openheart

Prevalence of iatrogenic atrial septal defects (iASD) after mitral valve (MV) transcatheter edge-to-edge repair (TEER) in the long-term follow-up

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► Additional supplemental material is published online only. To view, please visit the journal online (http://dx.doi.org/10.1136/openhrt-2021-001732).

To cite: Paukovitsch M, Schneider LM, Reichart C, *et al*. Prevalence of iatrogenic atrial septal defects (iASD) after mitral valve (MV) transcatheter edge-to-edge repair (TEER) in the long-term follow-up. *Open Heart* 2021;**8**:e001732. doi:10.1136/openhrt-2021-001732

Received 25 May 2021
Accepted 22 September 2021

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ABSTRACT

Objectives To investigate prevalence of iatrogenic atrial septal defects (iASDs) after mitral valve (MV) transcatheter edge-to-edge repair (TEER) with the MitraClip in the long-term follow-up.

Background MV TEER requires transseptal puncture using a large 22 F sheath. Prevalence, impact and haemodynamic effects of these iASDs remain unknown in the long-term follow-up.

Methods This prospective study enrolled patients who had undergone first-time TEER at our university hospital between January 2017 and June 2018 for a clinical long-term follow-up study. Prevalence of iASD was investigated 12 months post-TEER using transoesophageal echocardiography (TEE). Study protocol further consisted of transthoracic echocardiography (TTE) and exercise testing. Incidence of all-cause death was compared 12 months post-TEE follow-up. This study was approved by local ethics committee.

Results 48 patients participated in clinical follow-up examinations. Median time between TEER and clinical follow-up examination (TEE, TTE, exercise testing) was 19.5 (IQR: 7.0) months after TEER. Persistent iASD was found in 41.7% of patients. TEER was found to be equally effective in reducing MR and clinical symptoms in both groups at baseline as well as follow-up. Procedural fluoroscopy and device times were significantly longer in the iASD group. MR reduction and functional status (New York Heart Association Class, 6 Minute Walking Test distance) were similar in both groups. Nevertheless, a significant decrease in systolic pulmonary artery pressure (sPAP) and significantly smaller atrial diameters were observed in patients with iASD at follow-up.

Conclusion Prevalence of iASDs after TEER in long-term follow-up was about 41%. Although a significant reduction of sPAP and better left atrial reverse remodelling were accomplished in patients with iASD, clinical impact appears low. Manipulation at the atrial septum might play a key role in creating persisting iASD.

Key messages

What is already known about this subject?

► Previous studies found varying rates and effects of persisting iatrogenic atrial septal defects (iASD) after mitral valve (MV) transcatheter edge-to-edge repair (TEER).

What does this study add?

► Persistence rate of iASD after MV TEER in the long-term follow-up is similar to previous findings from short-term follow-up studies.
► Longer fluoroscopy and device time in patients with persisting iASD support the concept of manipulation at the atrial septum as a key mechanism leading to persisting iASD.
► Patients with iASD experience a significant reduction in systolic pulmonary artery pressure and a better left atrial reverse remodelling when compared with non-iASD patients.

How might this impact on clinical practice?

► Especially interventional cardiologists should be aware that even in the long-term follow-up, many patients with a persisting iASD can be found. While an impact on haemodynamics and remodelling processes can be observed in patients with a persisting iASD, its clinical impact appears low.

INTRODUCTION

Transcatheter edge-to-edge repair (TEER) using the MitraClip system has proven to be safe and efficious in reducing mitral regurgitation (MR) in a wide range of cohorts including patients with degenerative (DMR) and functional MR (FMR).[1–3] Given the minimally invasive approach of TEER, patients suffering from severe MR with high surgical risk due to age or comorbidities can be offered a low-risk therapy. EVEREST II (Endovascular Valve Edge-to-Edge Repair Study) investigators confirmed clinical outcome to be similar to conventional surgery, although less reduction in MR was observed.[4] Moreover, results from the COAPT Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients With Functional Mitral Regurgitation) trial

outlined prognostic value of MitraClip therapy in patients with FMR.[5] TEER uses transseptal puncture (TSP) with a 22F catheter to gain access to the left atrium and mitral valve.[1] However, recently concerns were raised about the iatrogenic atrial septal defect (iASD), which might persist after TEER. Indeed, despite increasing use, there is still limited data on effects of increasing use of large catheter sheaths for TSP.[6] Besides TEER, TSP is widely applied in ablation therapy and left atrial (LA) appendage occlusion device implantation. Different persistence rates of iASDs have been reported in the literature, depending on follow-up time and type of procedure.[6 7 8 9] While it seems that persis- tence is largely correlated with catheter size,[6] the exact prevalence and effect of iASDs in the long-term follow-up are unknown.

