JACC: CARDIOVASCULAR INTERVENTIONS VOL. 8, NO. 3, 2015

ISSN 1936-8798/$36.00
PUBLISHED BY ELSEVIER INC. http://dx.doi.org/10.1016/j.jcin.2014.10.024

STRUCTURAL

Persistence of Iatrogenic Atrial Septal Defect After Interventional Mitral Valve Repair With the MitraClip System

A Note of Caution

Robert Schueler, MD,* Can Öztürk, MD,* Jan Arne Wedekind, MD,† Nikos Werner, MD,* Florian Stöckigt, MD,* Fritz Mellert, MD,‡ Georg Nickenig, MD,* Christoph Hammerstingl, MD*

ABSTRACT

OBJECTIVES The purpose of this study was to investigate the persistence rates of iatrogenic atrial septal defect (iASD) after interventional edge-to-edge repair with serial transesophageal echocardiography examinations and close clinical follow-up (FU).

BACKGROUND Transcatheter mitral valve repair (TMVR) with the MitraClip system (Abbott Vascular, Abbott Park, Illinois) is a therapeutic alternative to surgery in selected high-risk patients. Clip placement requires interatrial transseptal puncture and meticulous manipulation of the steerable sheath. The persistence of iASD after MitraClip procedures and its clinical relevance is unknown.

METHODS A total of 66 patients (76.7% male, mean age 77.1 ± 7.9 years) with symptomatic mitral regurgitation (MR) at prohibitive surgical risk (EuroSCORE II 10.1 ± 6.1%) underwent MitraClip procedures and completed 6 months of FU.

RESULTS Transesophageal echocardiography after FU showed persistent iASD in 50% of cases. Patients with iASD did not significantly differ from patients without ASD concerning baseline characteristics, New York Heart Association functional class, severity of MR, and acute procedural success rates ($p > 0.05$). When comparing procedural details and hemodynamic measures between groups, MitraClip procedures took longer in patients without iASD (82.4 ± 39.7 min vs. 68.9 ± 45.5 min; $p = 0.05$), and echocardiography after FU showed less decrease of systolic pulmonary artery pressures in the iASD group (−1.6 ± 14.1 mm Hg vs. 9.3 ± 17.4 mm Hg; $p = 0.02$). Clinically, patients with iASD presented more often with New York Heart Association functional classes >II after FU (57% vs. 30%; $p = 0.04$), showed higher levels of N-terminal pro-brain natriuretic peptide (6,667.3 ± 7,363.9 ng/dl vs. 4,835.9 ± 6,681.7 ng/dl; $p = 0.05$), and had less improvement in 6-min walking distances (20.8 ± 107.4 m vs. 114.6 ± 116.4 m; $p = 0.001$). Patients with iASD showed higher death rates during 6 months (16.6% vs. 3.3%; $p = 0.05$). Cox regression analysis found that only persistence of iASD ($p = 0.04$) was associated with 6-month survival.

CONCLUSIONS The persistence rate of 50% iASD after MitraClip procedures is considerably high. Persistent interatrial shunting was associated with worse clinical outcomes and increased mortality. Further studies are warranted to investigate if persistent interatrial shunting is the mediator or marker of advanced disease in these patients. (J Am Coll Cardiol Intv 2015;8:450–9) © 2015 by the American College of Cardiology Foundation.

From the *Heart Centre Bonn, Department of Cardiology, University of Bonn, Bonn, Germany; †Asklepios Children's Hospital Sankt Augustin, Stankt Augustin, Germany; and the ‡Heart Centre Bonn, Department of Cardiac Surgery, University of Bonn, Bonn, Germany. Dr. Mellert has served as a proctor for Medtronic. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose. Drs. Schueler and Öztürk contributed equally to this work.

Manuscript received July 27, 2014; revised manuscript received October 15, 2014, accepted October 23, 2014.

Transcatheter mitral valve repair (TMVR) has been developed as a therapeutic alternative to mitral valve (MV) surgery for symptomatic patients with relevant mitral regurgitation (MR) at prohibitive surgical risk. Interventional edge-to-edge repair with the MitraClip system (Abbott Vascular, Abbott Park, Illinois) has proven to be safe and effective for the reduction of MR in different patient cohorts with either functional mitral regurgitation (FMR) or degenerative mitral regurgitation (DMR) valve disease (1,2), and this technique has been widely adapted for clinical use, with more than 13,000 documented implants worldwide.

In clinical practice, TMVR with the MitraClip is mainly used to reduce FMR in end-stage heart failure patients with either dilated or ischemic cardiomyopathy (3-6). In this high-risk population, acute procedural success rates of up to 99% with significant MR reduction were reported (7), followed by symptomatic improvement in approximately 80% of cases.

SEE PAGE 460

Nevertheless, TMVR with the MitraClip is still an evolving technique, and factors predicting clinical outcomes after technically-successful clip implantation are not well defined. Cardiologists are facing a complex procedure, and clip placement requires venous groin access, interatrial transseptal puncture, and advancement of a 21-F (7.2 mm) steerable sheath into the left atrium. Despite increasing knowledge on specific procedural characteristics and technical aspects of TMVR, the persistence rate of iatrogenic atrial septal defects (iASDs) after MitraClip procedures is unknown. Furthermore, the effect of iASD on clinical outcomes in patient cohorts with advanced stages of chronic heart failure has not been systematically investigated.

METHODS

In this prospective, single-center study, we included consecutive patients undergoing TMVR with the MitraClip system. All patients underwent close clinical follow-up (FU) and echocardiography after 6 months to determine functional results after TMVR and clinical outcomes.

PATIENTS. Symptomatic patients with relevant DMR grade 3 to 4+ were evaluated for TMVR or surgery. Patients with FMR and mitral regurgitation grade 2+ were considered for MR treatment when having an effective regurgitation orifice area of >20 mm^2, New York Heart Association (NYHA) functional class III to IV, concomitant atrial fibrillation, and/or elevated pulmonary pressure despite optimized medical and device therapy (8). TMVR was planned for patients if the heart team recommended against open-heart surgery.

