value in patients following transcatheter mitral valve repair using the MitraClip.

***Methods and Results*—**A total of 88 consecutive patients undergoing MitraClip implantation with complete echocardiography at baseline and follow-up between 3 and 6 months postprocedure were enrolled. LAEF improved in 58% of the population. Change in LAEF was associated with residual mitral regurgitation, residual transmitral gradient and left ventricular ejection fraction changes. Compared with their counterparts, patients with residual mitral regurgitation ≥grade 2 (change in LAEF, −6% [Interquartile [IQR], −9–1%] versus 4% [IQR, −5–15%]; P=0.05) and with residual transmitral gradient ≥5 mm Hg (change in LAEF, −2% [IQR, −9–9%] versus 5% [IQR, −4–16%]; P=0.03) showed a decline in LAEF, respectively. Furthermore, LAEF significantly correlated with changes in left ventricular ejection fraction (r=0.40; P=0.001). With regards to clinical outcome, heart failure symptoms as assessed by New York Heart Association class were more severe in patients with worsened LAEF at follow-up. Finally, LAEF change was identified as an independent predictor of all-cause mortality (hazard ratio, 0.94; 95% CI, 0.90–0.98 [P=0.008]).

***Conclusions*—**The present analysis showed that changes in LA function in patients undergoing MitraClip implantation are associated with important measures including residual mitral regurgitation, elevated transmitral gradient, and left ventricular function. Importantly, LA function alterations represent a strong predictor for all-cause mortality. **(*J Am Heart Assoc*. 2019;8: e011727. DOI: 10.1161/JAHA.118.011727.)**

Key Words: mitraclip • mitral valve regurgitation • left atrial systolic function • transcatheter mitral valve repair

Assessment of left atrial (LA) volumes and function as prognostic factors has gained increasing attention in recent years in different areas of cardiovascular research including coronary artery disease, myocardial infarction, heart failure, and arterial hypertension.[1–3]

The left atrium plays a central role in patients with chronic mitral regurgitation (MR) since the regurgitant volume leads to negative LA remodeling and decline in LA function.[4] The MitraClip technique has the potential to induce LA reverse remodeling and improve LA function by reducing volume overload to the LA. We hypothesize that change in LA function may serve as a strong predictor for clinical outcomes in these patients since it may be associated with prognostically important factors such as residual MR, transmitral gradient, and left ventricular (LV) remodeling. Changes in LA function were analyzed in patients undergoing mitral valve surgery, however, without assessment of outcome prediction.[4,5] Furthermore, no data regarding LA alterations exist in patients following transcatheter mitral valve repair.

The aim of the present study was to assess LA remodeling, its influencing factors, and the prognostic value of LA function in patients undergoing MitraClip implantation.

Methods

Population

The data that support the findings of this study are available from the corresponding author upon reasonable request. All consecutive patients with severe MR undergoing

From the Klinik und Poliklinik für Innere Medizin I, Klinikum rechts der Isar, Technical University of Munich; DZHK (German Center for Cardiovascular Research), Partner Site Munich Heart Alliance, Munich, Germany (J.L., K.L., C.F., F.P., I.O., R.T., H.K., M.D., R.D., A.S., K.-L.L., C.K., P.H.).

Accompanying Figures S1 and S2 are available at https://www.ahajournals.org/doi/suppl/10.1161/JAHA.118.011727

Correspondence to: Jakob Ledwoch, MD, Klinik und Poliklinik für Innere Medizin I, Klinikum rechts der Isar, Technical University of Munich, Munich, Germany. Email: jakobledwoch@yahoo.de

Received December 10, 2018; accepted March 25, 2019.

Clinical Perspective

What Is New?

- Left atrial function is an important echocardiographic measure since it was found to be an independent predictor for survival following MitraClip procedure.
- Change in left atrial function was influenced by residual mitral stenosis, residual mitral regurgitation, and left ventricular function but had a stronger prognostic value than each of these individual variables.

What Are the Clinical Implications?

- Left atrial function measurement after MitraClip implantation should be included in clinical practice to improve outcome prediction.
- It may help to identify patients at risk with need for increased patient surveillance and to identify those who do not tolerate residual mitral regurgitation and qualify for reintervention.

transcatheter mitral valve repair with the MitraClip in our institution have been enrolled into the present prospective, open-label, observational study (NCT03488732). Patients were not included in cases of missing written informed consent. Baseline, procedural, and follow-up data were prospectively collected and entered into the internal database. The study was approved by the local ethics committee and performed according to the Declaration of Helsinki.