Moreover, in one study, the persistence of iASD was associated with increased mortality.[7] However, Hoffman *et al* mention positive effects of iASD by pressure relief of the left atrium.[10]

METHODS

This is a prospective, single-centre follow-up study of patients who had undergone successful first-time TEER using the MitraClip system at our institution between January 2017 and June 2018. Symptomatic patients under guideline-directed medical therapy suffering from either functional (FMR) or degenerative (DMR) severe MR (grades 3+and 4+) were treated with TEER using the MitraClip system. Treatment decision was based on joint evaluation by the interdisciplinary heart time entailing cardiac surgeons and interventional cardiologists according to current guidelines and standards.[11]

Patients were recruited from our MitraULM registry (NCT03104660), a record database of patients was treated with TEER. All patients treated between January 2017 and June 2018 were invited to take part in a clinical follow-up examination. This check-up was performed with a minimum duration of 12 months post-TEER at our institution and included physical examination, transthoracic echocardiography (TTE), transoesophageal echocardiography (TEE) and a Six Minute Walking Test (6MWT). The MitraULM registry's follow-up protocol does not include a TEE examination. Furthermore, all participating and non-participating patients gave written informed consent for data collection and publication for the MitraULM registry. No exclusion criteria existed. Patients from the MitraUlm registry who were invited, but refused to participate in the study, were compared with participating patients regarding baseline characteristics and procedural outcome to reduce a possible selection bias.

Baseline characteristics and procedural details

Baseline characteristics, procedural data and outcome had been recorded in patients' files and were accessed for this study. TEER using the MitraClip system has been described elsewhere.[1 12] In brief, placement of the MitraClip requires TSP using a steerable 24F catheter with a 22F tip. Placement of the device fuses parts of the anterior and posterior leaflets (edge-to-edge), thus reducing mitral valve area and MR. For the procedure, patients are placed under general anaesthesia and fluoroscopy and TEE guidance were used to adequately place the MitraClip.[1 12] TSP was performed mid to posterior in the short axis view and at the maximum height in the bicaval view. In this study, mean LA pressure and LA v wave were measured invasively before and after placement of the MitraClip. Similarly, mitral valve gradient was measured using TEE before and after placement of the device. Device time was defined as time between insertion of the guide catheter and its removal.

Clinical follow-up

Echocardiography including TTE and TEE follow-up was performed by experienced physicians. Severity of MR was graded using current principles including effective regurgitant orifice area, vena contracta, following recommendations from the EVEREST investigators as well as current guidelines.[1 11 13] TEE examination consisted of visualisation of the atrial septum at different angles as well as 2D and 3D visualisation. 3D echocardiography was used for qualitative assessment of the jet and the deviation of the jet in the atrium. Persistence of iASD was determined using colour Doppler. If no spontaneous colour Doppler flow could be determined, iASD persistence was definitively ruled out by the use of agitated saline similar to excluding a persisting foramen ovale. Dimensions of iASDs were evaluated both in short axis as well as in bicaval view and the longer of both was used to measure iASD size. TTE examination was undertaken to measure heart chambers, left and right ventricular (RV) function. Diastolic dysfunction was defined as LVEF >55%, elevated NT-proBNP (>220 pg/mL in sinus rhythm and 660 pg/mL in atrial fibrillation), and presence of either echocardiographic or cardiac MRI evidence for impaired left ventricular relaxation (E/e'≥15).[14] 6 MWT was performed to determine functional status in addition to New York Heart Association (NYHA) classification and physical examination. 12-month follow-up after identification of iASD persistence was conducted by telephone interview.

Statistical analysis

Continuous variables were expressed using mean and SD or median and IQR. Categorical variables are shown as frequencies and percentages. Variables were compared between the non-iASD and iASD group. Distribution of variables was analysed using Kolmogorov-Smirnov test. Box-Whisker plots were used to identify outliers. Due to the small sample size, any outliers were not removed from the data set. Student's t-test or Mann-Whitney U test were used for comparison of continuous variables as appropriate. Similarly, for paired variables, the paired Student's t-test or the Wilcoxon test were used. χ^2 test or Fisher exact test were used for comparison of categorical variables. Kaplan-Meier analysis of survival and log-rank

test were used to compare survival between patients with iASD and non-iASD. A p value of <0.05 was considered statistically significant. Statistical analysis was performed using SPSS, IBM Statistics, V.25.

RESULTS

Baseline and procedural data

Variables were calculated for the entire patient population as well as for the iASD and non-iASD groups independently. 48 patients volunteered for a follow-up examination with a median follow-up time of 19.5 months (IQR: 7.0) (duration between TEER and TEE). The initial TEER procedure was deemed successful in all patients. Table 1 shows baseline patient characteristics. The majority of patients suffered from FMR. To minimise a possible selection bias, baseline characteristics of participating patients (N=48) were compared with non-participating patients (N=118) (see Methods section for