The study was approved by local ethics committee and in concordance with the Declaration of Helsinki, and all patients had to provide written informed consent before study inclusion.

ECHOCARDIOGRAPHY AND FU ASSESSMENT. Echocardiographic assessment before and after TMVR was done following current recommendations and guidelines, including comprehensive transthoracic echocardiography (TTE) and transesophageal echocardiography (TEE) (9,10). Severity of MR was graded after determination of proximal isovelocity surface area, effective regurgitation orifice area, as well as vena contracta width and regurgitant volume (8,9). According to the EVEREST (Endovascular Valve Edge-to-Edge REpair Study) (7) and the recommendations of the European Society of Cardiology (9), we established an institutional standard categorizing the severity of MR following a scale ranging between 1 and 4+: grade 1 defines "mild," 2 refers to "moderate," 3 stands for "moderate to severe," and 4 stands for "severe" MR. TEE and TTE were performed with a commercially-available echocardiographic system (iE 33, Philips Medical Systems, Andover, Massachusetts) and echocardiography probes (X5-1, X7-2t) allowing acquisition of 2- and 3-dimensional datasets. For the determination of iASD during FU, the interatrial septum was visualized in multiple angulations with and without color Doppler to identify visible structural defect or atypical interatrial Doppler flow (**Figure 1**).

Different experienced echocardiographers obtained procedural (C.H., F.S.) and FU (R.S., C.Ö.) images. The echocardiographer who performed FU evaluation was blinded to procedural outcomes and the patients' characteristics. Trained study nurses carried out clinical FU evaluation, unattended by the interventionalists or procedural echocardiographer.

INTERVENTIONAL EDGE-TO-EDGE REPAIR OF MR. TMVR using the MitraClip system has been described in detail previously (7). During the MitraClip procedure, severity and acute changes of MR were assessed as supposed by Foster et al. (11) and Wunderlich and Siegel (12). We defined acute procedural success as a reduction of MR by at least 1 grade, with a residual MR $<2+$. The number of clips that were implanted to reach procedural success was left to the discretion of

ABBREVIATIONS AND ACRONYMS

DMR = degenerative mitral regurgitation

FMR = functional mitral regurgitation

FU = follow-up

iASD = iatrogenic atrial septal defect

MR = mitral regurgitation

NYHA = New York Heart Association

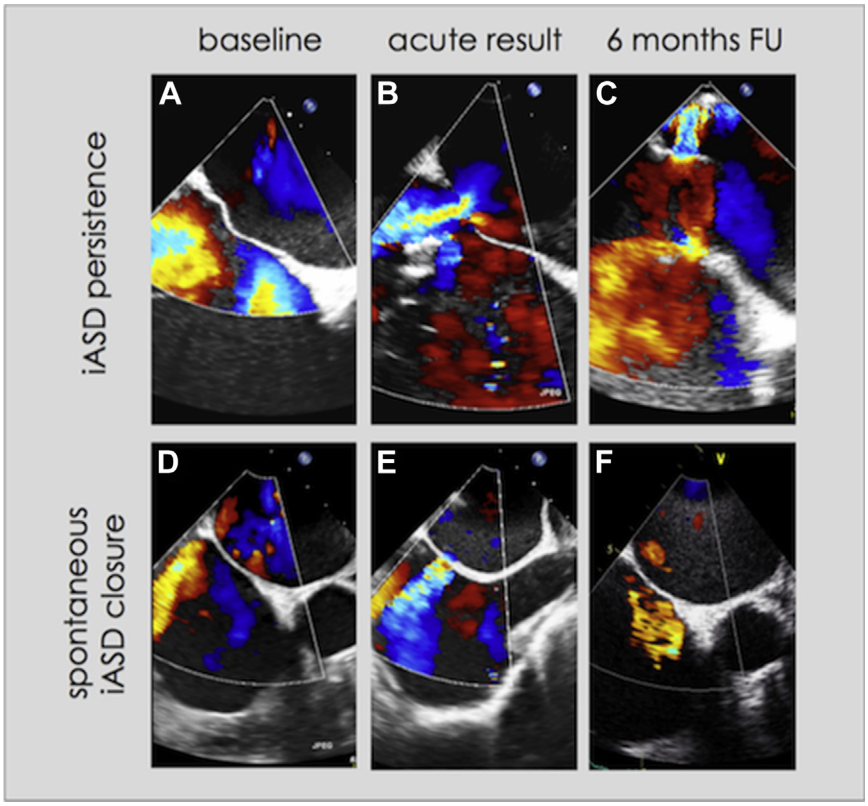
TEE = transesophageal echocardiography

TMVR = transcatheter mitral valve repair

TTE = transthoracic echocardiography

JACC: CARDIOVASCULAR INTERVENTIONS VOL. 8, NO. 3, 2015
MARCH 2015:450–9

FIGURE 1 Examples of Spontaneous iASD Closure and Persistent iASD 6 Months After MitraClip Treatment



(A to C) Spontaneous iatrogenic atrial septal defect (iASD) closure. **(D to F)** Persistent iASD. **(A and D)** No interatrial shunt defect detectable with color Doppler prior to transseptal puncture in both cases. **(B and E)** iASD immediately after MitraClip implantation with left-to-right shunting. **(C)** Spontaneous iASD closure 6 months after MitraClip implantation. **(F)** Persistent iASD at 6-month follow-up (FU), with new right-to-left shunt and interatrial septum deviation. This patient presented increasing systolic pulmonary arterial pressure of 70 mm Hg and increasing levels of N-terminal pro-brain natriuretic peptide.

the treating physician. Before clip release, echocardiography was performed to exclude clinical relevant MV stenosis (mean pressure gradient >5 mm Hg). Clinical success was defined by a decrease of ≥1 NYHA functional class during FU.