Echocardiography Assessment

Patients underwent echocardiography (transthoracic and transesophageal) for evaluation of the severity and etiology of MR, ventricular function, and dimensions for conformation of suitability for the MitraClip procedure. MR severity was graded on a 3-stage scale from mild to severe according to current guidelines.[6] LV function was assessed using biplane measures in 2- and 4-chamber view. Right ventricular function was expressed by means of tricuspid annular plane systolic excursion and fractional area change. Mean transmitral gradients were measured using the mitral inflow continuous wave Doppler signal before discharge. As suggested by guidelines, mitral stenosis (MS) was defined on a 3-stage scale from mild to severe according to transmitral mean gradients of <5, 5 to 10, and >10 mm Hg, respectively.

For LA volume assessment, area-length calculation was used. The endocardial border of the LA in both apical 4- and 2-chamber view was traced. At the mitral valve level, the contour was closed connecting the 2 opposite points of the mitral annulus. The LA appendage and pulmonary veins were excluded from tracing. The LA length was calculated using the shortest distance between the mitral annular plane and LA roof. Measurements were performed at 2 specific time points during the cardiac cycle: at the end of atrial systole when the minimum LA area was reached before MV closing, and at the end of atrial diastole when the maximum LA area was reached before MV opening. In case of atrial fibrillation, 5 measurements were conducted and the mean value was built afterwards. LA function was calculated as global LA ejection fraction (LAEF) according to the formula: LAEF=(LA end-diastolic volume–LA end-systolic volume)/LA end-diastolic volume.

The population was divided into 2 groups according to the changes in LA function (LA function worsening versus improvement) from baseline to the echocardiography follow-up performed between 3 and 6 months after the MitraClip procedure.

All echocardiographic examinations were performed according to the guidelines of the American Society of Echocardiography.[7,8]

Procedure and Follow-Up

The preprocedural operative risk was calculated using the logistic EuroSCORE.[9] MitraClip implantation was performed in general anesthesia using fluoroscopy and transesophageal echocardiography for guidance. Procedural details have previously been described in detail.[10] Acute procedural success was defined as implantation of at least 1 MitraClip, residual MR ≤II, and absence from conversion to open heart surgery.

Follow-up was performed routinely at 1, 3, 6, and 12 months following implantation and yearly thereafter. If patients were not available for clinical follow-up they were contacted by telephone.

Statistical Analysis

Categorical variables were expressed as numbers and percentages. Continuous variables were expressed as mean with SD or median with quartiles. For comparison between the groups, the chi-square or exact Fisher test were used for categorical variables and the *t* test or Mann–Whitney–*U* test for continuous variables. Changes between baseline and follow-up within the respective groups were assessed using paired *t* test or Wilcoxon test. The Spearman correlation coefficient was used for correlation analysis.

For assessment of clinical outcome, time to death by Kaplan–Meier method was performed. To identify independent predictors for all-cause mortality, Cox regression was performed including all variables, which showed significant differences in the univariate model. All *P* values were calculated by 2-tailed tests and statistical significance was defined as $P<0.05$. Analysis was performed by SPSS software, version 22 (SPSS Inc).

Results

Baseline Characteristics

Between August 2015 and March 2018, a total of 103 patients underwent MitraClip implantation at our institution. Of them, 2 patients had an unsuccessful procedure, 6 patients died before the echocardiography follow-up, 5 patients were not available for echocardiography follow-up, and 2 patients were lost to follow-up. Finally, 88 patients were available for the primary analysis. Mean age of the study population was 77±9 years and mean logistic EuroSCORE was 25±15. The etiology of MR was functional in the majority of the population (93%). No relevant differences in baseline characteristics were observed in patients with available echocardiography follow-up compared with those without follow-up.

LA Remodeling

After a mean echocardiography follow-up of 4.9±2.8 months following MitraClip implantation, LAEF increased from 23% (10–32%) to 30% (18–39%) in the overall study population. Furthermore, significant reductions in LA end-diastolic and end-systolic volumes were observed (Figure 1A–C). A total of 37 patients (42% of the study population) experienced a decline in LAEF. These patients also showed an increase in LA volumes in contrast to patients with improved LAEF (Figure 1D–I).

Except for the presence of peripheral artery disease, no differences in baseline clinical characteristics were detected between both groups (Table 1). Regarding baseline echocardiographic parameters, patients with worsened LAEF were characterized by higher LAEF and a higher prevalence of tricuspid regurgitation grade ≥2 (Table 2).

Factors Associated With Changes in LA Function

Residual transmitral mean gradients did not show a meaningful linear correlation with changes in LAEF ($r=-0.1$; $P=0.79$). However, the correlation analysis of LAEF dependent on transmitral gradients showed a distinct distribution pattern identifying clusters of LAEF in the upper left quadrant (improved LAEF and transmitral gradient <5 mm Hg) and lower right quadrant (worsened LAEF and transmitral gradient ≥5 mm Hg) (Figure S1). Correspondingly, a favorable change in LAEF was observed in patients with transmitral mean gradients <5 mm Hg (Figure 2A). Furthermore, improved LAEF was detected among patients who presented with residual MR grade <II after MitraClip implantation (Figure 2B).