Table 1 Baseline patient characteristics

Parameter	Total	non-iASD	iASD	P value
Patients, N (%)	48	28 (58.3)	20 (41.7)	
Age (years)	75.3±8.5	74.0±8.3	77.1±8.5	0.21
BMI (kg/m^2)	27.3±4.1	26.8±4.0	27.9±4.3	0.36
Male, N (%)	23 (47.9)	12 (42.9)	11 (55.0)	0.41
Arterial hypertension, N (%)	40 (83.3)	23 (82.1)	17 (85.0)	1.00
Hyperlipidaemia, N (%)	34 (70.8)	22 (78.6)	12 (60.0)	0.16
Diabetes mellitus, N (%)	15 (31.3)	10 (35.7)	5 (25.0)	0.43
Coronary artery disease, N (%)	34 (70.8)	18 (64.3)	16 (80.0)	0.34
Pulmonary hypertension, N (%)	12 (25.0)	7 (25.0)	5 (25.0)	1
COPD, N (%)	5 (10.4)	3 (10.7)	2 (10.0)	1.00
AF, N (%)	31 (64.6)	18 (64.3)	13 (65.0)	0.96
LBBB, N (%)	11 (22.9)	5 (17.9)	6 (30.0)	0.49
CRT-D/P, N (%)	7 (14.6)	2 (7.1)	5 (25.0)	0.11
FMR, N (%)	32 (66.7)	19 (67.9)	13 (65.0)	0.84
DCM, N (%)	8 (16.7)	5 (17.9)	3 (15.0)	1.00
Diastolic dysfunction, N (%)	12 (25.0)	9 (32.1)	3 (15.0)	0.18
NYHA Class pre Clip	3.0±0.6	2.93±0.5	3.2±0.7	0.13
NYHA Class IV pre Clip	10 (20.8)	3 (30.0)	7 (70.0)	0.07 (0.05)
Euro SCORE II	5.9±5.6	5.0±4.4	7.2±6.9	0.19
STS Risk of Mortality Score	4.2±4.0	3.5±3.5	5.1±4.4	0.17
Troponin-T pre (µg/L)	27.1±21.0	23.5±13.3	31.4±27.6	0.24
NT-pro-BNP pre (pg/mL)	3901.9±4077.6	3068.7±2877.9	4954.4±5110.6	0.13
eGFR (mL/min)	50.7±22.4	54.46±23.7	45.3±19.8	0.16
Systolic BP (mm Hg)	126.1±19.1	128.7±19.1	122.5±18.8	0.28
Diastolic BP (mm Hg)	72.4±12.0	70.9±12.9	74.3±10.6	0.34
Loop diuretics, N (%)	39 (81.3)	21 (75)	18 (90)	0.27
Other diuretics, N (%)	6 (12.5)	4 (14.3)	2 (10.0)	1.0
MRA, N (%)	24 (50)	13 (46.4)	11 (55.0)	0.77
ACEI, N (%)	21 (43.8)	14 (50)	7 (35)	0.38
ARB, N (%)	14 (29.2)	7 (25.0)	7 (25.0)	0.53
ARNI, N (%)	10 (20.8)	6 (21.4)	4 (20)	1.0
BB, N (%)	40 (83.3)	22 (78.6)	18 (90)	0.44

Values are mean±SD, or number (%). P values in parentheses refer to one-sided testing.
ACEI, angiotensin-converting enzyme inhibitor; AF, atrial fibrillation; ARB, AT receptor blocker; ARNI, angiotensin-neprilysin inhibitor; BB, beta-blocker; BMI, body mass index (kg/m^2); BP, blood pressure; COPD, chronic obstructive pulmonary disease; CRT, cardiac resynchronisation therapy; DCM, dilatative cardiomyopathy; eGFR, estimated glomerular filtration rate; FMR, functional mitral regurgitation; LBBB, left bundle branch block; MRA, mineralocorticoid receptor antagonist; NT-proBNP, N-terminal pro hormone brain natriuretic peptide; NYHA, New York Heart Association; STS, Society of Thoracic Surgeons.

Table 2 Baseline echocardiography

Parameter	Total	non-iASD	iASD	P value
LVEF (%)	40.9±16.9	41.1±16.6	40.5±17.9	0.9
LVEDd (mm)	60.2±12.1	59.0±13.2	62.3±9.9	0.41
LVESd (mm)	46.7±14.7	45.19±15.5	49.3±13.4	0.4
IVSd (mm)	10.1±1.8	10.2±1.8	9.9±1.8	0.62
PWd (mm)	10.4±1.6	10.4±1.4	10.3±1.9	0.85
LA diameter (mm)	55.3±8.2	56.1±9.6	54.2±5.9	0.43
Grade of MR preprocedural	3.73±0.4	3.71±0.5	3.75±0.4	0.79
Severe MR (IV) pre, N (%)	35 (72.9)	20 (71.4)	15 (75.0)	0.79
Grade of MR post-procedural	1.44±0.6	1.36±0.6	1.55±0.6	0.23
Grade of TR	1.58±0.7	1.4±0.7	1.9±0.6	**0.01**
Severe TR (grade 3), N (%)	6 (12.5)	3 (10.7)	3 (15.0)	0.68
sPAP (mm Hg)	54.2±17.2	50.9±15.8	58.4±18.3	0.14 (0.07)
TAPSE (mm)	19.8±5.2	20.3±3.7	19.0±6.6	0.41

Values are mean±SD, or number (%). P values in parentheses refer to one-sided testing. **Bold** p values indicate statistically significant results.
IVSd, septum diameter; LA, left atrium; LVEDd, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; LVESd, left ventricular end-systolic diameter; MR, mitral regurgitation; PWd, posterior wall diameter; sPAP, systolic pulmonary artery pressure; TAPSE, tricuspid annular plane systolic excursion; TR, tricuspid regurgitation.

further details). This comparison revealed no relevant differences between participating and non-participating patients. This data are provided as supplemental information (online supplemental tables 2–4).