STATISTICAL ANALYSIS. Normal distribution of continuous variables was examined using the Kolmogorov-Smirnov test. Comparisons between FMR and DMR groups at 6 months were done using analysis of covariance for continuous variables. Further comparisons were performed with using the Student 2-sample *t* test or Mann-Whitney *U* test depending on the distribution of data. For categorical data, the Fisher exact test or chi-square test was calculated. Continuous data were expressed as mean ± SD or median (with interquartile ranges) where applicable. The 2-tailed p values were calculated, and $p < 0.05$ was considered to be significant. The cumulative survival plot in relation to iASD was estimated by the Kaplan-Meier method. Survival in groups was compared using the log-rank test. Cox regression was performed to analyze the influence of single variables on 6-month mortality. Variables were chosen for Cox regression if they have been shown independently to increase heart failure-related mortality in MR patients. Due to the relatively low event rate at 6-month FU, multivariate analysis was not performed.

Intraclass correlation coefficients for absolute agreement was used to assess method agreement, with good agreement defined as >0.80. For the assessment of intraobserver reliability, 20 randomly-chosen patients from each group (iASD and no iASD) were analyzed by the same investigator twice (C.H.), then by a second investigator (R.S.) who was blinded to the results of the first investigator, to determine interobserver variability. Mean values and SDs between the measurements were obtained, and absolute agreement among the observations was calculated using intraclass correlation coefficient analysis.

Statistics were performed using the SPSS for Windows PASW statistic, version 20.0.0.0 (SPSS Inc., Chicago, Illinois) and MedCalc statistical software version 11.4.1.0 (MedCalc, Mariakerke, Belgium).

RESULTS

BASELINE DATA AND PROCEDURAL OUTCOMES. From February to December 2013, 66 consecutive patients (age 77.1 ± 7.9 years, 76.7% male, EuroSCORE II 10.1 ± 6.1%, 73.3% FMR) (Table 1) underwent TMVR with the MitraClip system at our institution and completed the 6-month FU procedure including TTE and TEE. The patients underwent MitraClip procedures primarily for the treatment of advanced stages of symptomatic heart failure, with 96.7% of patients in NYHA functional class III or IV and 51% of patients with documented left ventricular ejection fraction (LVEF) <35%. The procedure was successfully completed in 65 patients (98.5%), with implantation of >1 clip in 40% of cases. Mean procedural time was 75.8 ± 42.8 min (interquartile range: 26 to 221 min) with a documented fluoroscopy time of 24.5 ± 17.7 min (interquartile range: 5 to 100 min) (Table 2). In 1 patient, TMVR was aborted because of relevant MV stenosis occurring after clip closure; in this case, the system was retrieved uneventfully without post-procedure changes in MR. Thereafter, the patient was treated conservatively, because of prohibitive surgical risk.

In-hospital, 30-day, and 6-month outcomes are shown in Table 2. The majority of patients improved significantly after FU, with documented decrease of ≥1 NYHA functional class in 81.6% of cases.

ECHOCARDIOGRAPHIC MEASURES AFTER FU. Echocardiography after 6 months revealed sustained reduction of MR <2+ in 91.6% of patients (Figure 2A). Concomitantly, we found a significant reduction in estimated systolic pulmonary arterial pressure (sPAP) (43.6 ± 14.1 mm Hg vs. 35.6 ± 16.6 mm Hg; p = 0.02) and left ventricular (LV) end-diastolic volume (195.1 ± 77.2 ml vs. 176.9 ± 84.7 ml; p = 0.03) in the overall cohort, without significant changes in LV end-systolic volume (121.7 ± 69.4 ml vs. 109.8 ± 73.3 ml; p = 0.1) or LVEF (41.2 ± 15.8% vs. 42.3 ± 14.5%; p = 0.7).

Mean MV pressure gradients were significantly increased after MitraClip procedures (1.5 ± 0.8 mm Hg vs. 3.4 ± 1.5 mm Hg; p = 0.001) without incidence of significant MV stenosis (Online Table 1).

PERSISTENCE OF IASD AND COMPARISON OF BASELINE CHARACTERISTICS. Persistence rate of iASD as documented with TEE was 50%, with measured maximal and minimal diameters of 4.3 ± 1.7 mm (interquartile range: 1.1 to 7.9 mm) and 3.8 ± 2.1 mm (interquartile range: 1.2 to 7.1 mm), respectively. In 2 of 33 cases (6%), TEE showed

TABLE 1 Baseline Characteristics Separated by iASD Persistence

	All Patients (n = 66)	iASD (n = 33)	no iASD (n = 33)	p Value
Age, yrs	77.1 ± 7.9	76.6 ± 8	77.7 ± 8	0.6
Female	15 (23.3)	7 (21)	8 (24)	0.7
Body mass index, kg/m^2	26.2 ± 4.2	26.3 ± 4.2	26.1 ± 4.2	0.8
EuroSCORE II, %	10.1 ± 6.1	11 ± 7.2	9.2 ± 4.6	0.2
Functional MR	48 (73)	24 (73)	24 (73)	1
AF	46 (70)	26 (79)	21 (62)	0.2
History of cardiac decompensation	39 (65)	18 (60)	21 (70)	0.3
Coronary heart disease	40 (60)	22 (67)	18 (55)	0.3
Diabetes mellitus	18 (27)	11 (33)	7 (21)	0.1
AHT	47 (72)	23 (70)	24 (73)	0.5
Smoking	24 (37)	13 (39)	11 (33)	0.4
Hyperlipidemy	28 (42)	15 (45)	13 (39)	0.3
Stroke	3 (5)	1 (3)	2 (6)	0.5
NYHA functional class	3.3 ± 0.5	3.2 ± 0.5	3.3 ± 0.5	0.6