LAEF was found to significantly correlate with LV ejection fraction (Figure 3). Patients who presented with LAEF improvement also showed significantly increased LV ejection fraction (Table 3). Among right-sided cardiac parameters, LAEF worsening was associated with a decline in tricuspid annular plane systolic excursion (Table 3).

Clinical Outcome

Mean follow-up duration was 10±7 months with a maximum follow-up of 29 months. Patients with worsened LAEF showed significantly higher all-cause mortality compared with patients with improved LAEF (Figure 4). The remaining heart failure symptoms as assessed by New York Heart Association class were more severe in patients with declined LAEF (Figure S2).

Besides female sex and renal function, Cox regression analysis showed changes in LAEF to be an independent predictor for all-cause mortality (Table 4). Transmitral gradient, residual MR, and changes in LV ejection fraction were not independently associated with mortality. Baseline LAEF was associated with all-cause mortality in univariate analysis (hazard ratio, 0.96; 95% CI, 0.93–0.99). However, after adjustment for age, sex, EuroSCORE, renal function, and change in LAEF, no statistical significance was reached (hazard ratio, 0.98; 95% CI, 0.91–1.05).

Discussion

The major findings of the present study include: (1) approximately 60% of patients experienced an improvement in LAEF after 3 to 6 months following MitraClip implantation; (2) patients with worsened LAEF showed increased all-cause mortality and more severe heart failure symptoms during follow-up; and (3) change in LAEF proved to be an independent predictor for all-cause mortality.

The aim of the present study was the identification of an echocardiographic marker that combines several other already known risk factors to facilitate and improve risk prediction by expressing them in 1 parameter. The study shows for the first time a deeper analysis of LA remodeling patterns including global LA systolic function and its prognostic value in patients undergoing MitraClip implantation.

Reduction of MR, either surgically or percutaneously, leads to a reduction in LA volumes.[4,11–13] However, global LAEF was studied only in patients undergoing mitral valve surgery showing conflicting results with respect to LAEF restoration.[4,5] The reason the study by Le Bihan et al[4] did not show improvements in global LA function in contrast to that by Marsan et al[5] is most probably the short follow-up of 30 days, compared with 6 months in the latter. Similar to our analysis, this time is needed to observe a relevant remodeling process. For patients with MitraClip implantation, LA function was only