Table 2 shows baseline echocardiographic data. Average preprocedural grade of MR was 3.73±0.4. MR severity between groups differed neither before (non-iASD: 3.71±0.5; iASD: 3.75±0.4; p=0.79) nor after (non-iASD: 1.36±0.6; iASD: 1.55±0.6; p=0.23) TEER. Notably, iASD patients displayed greater severity in grade of TR (non-iASD: 1.4±0.7; iASD: 1.9±0.6; p=0.01). Moreover, a tendency towards higher systolic pulmonary artery pressure (sPAP) was observed in patients with iASD at baseline (non-iASD: 50.9±15.8 mm Hg; iASD: 58.4±18.3 mm Hg; p=0.14 (two sided); p=0.07 (one sided)). None of the patients investigated had any type of pre-existing atrial septal defect. Fluoroscopy (non-iASD: 22.6±8.1 min; iASD: 29.1±13.3 min; p=0.04) and device times (non-iASD: 46.4±21.1 min; iASD: 61.4±27.7 min; p=0.04) were significantly longer in the iASD group (see table 3). We also observed a trend towards more frequent leaflet grasping to optimally position the MitraClip in patients with iASD (total: 2.0±1.5; non-iASD: 1.8±1.0; iASD: 2.4±1.9; p=0.2). All patients experienced significant reduction in mean LA pressure and LA v-wave in the process of TEER (see table 3). The number of clips needed to reach proper MR reduction did not differ between both groups (non-iASD: 1.1±0.4; iASD: 1.3±0.6; p=0.29). Mean mitral valve gradients increased significantly during procedure in both groups (see table 3); yet no mitral valve stenosis was detected.

Clinical and echocardiography follow-up

Persistent iASD was observed in 20 out of 48 patients by use of TEE, constituting a persistence rate of 41.7%. Further patient characteristics at follow-up are shown in table 4. All iASDs were found using colour Doppler imaging. No further iASDs were detected by use of agitated saline (bubble study). Mean size of iASD was 7.2±7.4 mm. Left-to-right shunting was observed in all patients with iASD without exception. Both groups showed lasting reduction in MR (average grade of MR at follow-up: non-iASD: 1.5±0.7; iASD: 1.35±0.6; p=0.34; further, see table 5). Additionally, a total of 85.4% of patients reported an improvement of dyspnoea symptoms (non-iASD: 78.6%; iASD: 95.0%; p=0.21). Significant reduction in average NYHA class was reached among both patient groups (see table 5). Non-iASD patients reported symptoms equivalent to NYHA I more often at clinical follow-up, however, statistical testing could not confirm a significant difference (non-iASD: 42.9%; iASD: 20%; p=0.1). Precise evaluation of physical status using 6MWT revealed no difference in exercise capacity between groups (non-iASD: 316.5±90.8 m; iASD: 297.9±105.63 m; p=0.55).

In echocardiography, LVEF was similar in the non-iASD and iASD group (non-iASD: 41.5%±17.7%; iASD: 39.7%±14.4%; p=0.73). Further details from follow-up echocardiography are found in the online supplemental table 1. In the follow-up examination, LA diameters were significantly smaller in the iASD group (non-iASD: 56.7±6.8 mm; iASD: 51.6±7.0 mm; p=0.03). Comparison of baseline and follow-up parameters revealed significant reduction of sPAP in the iASD group only (mean change in sPAP: non-iASD: −0.4±23.3 mm Hg; p=0.94; iASD: −10.2±18.0 mm Hg; p=0.03). Moreover, a reduction in grade of TR was observed in the iASD group compared with the baseline grade (non-iASD: 0.5±1.0; iASD:−0.04±1.0; p=0.07 (two-sided test); p=0.04 (one-sided test); see table 5). Preprocedural RV function measured

Table 3 Procedural details

Parameter	Total	non-iASD	iASD	P value
Fluoroscopy time (min)	25.3±11.0	22.6±8.1	29.1±13.3	**0.04**
Device time (min)	52.6±25.0	46.4±21.1	61.4±27.7	**0.04**
Number of clips implanted	1.2±0.5	1.1±0.4	1.3±0.6	0.29
mPG preprocedural (mm Hg)	1.6±1.0	1.6±1.2	1.5±0.7	0.72
mPG postprocedural (mm Hg)	3.5±1.6	3.4±1.8	3.7±1.5	0.52
Mean change in mPG (mm Hg)	1.9±1.4	1.8±1.5	2.2±1.2	0.32
P value	**<0.01**	**<0.01**	**<0.01**	
Mean LA pressure preprocedural (mm Hg)	23.9±6.9	23.6±7.1	24.3±6.8	0.72
Mean LA pressure postprocedural (mm Hg)	17.6±5.3	16.92±5.2	18.6±5.6	0.31
Mean change in LA pressure (mmHg)	−6.0±5.3	−6.2±6.2	−5.8±4.1	0.79
P value	**<0.01**	**<0.01**	**<0.01**	
LA v-wave preprocedural (mm Hg)	34.2±11.5	33.0±11.1	35.8±12.0	0.43
LA v-wave postprocedural (mm Hg)	25.8±9.2	24.4±9.0	27.9±9.3	0.2
Mean change in LA v-wave (mm Hg)	−8.6±9.4	−8.6±10.2	−8.7±8.4	0.98
P value	**<0.01**	**<0.01**	**<0.01**	

Values are mean±SD, or number (%). P values in parentheses refer to one-sided testing.
Bold p values indicate statistically significant results.
LA, left atrium; mPG, mean pressure gradient.