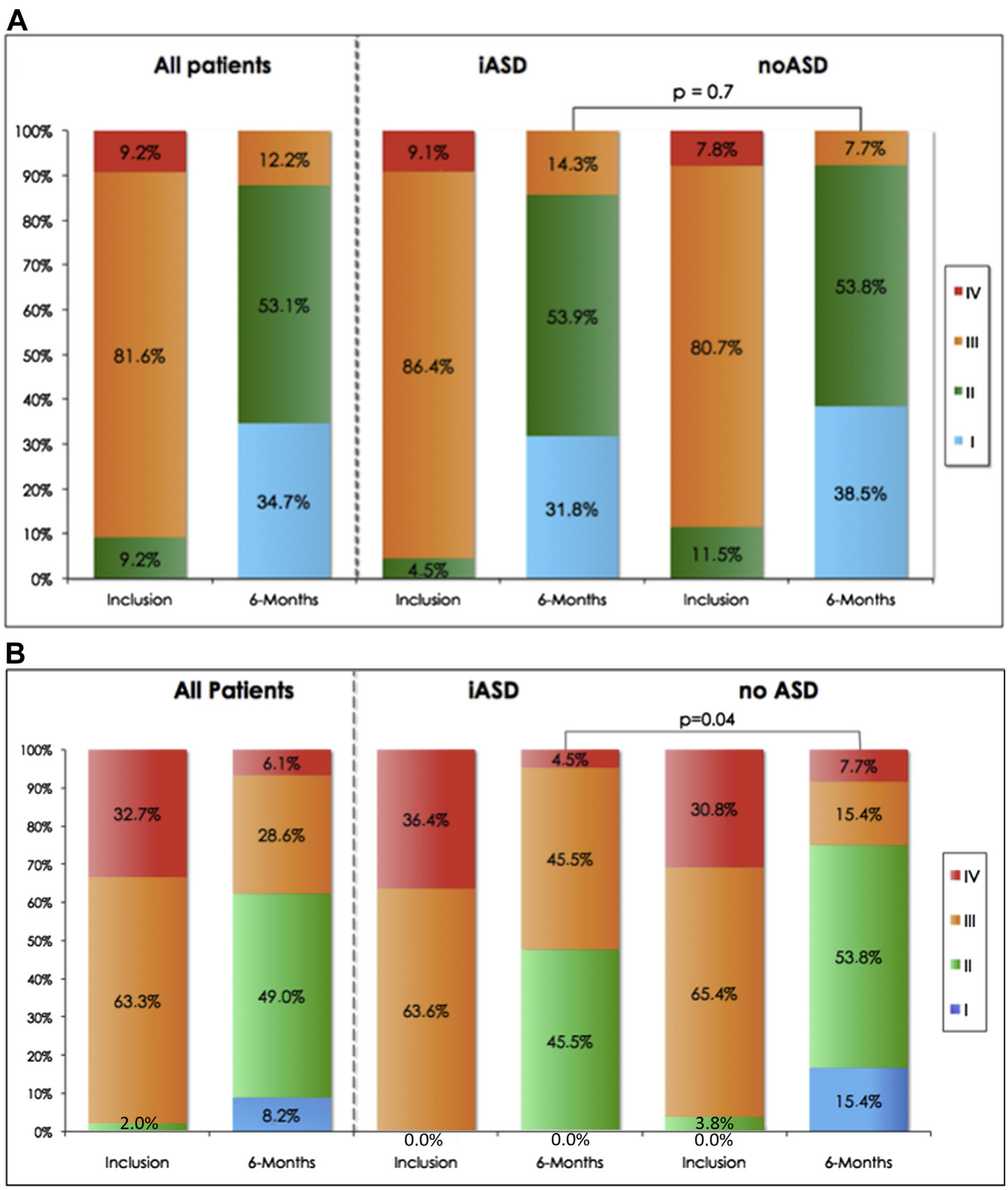
Values are mean ± SD or n (%).
AF = atrial fibrillation; AHT = arterial hypertension; iASD = iatrogenic atrial septal defect; MR = mitral regurgitation; NYHA = New York Heart Association functional class, 6MWD = 6-min walking distance.

TABLE 2 Procedural Details and Outcomes

	All Patients	iASD	No iASD	p Value
Procedure time, min	75.8 ± 42.8	82.4 ± 39.7	68.9 ± 45.5	**0.05**
Radiation time, min	24.5 ± 17.7	30.5 ± 20.6	18.6 ± 11.9	**0.05**
Number of clips				0.4
1 clip	40 (60)	19 (58)	21 (64)	
≥2 clips	26 (40)	14 (42)	12 (36)	
Procedural success	65 (98)	33 (100)	32 (97)	0.5
Repeated procedure	7 (10)	3 (9)	4 (12)	0.6
Surgery	0	0 (0)	0 (0)	–
Endovascular	7 (10)	3 (9)	4 (12)	0.6
Hospital death	0	0 (0)	0 (0)	–
Intraprocedural death	0	0 (0)	0 (0)	–
MACCE	0	0 (0)	0 (0)	–
Stroke	0	0 (0)	0 (0)	–
Minor bleeding	7 (10)	0 (0)	7 (21)	**0.03**
Transfusion/major bleeding requiring transfusion	5 (7)	0 (0)	5 (15)	**0.02**
Major vascular complications	0	0 (0)	0 (0)	–
30-day mortality	2 (3)	2 (6)	0 (0)	0.3
6-month mortality	7 (11)	6 (18)	1 (3)	**0.04**

Values are mean ± SD or n (%). **Bold** p values indicate statistically significant results.
iASD = iatrogenic atrial septal defect; MACCE = major adverse cardiac and cerebrovascular events (combined endpoint for cardiac events and mortality).

FIGURE 2 **Stapled Columns of MR Grading and NYHA Functional Classes Before and 6 Months After TMVR Procedures**



(A) Mitral regurgitation (MR) grading; **(B)** New York Heart Association (NYHA) functional classes. ASD = atrial septal defect; iASD = iatrogenic atrial septal defect.

spontaneous right-to-left shunt via iASD. When comparing groups separated by persistence of iASD after 6 months, we found no significant differences concerning baseline characteristics (Table 1), acute procedural success rates, MV gradient, and amount of residual MR after clip placement (Table 2). TMVR took longer in patients with iASD (82.4 ± 39.7 min vs. 68.9 ± 45.5 min; p = 0.05), which was associated with longer radiation times (30.5 ± 20.6 min vs. 18.6 ± 11.9 min; p = 0.05).

We found no significant differences between groups in baseline functional parameters, severity of

MR, or measured sPAP. Patients with persistent iASD had larger basal (5.1 ± 0.8 cm vs. 4.6 ± 0.8 cm; p = 0.01) and midventricular (3.7 ± 0.8 cm vs. 3.3 ± 0.7 cm; p = 0.03) right ventricular diameters at baseline (**Table 3**).