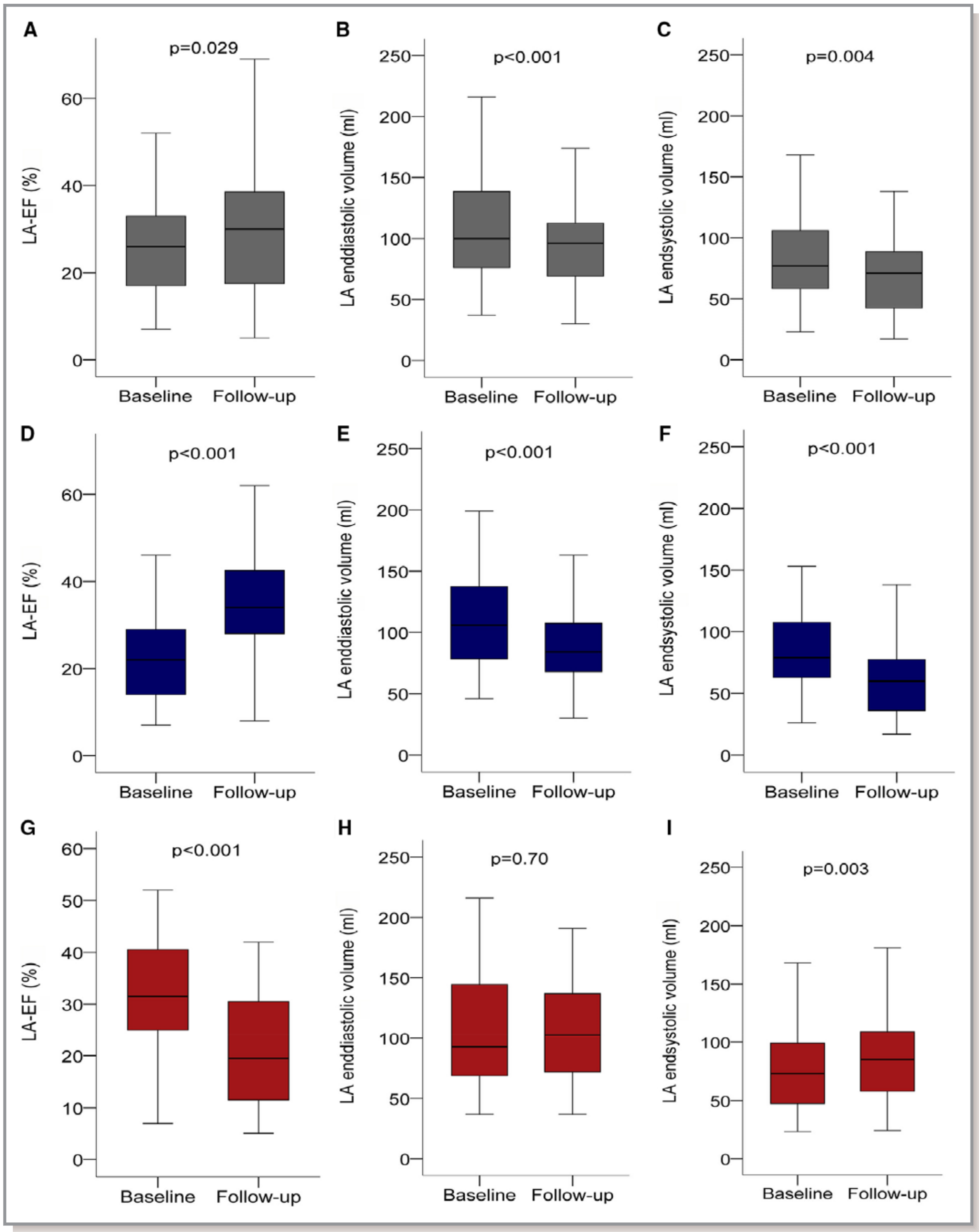

Figure 1. Changes in left atrial (LA) function. Median LA ejection fraction (LAEF), LA volume during end of atrial diastole and LA volume during end of atrial systole in the overall cohort (**A**–**C**), in patients with improved LAEF (**D**–**F**), and in patients with worsened LAEF (**G**–**I**).

assessed using LA strain analyses. Again, these studies report inconsistent changes associated with LA contractility after the procedure.[12–14] This may be reasoned by focusing on contractility analysis, which only mirrors intrinsic LA pump function instead of the entirety of passive conduit function plus active booster pump.

So far, the most important variable that determines outcome in patients undergoing MitraClip implantation is residual MR after the procedure. Even moderate MR after the procedure is associated with increased mortality,[15,16] particularly in certain subgroups such as patients with impaired LV function.[16] Residual MR is also discussed as one of the main drivers for the worse outcome of patients undergoing MitraClip implantation in the MITRA-FR (Multicentre Study of Percutaneous Mitral Valve Repair MitraClip Device in Patients With Severe Secondary Mitral Regurgitation) trial compared with the COAPT (Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients With Functional Mitral Regurgitation) trial, with 50% residual MR ≥2 in MITRA-FR and 31% residual

Table 1. Baseline and Procedural Characteristics

	LAEF Worsened (n=37)	LAEF Improved (n=51)	*P* Value
Age, y	78 (71–83)	79 (72–83)	0.55
Women	46 (17)	57 (29)	0.31
BMI, kg/m^2	24 (22–28)	25 (23–26)	0.73
Functional mitral regurgitation	95 (35)	92 (47)	0.65
Coronary artery disease	73 (27)	63 (32)	0.31
Previous myocardial infarction	35 (13)	24 (12)	0.23
Atrial fibrillation	76 (28)	75 (38)	0.90
Paroxysmal	27 (10)	31 (16)	0.66
Persistent/permanent	49 (18)	43 (22)	0.61
Diabetes mellitus	24 (9)	20 (10)	0.60
PAOD	24 (9)	8 (4)	0.031
COPD	14 (5)	26 (13)	0.17
Chronic renal failure	70 (26)	77 (39)	0.62
ICD	5 (2)	4 (2)	0.74
CRT	11 (4)	8 (4)	0.72
NYHA class III	62 (23)	55 (28)	0.50
NYHA class IV	22 (8)	26 (13)	0.67
EuroSCORE I	20 (11–29)	18 (15–29)	0.65
≥2 implanted clips	67 (25)	66 (33)	0.95

Values are expressed as percentage (number) or median (IQR). BMI indicates body mass index; COPD, chronic obstructive pulmonary disease; CRT, cardiac resynchronization therapy; ICD, implantable cardioverter-defibrillator; LAEF, left atrial ejection fraction; NYHA, New York Heart Association; PAOD, peripheral arterial occlusive disease.