Table 4 Follow-up patient characteristics

Parameter	Total	non-iASD	iASD	P value
Months post TEER (median; IQR)	19.5; IQR: 7.0	20.0; IQR: 6.0	19.0; IQR: 7.0	0.61
BMI (kg/m^2)	27.0±4.3	26.2±4.4	28.2±3.9	0.11
Systolic BP (mm Hg)	126.4±18.8	130.3±18.6	120.8±18.1	0.09
Diastolic BP (mm Hg)	71.7±11.4	73.4±10.2	69.2±12.7	0.22
NYHA Class	1.9±0.8	1.75±0.9	2.2±0.7	0.09
NYHA Class I	16 (33.3)	12 (42.9)	4 (20.0)	0.1 (0.09)
Improvement in dyspnoea, N (%)	41 (85.4)	22 (78.6)	19 (95.0)	0.21
6 MWT (m)	308.6±96.5	316.5±90.8	297.9±105.63	0.55
Peripheral oedema, N (%)	8 (16.7)	4 (14.3)	4 (20.0)	0.7
Oedema improvement since TEER, N (%)	11 (22.9)	5 (17.9)	6 (30.0)	0.45
Rehospitalisation due to heart failure, N (%)	8 (16.7)	3 (10.7)	5 (25.0)	0.25
Stroke, N (%)	3 (6.3)	1 (3.6)	2 (10.0)	0.56
Loop diuretics, N (%)	32 (66.7)	18 (64.3)	14 (70.0)	0.68
Other diuretics, N (%)	5 (10.4)	3 (10.7)	2 (10.0)	1.0
MRA, N (%)	30 (62.5)	16 (57.1)	14 (70.0)	0.36
ACEI, N (%)	18 (37.5)	10 (35.7)	8 (40.0)	0.76
ARB, N (%)	12 (25.0)	8 (28.6)	4 (20.0)	0.5
ARNI, N (%)	11 (22.9)	6 (21.4)	5 (25.0)	1.0
BB, N (%)	42 (87.5)	24 (85.7)	18 (90.0)	1.0
SGLT2 inhibitor, N (%)	4 (8.3)	3 (10.7)	1 (5.0)	0.63

Values are mean±SD, or number (%). P values in parentheses refer to one-sided testing.
ACEI, angiotensin-converting enzyme inhibitor; ARB, AT receptor blocker; ARNI, angiotensin-neprilysin inhibitor; BB, beta-blocker; BMI, body mass index (kg/m^2); BP, blood pressure; MRA, mineralocorticoid receptor antagonist; 6MWT, Six Minute Walking Test; NYHA, New York Heart Association; SGLT-2, sodium-glucose cotransporter-2.

Table 5 Comparison of baseline and follow-up parameters

Parameter	Total		non-iASD		iASD	
	Mean change FU – baseline	P value	Mean change FU – baseline	P value	Mean change FU – Baseline	P value
NYHA Class	−1.1±1.0	**<0.01**	−1.1±0.9	**<0.01**	−1.1±1.1	**<0.01**
LVEF (%)	−2.4±10.3	0.14	−1.4±10.5	0.5	−3.8±10.1	0.14
LVEDd (mm)	−0.1±11.0	0.96	2.6±11.3	0.33	−4.9±9.0	0.10 (0.05)
LVESd (mm)	1.0±11.6	0.67	4.0±11.7	0.15	−5.4±9.0	0.11
IVSd (mm)	0.5±2.8	0.35	0.3±3.2	0.67	0.7±2.3	0.3
PWd (mm)	0.8±3.2	0.2	0.1±2.7	0.87	1.8±3.9	0.13
LA diameter (mm)	−1.0±7.4	0.41	0.5±7.7	0.79	−2.7±6.9	0.13
sPAP (mm Hg)	−5.3±21.1	0.14	−0.4±23.3	0.94	−10.2±18.0	**0.03** (**0.02**)
Grade of MR	−2.3±0.7	**<0.01**	−2.2±0.7	**<0.01**	−2.4±0.6	**<0.01**
Grade of TR	−0.2±1.0	0.17	−0.04±1.0	0.86	−0.5±1.0	0.07 (**0.04**)
TAPSE (mm)	−0.5±4.6	0.48	−0.1±4.3	0.91	−1.2±4.9	0.3

Values are mean±SD, or number (%). P values in parentheses refer to one-sided testing. **Bold** p values indicate statistically significant results.
FU, follow-up; IVSd, septum diameter; LA, left atrium; LVEDd, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; LVESd, left ventricular end-systolic diameter; MR, mitral regurgitation; NYHA, New York Heart Association; PWd, posterior wall diameter; sPAP, systolic pulmonary artery pressure; TAPSE, tricuspid annular plane systolic excursion; TR, tricuspid regurgitation.

through tricuspid annular postsystolic annular excursion (TAPSE) was similar between both patient groups (non-iASD: 20.3±3.7 mm; iASD: 19.0±6.6 mm; p=0.41). A slight yet not significant decrease in RV function was observed in patients with persisting iASD (mean change: −1.2±4.9 mm; p=0.3). TAPSE remained almost unchanged in the non-iASD group (mean change: −0.1±4.3 mm; p=0.91).