ASSOCIATION OF IASD WITH ECHOCARDIOGRAPHIC MEASURES AFTER FU. When separating patients according to presence of iASD after 6 months, we found no significant differences in residual MR, MV gradients, or LV diastolic volume and function. In concordance with the obtained baseline measurements, right ventricular diameters remained larger in iASD patients but did not significantly differ from baseline (Online Table 1).

Interestingly, only patients without iASD experienced significant reductions in LV end-diastolic (198.4 ± 80.2 ml vs. 174.4 ± 94.1 ml; p = 0.04) and end-systolic (122.7 ± 74.1 ml vs. 103.9 ± 79.3 ml; p = 0.05) volumes during FU, without significant changes in measured LV function (LVEF: 42.1 ± 16.9% vs. 44.9 ± 14.7%; p = 0.3) (**Table 4**).

The decrease in echocardiographically-measured sPAP was significantly different between groups (**Figure 3A**); only patients without iASD experienced a significant decrease of measured sPAP (43.47 ± 15.1 mm Hg vs. 32.5 ± 11.9 mm Hg; p = 0.03), whereas sPAP remained unchanged in the iASD group (42.5 ± 13 mm Hg vs. 44.1 ± 19.2 mm Hg; p = 0.8) (Online Table 1). Furthermore, right atrial areas increased significantly in the iASD group during FU (28.9 ± 7.4 cm^2 vs. 34.2 ± 11.7 cm^2; p = 0.002) with a concomitant decrease in left atrial volumes (162.5 ± 63.3 ml vs. 139.1 ± 47.6 ml; p = 0.04) (**Table 4**). In patients without ASD, there were no significant changes in right and left atrial dimensions (p > 0.05).

ASSOCIATION OF IASD WITH FUNCTIONAL OUTCOMES AND SURVIVAL. Patients with iASD experienced a significantly lower increase in 6-min walking distances compared with patients without iASD (20.8 ± 107.4 m vs. 114.6 ± 116.4 m; p = 0.001) (**Figure 3B**) and showed higher levels of N-terminal pro-brain natriuretic peptide 6 months after clip placement (6,667.3 ± 7363.9 ng/dl vs. 4,835.9 ± 6,681.7 ng/dl; p = 0.05).

Overall, 57% of patients with iASD remained in functional NYHA functional class >II compared with 30% of patients without iASD (p = 0.04) (**Figure 2B**).

Survival rates were significantly different between groups: 6 patients (16.6%) with iASD died during FU compared with 1 patient (3.3%) in the groups without iASD (log rank p = 0.05) (**Figure 4**).

TABLE 3 Baseline Echocardiographic Measures of Patients Separated by Persistence of iASD

	All Patients	iASD	No iASD	p Value
LVEF, %	41.2 ± 15.8	40.4 ± 14.9	42.1 ± 16.9	0.6
LVVd, ml	195.1 ± 77.2	191.6 ± 75.3	198.4 ± 80.2	0.7
LVVs, ml	121.7 ± 69.4	120.7 ± 65.6	122.7 ± 74.1	0.9
LVEDD, cm	6.7 ± 0.9	7.3 ± 0.7	6.1 ± 0.7	0.08
LVESD, cm	5.1 ± 1.3	5.7 ± 1.4	4.5 ± 0.9	0.07
LA_{vol}, ml	154.8 ± 65.2	162.5 ± 63.3	147.5 ± 67.4	0.4
EROA, cm^2	0.5 ± 0.2	0.4 ± 0.2	0.5 ± 0.3	0.1
Reg. volume, ml	48.8 ± 18.1	46.4 ± 14.7	51.2 ± 21	0.3
PISA	0.8 ± 0.2	0.8 ± 0.2	0.8 ± 0.1	0.8
Vena contracta, cm	0.9 ± 1.6	0.7 ± 0.2	1.1 ± 2.2	0.3
MR grade	3 ± 0.4	3 ± 0.4	3 ± 0.4	1
I	0	0 (0)	0 (0)	
II	0 (0)	0 (0)	0 (0)	
>II	66 (100)	33 (100)	33 (100)	1
MV gradient	1.5 ± 0.8	1.7 ± 0.8	1.3 ± 0.7	0.08
RVD1, cm	4.8 ± 0.8	5.1 ± 0.8	4.6 ± 0.8	**0.01**
RVD2, cm	3.5 ± 0.8	3.7 ± 0.8	3.3 ± 0.7	**0.03**
RVD3, cm	8.3 ± 1	8.4 ± 1.0	8.1 ± 0.9	0.2
TAPSE, cm	1.8 ± 0.5	1.8 ± 0.5	1.8 ± 0.5	1
sPAP, mm Hg	42.9 ± 13.9	42.5 ± 13	43.4 ± 15.1	0.8
TR grade				
I	14 (21)	8 (24)	6 (18)	
II	25 (38)	14 (42)	11 (33)	
>II	27 (40)	12 (36)	15 (45)	0.3
RA_{area}, cm^2	26.9 ± 8.3	28.8 ± 7.4	24.9 ± 8.9	0.09

Values are mean ± SD or n (%). **Bold** p values indicate statistically significant results.

EROA = effective regurgitant orifice area; LA_{vol} = left atrial volume; LVEDD = left ventricular end-diastolic diameter; LVESD = left ventricular end-systolic diameter; LVEF = left ventricular ejection fraction; LVVd = left ventricular volume during diastole; LVVs = left ventricular volume during systole; PISA = proximal isovelocity surface area; RA = right atrium; Reg. = regurgitation; RVD = right ventricle diameter; sPAP = right ventricular systolic pressure; TAPSE = tricuspid annular plane systolic excursion; TR = tricuspidal regurgitation; other abbreviations as in **Table 1**.

After Cox regression analysis, only the presence of iASD was associated with survival during FU (**Table 5**).

The echocardiographic FU evaluation had a good reproducibility. We found a good intraclass and interclass absolute agreement, with all correlation coefficients ranging above 0.8 (**Table 6**).