Table 2. Baseline Echocardiography Parameters

	LAEF Worsened (n=37)	LAEF improved (n=51)	*P* Value
LV parameter			
LVEF, %	42 (31–54)	42 (34–52)	0.90
LVEDD, mm	56 (50–61)	54 (48–59)	0.79
LVESD, mm	43 (33–51)	40 (35–51)	0.82
LA parameter			
LAEF, %	29 (20–39)	21 (12–30)	0.001
LA end-diastolic volume, mL	98 (71–149)	103 (77–132)	0.61
LA end-diastolic volume index, mL/m^2	50 (39–83)	60 (45–76)	0.46
LA end-systolic volume, mL	73 (59–116)	79 (63–103)	0.19
LA end-systolic volume index, mL/m^2	39 (26–55)	45 (36–57)	0.13
RV parameter			
TAPSE, mm	17 (14–20)	17 (15–21)	0.93
Fractional area change, %	27 (21–39)	31 (25–36)	0.34
RV area end-diastolic, cm^2	26 (21–31)	23 (21–26)	0.68
RV area end-systolic, cm^2	17 (14–21)	16 (14–19)	0.53
RV/RA gradient, mm Hg	43 (35–55)	43 (38–56)	0.91
Concomitant valvular function			
Aortic stenosis grade ≥II	6% (2)	4% (2)	1.00
Tricuspid regurgitation grade ≥II	61% (22)	36% (18)	0.021

Values are expressed as percentage (number) or median (IQR). LA indicates left atrial; LAEF, left atrial ejection fraction; LV, left ventricular; LVEF, left ventricular ejection fraction; LVEDD, left ventricular end-diastolic diameter; LVESD, left ventricular end-systolic diameter; RA, right atrial; RV, right ventricular; TAPSE, tricuspid annular plane systolic excursion.

MR ≥2 in COAPT after 1 year.[17,18] A subanalysis of EVEREST (Endovascular Valve Edge-to-Edge Repair Study) revealed a strong correlation of the extent of LA volume reduction with the severity of residual MR.[11] This result suggests the incremental impact of residual MR on LA remodeling. The present analysis showed that the grade of residual MR is not only associated with reverse LA remodeling but also change in LAEF. From a pathophysiological point of view, both direct volume overload by MR to the left atrium and sustained elevated end-diastolic LV pressure in the presence of higher degrees of residual MR may explain the lack of LA function improvement. The fact that baseline LAEF was significantly impaired in patients with improved LAEF contradicts the hypothesis of irreversible LA damage before the procedure such as deteriorated contractility or interstitial fibrosis of the left atrium.

Another major factor after MitraClip implantation is the transmitral gradient created by impaired mitral valve opening. We were able to show that patients with transmitral mean gradient ≥5 mm Hg declined with respect to their LAEF. The increased afterload caused by moderate MS most probably leads to deterioration of LAEF in an already enlarged and stressed left atrium after longer-lasting MR. The relationship of LAEF with transmitral gradient was not evaluated in other reports regarding LA assessment following MitraClip implantation.[12–14] The abrupt change of the LA hemodynamic status from elevated preload caused by MR to elevated afterload caused by iatrogenic MS by MitraClip implantation has a major impact on clinical outcome as indicated by the study by Neuss et al,[19] which showed increased mortality in patients with transmitral mean gradient >5 mm Hg. Conflicting results exist regarding the ratio of residual MR and MS. While Neuss et al reported slightly better outcomes in patients with moderate MR compared with those with mild or no MR and transmitral mean gradient >5 mm Hg,[19] Cheng et al showed the opposite.[16] Because of the limited number of patients with more than mild residual MR (n=10), we were not able to

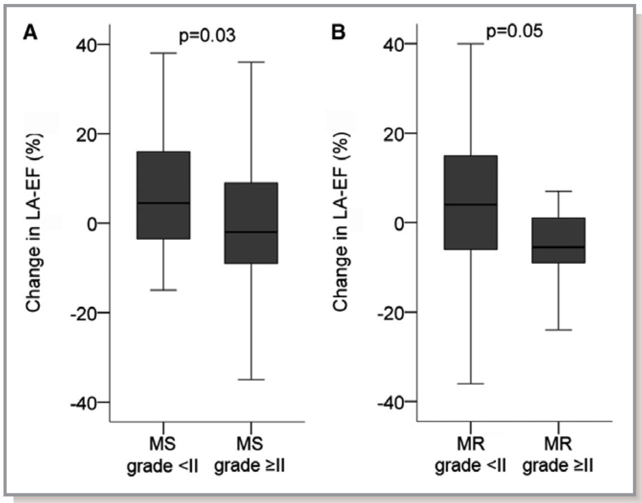

Figure 2. Left atrial ejection fraction (LAEF) change dependent on grade of mitral regurgitation (MR) and mitral stenosis (MS). Change in LAEF was influenced by residual MS, residual MR, and change in left ventricular ejection fraction (LVEF) following MitraClip implantation.