Analysis of survival and rehospitalisation

We compared 12 months survival (all-cause death) after clinical follow-up between patients with iASD and non-iASD (see figure 1). All 48 patients completed follow-up. In the iASD group, two patients had died within 12 months of follow-up as opposed to one patient in the non-iASD group. Log-rank test showed no significant difference in all-cause mortality among patients with iASD and non-iASD (p=0.38; see figure 1). Correspondingly, no difference in the rate of rehospitalisation after TEER until clinical follow-up due to heart failure was found (non-iASD: 10.7%; iASD: 25.0%; p=0.25).

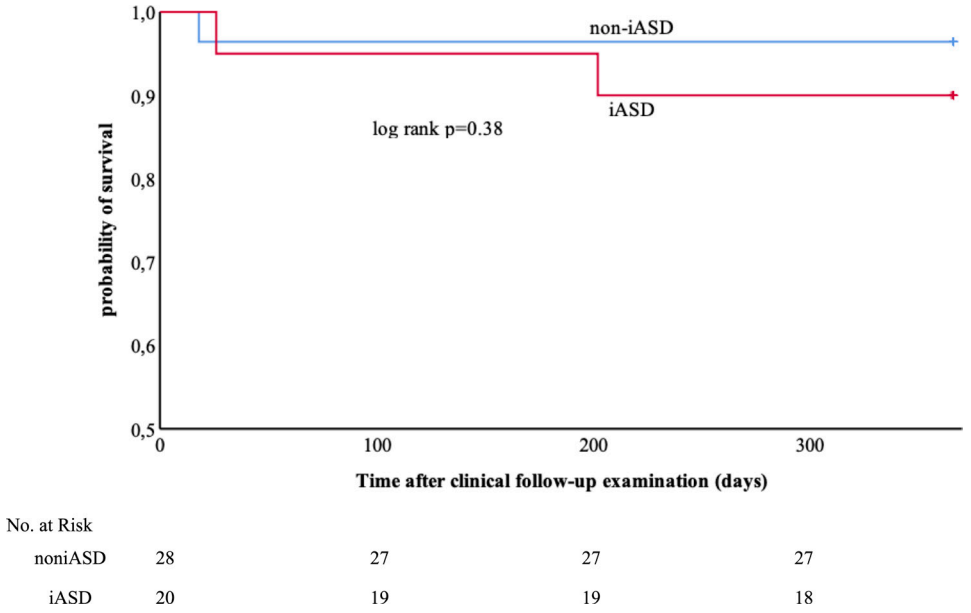

Figure 1 Kaplan-Meier analysis of probability of survival comparing patients with and without persisting iASD 12 months after iASD persistence had been confirmed in clinical follow-up (TEE). iASD, iatrogenic atrial septal defect; TEE, transoesophageal echocardiography.

DISCUSSION

To the best of our knowledge, we present for the first time findings concerning long-term prevalence and impact of iASD after mitral valve (MV) TEER using TEE, TTE and exercise testing. The main findings of this study were:

- Almost half of patients (41.7%) investigated in this study were found to have a persisting iASD in the long-term follow-up. This is within range of previously reported short-term persistence rates.
- Longer fluoroscopy and device time in the iASD group in this study support the concept of manipulation at the atrial septum as a key mechanism leading to persisting iASD.
- Short-term as well as long-term reduction of MR, functional status (NYHA Class, 6MWT) were similar in patients with iASD and non-iASD.
- Only patients with iASD experienced a significant reduction in sPAP and a better LA reverse remodelling. Left-to-right shunting was observed in patients with iASD without exception.

Prevalence of iASD after TEER

Several authors have previously investigated iASDs after TEER and found persistence rates ranging from 24% to 50% using either TTE or TEE.[7 8 15 16] Smith *et al* investigated 30 patients selected from the EVEREST II cohort in a 30-day, 6-month and 12-month follow-up using TTE. The investigators were able to show a declining persistence rate starting at 43% at 30 days with a steady 27% persistence rate in 6 and 12-month follow-ups. Greater MR and TR at 12-month follow-up in patients with iASD led Smith *et al* to suspect increased LA pressure as a mechanism for maintaining iASD.[16]

Ikenaga *et al* performed 1 and 12-month follow-up in their study using TTE. 35% of patients with iASD at 1-month follow-up were found to have persisting iASD at 12-month follow-up. In their study, LA pressure after clip deployment and MR grade 3+ or 4+ at follow-up were independently associated with iASD persistence.[15] Toyama *et al* reported a 27% persistence rate of iASD using TTE in a 12-month follow-up. In patients with persisting iASD, greater TR was observed in their cohort. They concluded that greater TR jet impacts iASD healing.[8] Schueler *et al* performed a 6-month follow-up using TEE and found a 50% persistence rate of iASD in a cohort of 66 patients.[7] While TEE can be considered more invasive, it seems to yield higher persistence rates in studies investigating persistence of iASD.[6–8 16] TTE might, in fact, underestimate iASD persistence rates.[17] Additionally, current guidelines recommend TEE for comprehensive evaluation of atrial septal defects.[18] Strikingly, the persistence rate found in our study with a minimum duration of 12 months post-TEER is almost as high as determined by Schueler *et al* after 6 months. Similar to the findings of Schueler *et al* persisting iASD was associated with longer fluoroscopy and procedure times equalling more extensive manipulation at the atrial septum.[7] Thus, our study supports the theory that both catheter size and manipulation at the atrial septum play a key role in persisting iASDs.[7 17]