DISCUSSION

To our knowledge, this is the first study investigating the persistence rates of iASD after interventional edge-to-edge repair with serial TEE examinations and close clinical FU. Following our results, the persistence rate of iASD after MitraClip procedures with transseptal left atrial access was high (50%). This finding is clinically important because persistent interatrial shunt was associated with worse hemodynamic and clinical development after TMVR and—more importantly—with an increased probability for all-cause death.

JACC: CARDIOVASCULAR INTERVENTIONS VOL. 8, NO. 3, 2015
MARCH 2015:450–9

TABLE 4 Echocardiographic Assessment of Patients Before and After Follow-Up

	iASD	No iASD	p Value
LVVd, ml			
Baseline	191.7 ± 75.29	198.4 ± 80.2	0.7
Follow-up	179.6 ± 75.1	174.4 ± 94.1	0.8
p value	0.6	**0.04**	
LVVs, ml			
Baseline	120.7 ± 65.6	122.7 ± 74.1	0.9
Follow-up	116.1 ± 67.2	103.9 ± 79.3	**0.5**
p value	0.8	0.06	
LA_{vol}, ml			
Baseline	162.5 ± 63.3	147.5 ± 67.5	0.4
Follow-up	139.1 ± 47.6	147.3 ± 60.9	0.6
p value	**0.04**	0.9	
MR >II			
Baseline	33 (100)	33 (100)	1
Follow-up	4 (13)	1 (3.3)	0.7
p value	**<0.0001**	**<0.0001**	
MV gradient			
Baseline	1.7 ± 0.8	1.3 ± 0.7	0.08
Follow-up	3.1 ± 1.1	3.7 ± 1.9	0.4
p value	**<0.0001**	**<0.0001**	
sPAP, mm Hg			
Baseline	42.5 ± 13	43.4 ± 15.1	0.8
Follow-up	44.1 ± 19.2	32.5 ± 11.9	**0.03**
p value	0.2	**0.03**	
RVD2, cm			
Baseline	3.7 ± 0.8	3.3 ± 0.7	**0.03**
Follow-up	3.9 ± 0.9	3.3 ± 0.9	**0.04**
p value	0.2	0.8	
RA area, cm^2			
Baseline	28.8 ± 7.4	24.9 ± 8.9	0.09
Follow-up	34.2 ± 11.7	24.3 ± 6.2	**0.001**
p value	**0.002**	0.7	

Values are mean ± SD or n (%). **Bold** p values indicate statistically significant results.
MV = mitral valve; other abbreviations as in Table 3.

The reasons for these unfavorable outcomes remain unclear at the current stage. As a matter of fact, at-risk patients need special care, because the hemodynamic effects of interatrial shunt defects in patients with predominantly advanced stages of chronic heart failure have not been systematically investigated.

PERSISTENCE RATES OF IASD AFTER CARDIAC INTERVENTIONS WITH TRANSSEPTAL ACCESS. Limited data are available on persistence rates and predictors for iASD after different cardiac procedures. According to our own experiences, the underlying pathomechanism combines technical, interventional, and patient-derived factors. We investigated 42 patients undergoing pulmonary vein isolation with either single (n = 27) or double (n = 15) transseptal 8-F catheters. Factors associated with iASD persistence after FU were the use of a single transseptal sheath demanding more extensive interatrial movement (p = 0.01) and the prevalence of pulmonary hypertension before pulmonary vein isolation (p = 0.05) (13). More recently, Sieira et al. (14) described a 12-month persistence rate of 20% for iASD in 39 patients undergoing pulmonary vein isolation with considerably larger 15-F transseptal sheaths.

When regarding other structural/transseptal interventions, iASD persisted in 18% of patients undergoing mitral valvuloplasty with dilation of the interatrial septum by using an 8-mm balloon (15) and in 7% of patients after left atrial appendage closure with a 12-F transseptal sheath (16).

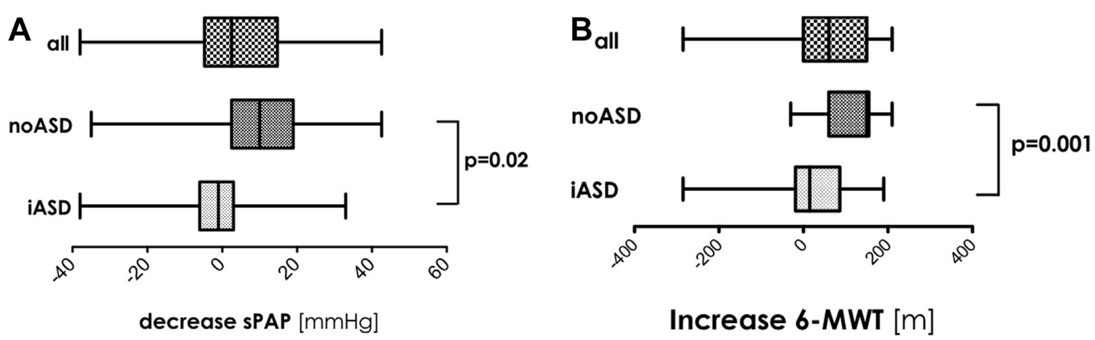
At this time, only 1 study has investigated persistence rates for iASD after MitraClip implantations with TEE. Saitoh et al. (17) examined 10 patients 1 month after MitraClip implantation and found a 90% iASD persistence rate. In our study, iASD persistence was considerably less, which can be explained by the fact that the FU period was relevantly longer, allowing for further defect healing. We did not compare intraprocedural iASD diameters of patients separated by iASD persistence.

When putting our findings in context with the available evidence, the iASD persistence rate of 50% seems caused by predominantly 2 factors: 1) TMVR with the MitraClip requires extensive movement of a large transseptal sheath (21-F, 7.3 mm); and 2) local trauma increases with rising procedural time in the iASD group.

CLINICAL EFFECT OF INTERATRIAL SHUNT DEFECTS IN A "MITRACLIP POPULATION". Available evidence is sparse investigating hemodynamic effects and clinical consequences of iASD after TMVR with the MitraClip systems. Theoretically, iASD with bidirectional interatrial shunt can provoke paradoxical embolism and worsen clinical symptoms of heart failure due to volume overload. However, Hoffman et al. (18) found evidence for beneficial hemodynamic consequences of iASD in 28 patients undergoing MitraClip procedures caused by acute left atrial pressure relief. Our findings on reverse changes of right and left atrial dimensions in patients with iASD support this hypothesis. However, according to the clinical outcomes in our cohort after 6 months, persistent right atrial volume overload seems to not be beneficial in this patient group.