accurately evaluate the impact of the MR/MS relationship on LAEF changes. However, our analysis indicates that there is a subset of patients who are not able to tolerate higher degrees of residual MR or MS, which can be identified by worsening LAEF. Despite the lack of information regarding postprocedural transmitral gradient in MITRA-HF, this implantation-related factor might be another reason for the negative result in that trial.[17]

The third important aspect in LAEF assessment is the association with LV function. Previous trials revealed LAEF to be associated with LV ejection fraction.[20] This is explained by increased LV filling pressures caused by a noncompliant left ventricle and results in negative LA remodeling and decline in LA function.[20,21] Our study also demonstrates that changes of LA function are dependent on changes in LV function after correction of MR. However, the causal relationship in the interplay between the left atrium and the left ventricle is difficult to interpret. Other than the influence of LV compliance on LAEF, LAEF itself has an impact on LV function by determining LV preload. Furthermore, impaired LAEF may also lead to backward transmission of elevated filling pressure to the right side of the heart and cause right ventricular deterioration, as shown by reductions in tricuspid annular plane systolic excursion in the group with decreased LAEF in our analysis.

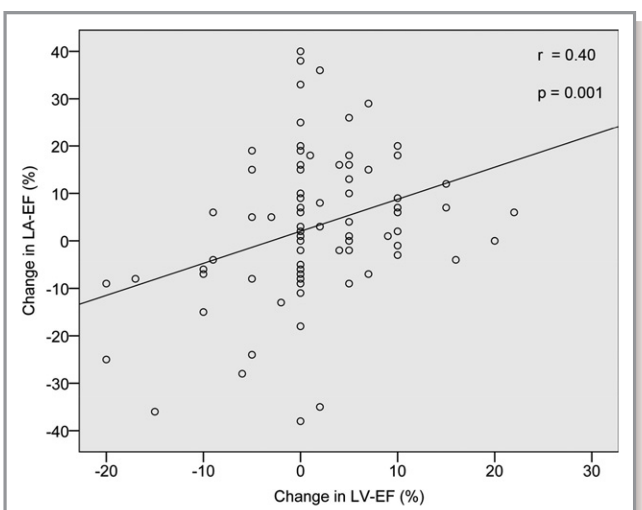

Figure 3. Correlation of changes between left atrial ejection fraction (LAEF) and left ventricular ejection fraction (LVEF).

Table 3. Changes in Echocardiography Parameters

	LAEF worsened (n=37)	LAEF improved (n=51)	*P* Value
LV parameter			
Δ LVEF, %	−1 (−5 to 2)	3 (0–6)	0.004
Δ LVEDD, mm	0 (−4 to 4)	−1 (−4 to 2)	0.50
Δ LVESD, mm	0 (−4 to 3)	−1 (−5 to 2)	0.34
RV parameter			
Δ TAPSE, mm	0 (−5 to 2)	2 (1–4)	0.001
Δ Fractional area change, %	0 (−0.1 to 0.1)	0.1 (−0.1 to 0.1)	0.18
Δ RV area end-diastolic, cm^2	0 (−3 to 1)	−2 (−4 to 1)	0.12
Δ RV area end-systolic, cm^2	0 (−3 to 2)	−2 (−4 to 0)	0.08
Δ RV/RA gradient, mm Hg	−7 (−16 to −1)	−9 (−14 to −1)	0.76
Concomitant valvular function			
Tricuspid regurgitation reduction ≥1 grade	42 (15)	39 (19)	0.79

Values are expressed as median (IQR) or percentage (number). LAEF indicates left atrial ejection fraction; LV, left ventricular; LVEF, left ventricular ejection fraction; LVEDD, left ventricular end-diastolic diameter; LVESD, left ventricular end-systolic diameter; RV, right ventricular; RA, right atrial; TAPSE, tricuspid annular plane systolic excursion.

Study Limitations

Several limitations need to be reported. First, the study population size is limited and, hence, the statistical analysis may be of limited robustness. Second, LA volumes and function were calculated using the area-length method. Although this method is validated, other modalities for volume