Haemodynamics in patients with iASD after TEER

iASD after TEER was shown to cause immediate LA pressure relief.[10] On the other hand, detrimental effects on haemodynamics of left-to-right as well as right-to-left shunting have been reported in a few smaller studies.[19–22] While most patients experience left-to-right shunting, right-to-left shunting is associated with a poorer prognosis.[23] Both patient groups in our study experienced similar reduction in LA pressure during TEER and mitral valve repair was equally successful at baseline and follow-up. In our study, left-to-right shunting was observed without exception. Only patients with persisting iASD experienced a significant reduction in sPAP (mean change in sPAP: non-iASD: −0.4±23.3 mm Hg; p=0.94; iASD: −10.2±18.0 mm Hg; p=0.03). In contrast, a tendency towards worsened RV function (TAPSE) in patients with iASD was noticed in our cohort (non-iASD:19.9±4.6 mm; iASD: 17.6±4.1 mm; p=0.1). Similarly, TAPSE decreased slightly in the iASD group (mean change: −1.2±4.9 mm; p=0.3), while TAPSE remained almost unchanged in the non-iASD group (mean change: −0.1±4.3 mm; p=0.91). LA diameters were significantly smaller in the iASD group at follow-up compared with the non-iASD group. Hence, these observations reflect continuous left-to-right shunting across the atrial septum.

In contrast to our findings, in the cohort studied by Schueler *et al*, only patients without iASD experienced a significant decrease in sPAP. Furthermore, iASD was associated with increased mortality and worse functional outcome in their study. Schueler *et al* concluded that right atrial volume overload could be harmful in these patients.[7] Baseline differences between the cohorts of Schueler *et al* and our study might be responsible for differing results. Average sPAP at baseline was far higher in our study population (total: 54.2±17.2 mm Hg; non-iASD: 50.9±15.8 mm Hg, iASD: 58.4±18.3 mm Hg; p=0.14) compared with those patients presented by Schueler *et al* (total: 42.9±13.9 mm Hg; non-iASD: 43.4±15.1 mm Hg; iASD: 42.5±13 mm Hg; p=0.8).[7] As a result, haemodynamic changes over the course of the follow-up period might neither be readily comparable.

Should we close it?

Reports about iASD closure showed that if iASD closure became necessary, this would be within or closely after the procedure mostly due to acute and unfavourable haemodynamic changes.[19 21 22 24] Lurz *et al* recently presented preliminary results of the first randomised study comparing iASD closure to conservative therapy. Patients were eligible for iASD closure if a relevant iASD (Qp/Qs>1.3) with left-to-right shunting was observed in TEE 30 days post-TEER. Neither primary endpoint (6MWT distance) nor secondary endpoint (changes in peripheral oedema, NT-proBNP, death or hospitalisation) analysis was able to show superiority of iASD closure over conservative therapy. Lurz *et al* reasoned that iASD closure might be positive in reducing right-sided volume overload, while these effects might be evened out by the negative impact

on LA pressure relief.[25] In our study, neither increased use of diuretics nor greater severity in heart failure symptoms was observed in patients with iASD. Exercise capacity of patients determined by 6MWT distance was similar in both patient groups. Three patients (10.7%) in the non-iASD group versus five (25.0%) patients in the iASD group were rehospitalised due to heart failure (p=0.25). Despite statistical insignificance patients with iASD seemed to experience rehospitalisation due to heart failure more often. Based on our records, rehospitalisation occured due to global heart failure in four of these patients, while left-sided heart failure was the leading cause in the latter one. Thus, rehospitalisation was not associated with acute right-heart failure that would imply a massive burden due to excessive left-to-right shunting. Kaplan-Maier analysis of survival indicated no difference in all-cause mortality of patients with iASD and non-iASD. However, this should be viewed in terms of a limited sample size and a low overall incidence of all-cause death. Thus, considering all that is known so far and our current findings, it seems that the overall effect of a persisting iASD is rather low. Similarly, none of the patients investigated in our study was found to require iASD closure.

Persisting iASDs theoretically increase the risk of thrombembolic stroke by paradoxical embolism[7] based on what is known about congenital ASD.[26] However, this effect might again be influenced by the high rate of patients prescribed with oral anticoagulants due to atrial fibrillation, especially in TEER-treated populations. Only a few studies investigating persisting iASD after MV TEER report the stroke incidence in their population. Thus, data concerning incidence of stroke after TSP is scarce. If reported, stroke incidence was similar in patients with iASD versus those without iASD[8] or no event of stroke occurred at all.[15] We also found the stroke incidence to be similar in our cohort (non-iASD: 1 (3.6%), iASD: 2 (10%); p=0.56).

Strengths and limitations

We presented a single-centre investigation into iASD after TEER with only a small number of patients. Follow-up time after TEER until clinical follow-up using TEE for detection of iASD was the longest so far seen in the literature. However, our study might be underpowered to detect a significant baseline difference in sPAP, although a clear tendency towards higher sPAP values was observed. Further evaluation of larger cohorts of TEER-treated patients with repetitive follow-up to highlight haemodynamic changes over time and invasive measurement at best could yield further insights.