Conversely, several case reports have been published describing detrimental clinical effects of iASDs in selected patients with predominantly advanced stages of chronic heart failure. In all cases, symptoms abated after interventional iASD closure, supporting

FIGURE 3 **Improvement in Measured sPAP and 6MWT After FU**

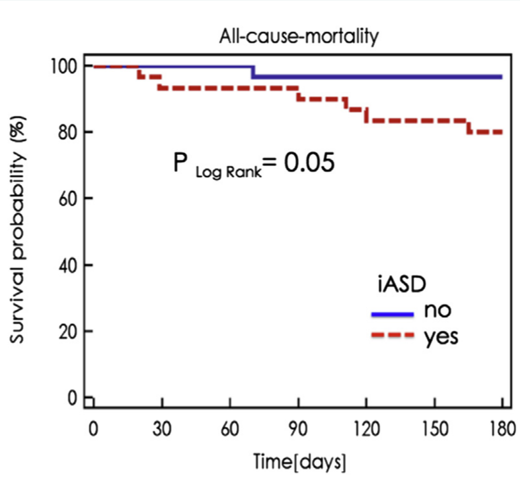


(A) Measured systolic pulmonary arterial pressure (sPAP); **(B)** 6-min walk test (6MWT). Abbreviations as in Figure 2.

the hypothesis of the iASD being the underlying cause of disease (19,20). Sirker et al. (20) found increased oxygen requirements in a patient with persistent iASD after transseptal MV surgery; the patient improved immediately after iASD device closure. Huntgeburth et al. (19) found worsening of right-heart failure related symptoms in 3 patients after MitraClip procedures, and all patients were treated successfully with interventional defect closure (19).

When adding these findings with the available evidence on procedural shunt defects, a negative hemodynamic or clinical effect of iASD was never shown in larger cohorts of patients undergoing pulmonary vein isolation (14,21), mitral valvuloplasty (22) or LAA closure (16).

FIGURE 4 **Kaplan-Meier Curves for Survival After 6 Months**



iASD = iatrogenic atrial septal defect.

What makes the difference in MitraClip patients? First, MitraClip therapy is primarily performed in selected high-risk patients who receive TMVR for the treatment of advanced stages of symptomatic chronic heart failure accompanied by reduced LV function and increased LV end-diastolic pressures (6,23–25). Second, the atrial defect size after TMVR is considerably larger (17), increasing interatrial shunt volumes. Third, persistence rates are high due to extensive movement of a large sheath during complex procedures. The acute and persistent hemodynamic effects of interatrial shunting in this vulnerable population have not yet been investigated. In line with an increasing number of published case reports in this field, there is growing evidence that iASD might negatively affect clinical patient outcomes.

STUDY LIMITATIONS. We investigated only a small number of patients who underwent TMVR procedures with the MitraClip system, and other groups should confirm our findings independently. Ideally,

TABLE 5 **Cox Regression Analysis of Factors Predicting 6-Month Mortality**

	HR	95% CI	p Value
iASD	6.4	1.0–23.4	**0.04**
$Creatinine_{baseline}$, mg/dl	1.8	1.1–3.0	0.07
$NT\text{-}proBNP_{baseline}$, ng/dl	1.0	1.0–1.0	0.4
Age, yrs	1.0	0.9–1.1	0.7
LVEF, %	1.0	0.9–1.1	0.8
FMR	0.9	0.2–4.7	0.9
sPAP, mm Hg	1.0	0.9–1.0	0.4
Severe TI	1.1	1.0–1.4	0.4

Bold p values indicate statistically significant results.

CI = confidence interval; FMR = functional mitral regurgitation; HR = hazard ratio; NT-proBNP = N-terminal pro-brain natriuretic peptide; TI = tricuspid valve insufficiency; other abbreviations as in Tables 1 and 3.

TABLE 6 Intraclass Correlations for Intraobserver and Interobserver Agreement of Echocardiographic Follow-Up Parameters

	Interobserver Agreement	p Value	Intraobserver Agreement	p Value
LVEF	0.89	0.004	0.93	<0.001
sPAP	0.88	0.005	0.92	<0.001
TAPSE	0.90	0.002	0.91	<0.001
LVVS	0.91	0.002	0.95	<0.001
LVVD	0.87	0.007	0.91	0.002
LA_{vol}	0.90	0.002	0.92	<0.001
RA area	0.92	0.003	0.91	<0.001
RVD1	0.88	0.004	0.89	0.005
RVD2	0.89	0.003	0.91	<0.001

Abbreviations as in Table 3.

the hemodynamic effects of interatrial shunt defects would be determined invasively at baseline and during FU. At this stage, it remains unclear whether iASD is the reason for or effect of unfavorable hemodynamic and clinical outcome measures. We report the findings of a single-center study and cannot exclude that procedural details and interventional steps differ significantly from other sites, which might have a relevant effect on iASD persistence rates. We, furthermore, cannot exclude a documentation bias of clinical outcome measures, because statistical testing for reliability was not performed. However, in every patient, clinical assessment was performed by trained nurses, and the plausibility of the results was checked by experienced physicians. Additionally, clinical measures were correlated with quantitative parameters on functional capacity (N-terminal pro-brain natriuretic peptide, 6-min walk distance).

CONCLUSIONS

The iASD persistence rate of 50% after MitraClip procedures is considerably high. Persistence of interatrial shunting was associated with worse clinical outcomes and increased mortality rates. Further studies are warranted to investigate if iASD is a mediator or marker for advanced stages of chronic heart disease in these patients.

REPRINT REQUESTS AND CORRESPONDENCE: Priv. Doz. Dr. med. Christoph Hammerstingl, Medizinische Klinik und Poliklinik II, Universitätsklinikum Bonn, Sigmund-Freud-Strasse 25, 53105 Bonn, Germany. E-mail: christoph.hammerstingl@ukb.uni-bonn.de.