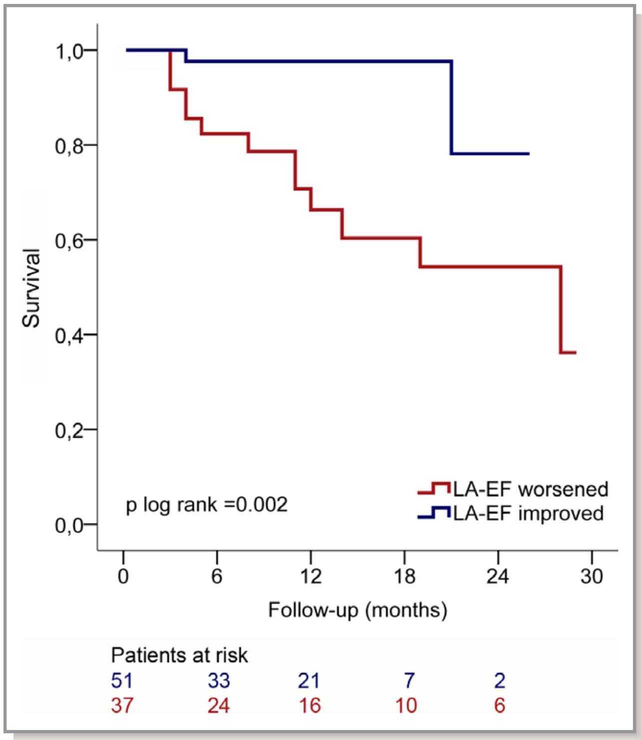

Figure 4. Kaplan–Meier estimates for survival according to changes in left atrial ejection fraction (LAEF). Patients with improved LAEF had significantly higher survival compared with patients with worsened LAEF.

and function assessment such as 3-dimensional analysis of data sets from echocardiography, cardiac computed tomography, or cardiac magnetic resonance imaging offer more accurate measurements. It is known that 2-dimensional echocardiography underestimate LA volumes compared with these 3-dimensional methods.[7] Furthermore, deformation analysis using speckle tracking might have added further information for LA functional assessment. Third, passive conduit or active booster pump function were not assessed for the left atrium. However, global LAEF better summarizes different structural and hemodynamic changes after MitraClip implantation and may therefore predict outcome more precisely.

Table 4. Cox Regression Regarding All-Cause Mortality

	HR (95% CI)	*P* Value
Age (increase per 1 y)	0.96 (0.89–1.04)	0.32
Women	0.09 (0.02–0.46)	0.003
EuroSCORE I (increase per 1%)	1.01 (0.95–1.06)	0.84
GFR (increase per 1 mL/min)	0.95 (0.91–0.98)	0.005
Change in LAEF (increase per 1%)	0.92 (0.86–0.98)	0.009
Transmitral gradient ≥5 mm Hg	0.67 (0.16–2.81)	0.59
Residual MR ≥II	0.19 (0.03–1.14)	0.07
Change in LVEF (increase per 1%)	0.96 (0.88–1.06)	0.44

GFR indicates glomerular filtration rate; HR, hazard ratio; LAEF, left atrial ejection fraction; LVEF, left ventricular ejection fraction; MR, mitral regurgitation.

Conclusions

The majority of patients undergoing MitraClip implantation show improvements with respect to LA function. Decline in LAEF was associated with residual MR, transmitral gradient, and changes in LV function. Most importantly, LAEF change was found to be an independent predictor for all-cause mortality. Therefore, including measures of LA function after MitraClip implantation may improve outcome prediction, enhance patient surveillance in patients at increased risk, and identify those who do not tolerate residual MR and qualify for reintervention.

Disclosures

None.

References

1. Facchini E, Degiovanni A, Marino PN. Left atrium function in patients with coronary artery disease. *Curr Opin Cardiol*. 2014;29:423–429.
2. Appleton CP, Kovacs SJ. The role of left atrial function in diastolic heart failure. *Circ Cardiovasc Imaging*. 2009;2:6–9.
3. Gerdts E, Wachtell K, Omvik P, Otterstad JE, Oikarinen L, Boman K, Dahlof B, Devereux RB. Left atrial size and risk of major cardiovascular events during antihypertensive treatment: losartan intervention for endpoint reduction in hypertension trial. *Hypertension*. 2007;49:311–316.
4. Le Bihan DC, Della Togna DJ, Barretto RB, Assef JE, Machado LR, Ramos AI, Abdulmassih Neto C, Moises VA, Sousa AG, Campos O. Early improvement in left atrial remodeling and function after mitral valve repair or replacement in organic symptomatic mitral regurgitation assessed by three-dimensional echocardiography. *Echocardiography*. 2015;32:1122–1130.
5. Marsan NA, Maffessanti F, Tamborini G, Gripari P, Caiani E, Fusini L, Muratori M, Zanobini M, Alamanni F, Pepi M. Left atrial reverse remodeling and functional improvement after mitral valve repair in degenerative mitral regurgitation: a real-time 3-dimensional echocardiography study. *Am Heart J*. 2011;161:314–321.
6. 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. Recommendations for evaluation of the severity of native valvular regurgitation with two-dimensional and Doppler echocardiography. *J Am Soc Echocardiogr*. 2003;16:777–802.
7. Lang RM, Badano LP, Mor-Avi V, Afilalo J, Armstrong A, Ernande L, Flachskampf FA, Foster E, Goldstein SA, Kuznetsova T, Lancellotti P, Muraru D, Picard MH, Rietzschel ER, Rudski L, Spencer KT, Tsang W, Voigt JU. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *J Am Soc Echocardiogr*. 2015;28:1–39.e14
8. Rudski LG, Lai WW, Afilalo J, Hua L, Handschumacher MD, Chandrasekaran K, Solomon SD, Louie EK, Schiller NB. Guidelines for the echocardiographic assessment of the right heart in adults: a report from the American Society of Echocardiography endorsed by the European Association of Echocardiography, a registered branch of the European Society of Cardiology, and the Canadian Society of Echocardiography. *J Am Soc Echocardiogr*. 2010;23:685–713; quiz 786–688.
9. Roques F, Nashef SA, Michel P. Risk factors for early mortality after valve surgery in Europe in the 1990s: lessons from the EuroSCORE pilot program. *J Heart Valve Dis*. 2001;10:572–577; discussion 577–578.
10. Feldman T, Wasserman HS, Herrmann HC, Gray W, Block PC, Whitlow P, St Goar F, Rodriguez L, Silvestry F, Schwartz A, Sanborn TA, Condado JA, Foster