REFERENCES

1. Chan PH, She HL, Alegria-Barrero E, Moat N, Di Mario C, Franzen O. Real-world experience of MitraClip for treatment of severe mitral regurgitation. Circ J 2012;76:2488–93.

2. Feldman T, Kar S, Rinaldi M, et al. Percutaneous mitral repair with the MitraClip system: safety and midterm durability in the initial EVEREST (Endovascular Valve Edge-to-Edge REpair Study) cohort. J Am Coll Cardiol 2009;54:686–94.

3. Franzen O, Baldus S, Rudolph V, et al. Acute outcomes of MitraClip therapy for mitral regurgitation in high-surgical-risk patients: emphasis on adverse valve morphology and severe left ventricular dysfunction. Eur Heart J 2010;31:1373–81.

4. Franzen O, van der Heyden J, Baldus S, et al. MitraClip(R) therapy in patients with end-stage systolic heart failure. Eur J Heart Fail 2011;13:569–76.

5. Baldus S, Schillinger W, Franzen O, et al. MitraClip therapy in daily clinical practice: initial results from the German transcatheter mitral valve interventions (TRAMI) registry. Eur J Heart Fail 2012;14:1050–5.

6. Tamburino C, Ussia GP, Maisano F, et al. Percutaneous mitral valve repair with the MitraClip system: acute results from a real world setting. Eur Heart J 2010;31:1382–9.

7. Feldman T, Foster E, Glower DD, et al. Percutaneous repair or surgery for mitral regurgitation. N Engl J Med 2011;364:1395–406.

8. Lancellotti P, Tribouilloy C, Hagendorff A, et al. Recommendations for the echocardiographic assessment of native valvular regurgitation: an executive summary from the European Association of Cardiovascular Imaging. Eur Heart J Cardiovasc Imaging 2013;14:611–44.

9. Lancellotti P, Moura L, Pierard LA, et al. European Association of Echocardiography recommendations for the assessment of valvular regurgitation. Part 2: mitral and tricuspid regurgitation (native valve disease). Eur J Echocardiogr 2010;11:307–32.

10. Vahanian A, Alfieri O, Andreotti F, et al. Guidelines on the management of valvular heart disease (version 2012): the Joint Task Force on the Management of Valvular Heart Disease of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS). Eur J Cardiothorac Surg 2012;42:S1–44.

11. Foster E, Wasserman HS, Gray W, et al. Quantitative assessment of severity of mitral regurgitation by serial echocardiography in a multicenter clinical trial of percutaneous mitral valve repair. Am J Cardiol 2007;100:1577–83.

12. Wunderlich NC, Siegel RJ. Peri-interventional echo assessment for the MitraClip procedure. Eur Heart J Cardiovasc Imaging 2013;14:935–49.

13. Hammerstingl C, Lickfett L, Jeong KM, et al. Persistence of iatrogenic atrial septal defect after pulmonary vein isolation—an underestimated risk? Am Heart J 2006;152:362–5.

14. Sieira J, Chierchia GB, Di Giovanni G, et al. One year incidence of iatrogenic atrial septal defect after cryoballoon ablation for atrial fibrillation. J Cardiovasc Electrophysiol 2014;25:11–5.

15. Casale P, Block PC, O'Shea JP, Palacios IF. Atrial septal defect after percutaneous mitral balloon valvuloplasty: immediate results and follow-up. J Am Coll Cardiol 1990;15:1300–4.

16. Singh SM, Douglas PS, Reddy VY. The incidence and long-term clinical outcome of iatrogenic atrial septal defects secondary to transseptal catheterization with a 12F transseptal sheath. Circ Arrhythm Electrophysiol 2011;4:166–71.

17. Saitoh T, Izumo M, Furugen A, et al. Echocardiographic evaluation of iatrogenic atrial septal defect after catheter-based mitral valve clip insertion. Am J Cardiol 2012;109:1787–91.

18. Hoffmann R, Altiok E, Reith S, Brehmer K, Almalla M. Functional effect of new atrial septal defect after percutaneous mitral valve repair using the MitraClip device. Am J Cardiol 2014;113:1228–33.

19. Huntgeburth M, Muller-Ehmsen J, Baldus S, Rudolph V. Postinterventional iatrogenic atrial septal defect with hemodynamically relevant left-to-right and right-to-left shunt as a complication of successful percutaneous mitral valve repair with the MitraClip. Int J Cardiol 2013;168:e3–5.

20. Sirker A, Hyde J, Hildick-Smith D. Refractory hypoxemia after mitral valve surgery: an unusual cause and its successful percutaneous treatment. J Invasive Cardiol 2006;18: E86–8.

21. McGinty PM, Smith TW, Rogers JH. Transseptal left heart catheterization and the incidence of persistent iatrogenic atrial septal defects. J Interv Cardiol 2011;24:254–63.

22. Rittoo D, Sutherland GR, Shaw TR. Quantification of left-to-right atrial shunting and defect size after balloon mitral commissurotomy using biplane transesophageal echocardiography, color flow Doppler mapping, and the principle of proximal flow convergence. Circulation 1993;87: 1591–603.

23. Grayburn PA, Foster E, Sangli C, et al. Relationship between the magnitude of reduction in mitral regurgitation severity and left ventricular and left atrial reverse remodeling after MitraClip therapy. Circulation 2013;128: 1667–74.

24. Maisano F, Godino C, Giacomini A, et al. Clinical trial experience with the MitraClip catheter based mitral valve repair system. Int J Cardiovasc Imaging 2011;27:1155–64.

25. Schillinger W, Hunlich M, Baldus S, Ouarrak T, Boekstegers P, Hink U, Butter C, Bekeredjian R, Plicht B, Sievert H, Schofer J, et al. Acute outcomes after MitraClip therapy in highly aged patients: results from the German TRAnscatheter Mitral valve Interventions (TRAMI) Registry. EuroIntervention 2013;9: 84–90.

KEY WORDS heart failure, iatrogenic ASD, MitraClip, prognosis

APPENDIX For supplemental tables, please see the online version of this article.