E. Percutaneous mitral valve repair using the edge-to-edge technique: six-month results of the EVEREST phase I clinical trial. *J Am Coll Cardiol*. 2005;46:2134–2140.

11. Grayburn PA, Foster E, Sangli C, Weissman NJ, Massaro J, Glower DG, Feldman T, Mauri L. Relationship between the magnitude of reduction in mitral regurgitation severity and left ventricular and left atrial reverse remodeling after MitraClip therapy. *Circulation*. 2013;128:1667–1674.
12. Avenatti E, Little SH, Barker CM, Nagueh SF. Changes in left atrial function after transcutaneous mitral valve repair. *Am J Cardiol*. 2018;122:1204–1209.
13. Toprak C, Kahveci G, Kilicgedik A, Pala S, Kirma C, Tabakci MM, Inanir M, Esen AM. Left atrial remodeling in patients undergoing percutaneous mitral valve repair with the MitraClip system: an advanced echocardiography study. *Echocardiography*. 2016;33:1504–1511.
14. Gucuk Ipek E, Singh S, Viloria E, Feldman T, Grayburn P, Foster E, Qasim A. Impact of the MitraClip procedure on left atrial strain and strain rate. *Circ Cardiovasc Imaging*. 2018;11:e006553.
15. Buzzatti N, De Bonis M, Denti P, Barili F, Schiavi D, Di Giannuario G, La Canna G, Alfieri O. What is a “good” result after transcatheter mitral repair? Impact of 2+ residual mitral regurgitation. *J Thorac Cardiovasc Surg*. 2016;151:88–96.
16. Cheng R, Dawkins S, Tat E, Makar M, Hussaini A, Makkar RR, Trento A, Siegel RJ, Kar S. Relation of Residual Mitral Regurgitation Despite Elevated Mitral Gradients to Risk of Heart Failure Hospitalization After MitraClip Repair. *Am J Cardiol*. 2017;120:1595–1600.
17. Obadia JF, Messika-Zeitoun D, Leurent G, Iung B, Bonnet G, Piriou N, Lefevre T, Piot C, Rouleau F, Carrie 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, MITRA-FR Investigators. Percutaneous repair or medical treatment for secondary mitral regurgitation. *N Engl J Med*. 2018;379:2297–2306.
18. Stone G, Lindenfeld J, Abraham W, Kar S, Lim S, Mishell J, Whisenant B. Transcatheter mitral-valve repair in patients with heart failure. *N Engl J Med*. 2018;379:2307–2318.
19. Neuss M, Schau T, Isotani A, Pilz M, Schopp M, Butter C. Elevated mitral valve pressure gradient after MitraClip implantation deteriorates long-term outcome in patients with severe mitral regurgitation and severe heart failure. *JACC Cardiovasc Interv*. 2017;10:931–939.
20. Kuhl JT, Kofoed KF, Moller JE, Hammer-Hansen S, Kristensen T, Kober L, Kelbaek H. Assessment of left atrial volume and mechanical function in ischemic heart disease: a multi slice computed tomography study. *Int J Cardiol*. 2010;145:197–202.
21. Tsang TS, Barnes ME, Gersh BJ, Bailey KR, Seward JB. Left atrial volume as a morphophysiologic expression of left ventricular diastolic dysfunction and relation to cardiovascular risk burden. *Am J Cardiol*. 2002;90:1284–1289.