CONCLUSION

Persistence rate of iASD after TEER using TEE in long-term follow-up is similar to previous findings from short-term follow-up studies. Although a significant reduction of sPAP and better LA reverse remodelling were accomplished in patients with iASD, clinical impact appears low. Manipulation at the atrial septum might play a key role in creating persisting iASD. Effects of iASD might, however, vary across study populations.

Contributors Study design: SM, WR, MK, MP. Data collection: MP, SM, MK, CR, LMS. Data analysis and statistical analysis: MP, SM. Manuscript draft: MP, SM. Critical revision, editing and approval of the final manuscript: all authors.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent for publication Consent obtained directly from patient(s)

Ethics approval The study was conducted according to the guidelines of the Declaration of Helsinki, and approved by the Institutional Review Board (Ethics Committee of the University of Ulm). Local approval number: 388/18.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement All data relevant to the study are included in the article or uploaded as supplementary information.

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SUPPLEMENTAL INFORMATION – IATROGENIC ATRIAL SEPTAL DEFECTS (iASD) AFTER MITRAL VALVE (MV) TRANSCATHTER EDGE-TO-EDGE REPAIR (TEER) IN THE LONG-TERM FOLLOW-UP

Supplemental Table 1 – Follow-up Echocardiography (Details)

Parameter	**Total (N=48)**	**non-iASD (N=28)**	**iASD (N=20)**	**p-value**
LVEF (%) FU	40.7±16.3	41.5±17.7	39.7±14.4	0.73
LVEDd FU (mm)	60.9±12.9	61.0±13.8	60.7±12.0	0.94
LVESd FU (mm)	46.4±14.7	46.8±15.6	45.8±13.5	0.84
IVSd FU (mm)	10.6±2.6	11.0±2.7	10.1±2.4	0.28
PWd FU (mm)	11.3±2.9	10.7±2.1	12.2±3.6	0.12
LA diameter FU (mm)	54.4±7.3	56.7±6.8	51.6±7.0	**0.03**
sPAP FU (mmHg)	48.8 ±14.8	48.4±15.1	49.2±14.9	0.89
Grade of TR FU	1.4±0.9	1.3±0.9	1.5±1.0	0.65
TAPSE (mm)	18.9±4.5	19.9±4.6	17.6±4.1	0.1 (0.05)
Grade of MR	1.5±0.7	1.5±0.7	1.35±0.6	0.34
mPG FU (mmHG)	3.1±1.9	3.04±1.9	3.2±2.0	0.8

Values are mean ± standard deviation, or number (%). p-values in parentheses refer to one-sided testing.

FU = Follow-up; LVEF = Left Ventricular Ejection Fraction, LVEDd = Left Ventricular End-Diastolic diameter; LVESd = Left Ventricular End-Systolic diameter; IVSd = Septum diameter; PWd = Posterior Wall Diameter; LA = Left Atrium; MR = Mitral Regurgitation; sPAP = Systolic Pulmonary Artery Pressure; TR = Tricuspid Regurgitation, TAPSE= Tricuspid Annular Plane Systolic Excursion; mPG = Mean Pressure Gradient

Supplemental Table 2 – Patient Characteristics of Non-participating and Participating Patients

Parameter	**Total**	**Non-Participating**	**Participating**	**p-value**
Patients, N (%)	166 (100)	118 (71.1)	48 (28.9)	
Patients alive at time of study initiation, N (%)	139 (83.7)	91 (65.5)	48 (34.5)	
Age (years)	76.6±8.4	77.2±8.3	75.3±8.5	0.2
BMI (kg/m2)	25.9±4.5	25.3±4.6	27.3±4.1	**0.01**
Male, N (%)	67 (40.4)	44 (37.3)	23 (47.9)	0.23
Arterial Hypertension, N (%)	132 (79.5)	92 (78.0)	40 (83.3)	0.53
Hyperlipidemia, N (%)	106 (63.9)	72 (61.0)	34 (70.8)	0.29
Diabetes mellitus, N (%)	42 (25.3)	27 (22.9)	15 (31.3)	0.33
Pulmonary Hypertension, N (%)	37 (22.3)	25 (21.2)	12 (25.0)	0.68
COPD, N (%)	18 (10.8)	13 (11.0)	5 (10.4)	1.0
AF, N (%)	114 (68.7)	83 (70.3)	31 (64.6)	0.47
LBBB, N (%)	22 (13.3)	11 (9.3)	11 (22.9)	0.03
CRT-D/P, N (%)	18 (10.8)	11 (9.3)	7 (14.6)	0.41
FMR, N (%)	79 (59.0)	47 (54.7)	32 (66.7)	0.2
DCM, N (%)	26 (15.7)	18 (15.3)	8 (16.7)	0.82
NYHA Class pre Clip	3.1±0.7	3.1±0.7	3.0±0.6	0.4
NYHA Class IV pre Clip	44 (26.5)	34 (28.8)	10 (20.8)	0.34
Euro SCORE II	7.1±7.7	7.6±8.4	5.9±5.6	0.22
STS Risk of Mortality Score	4.9±6.7	5.2±7.6	4.2±4.0	0.37
Troponin-T pre (µg/L)	37.35±40.7	40.6±45.5	27.1±21.0	0.12
NT-pro-BNP pre (pg/mL)	5279.5±6544.6	5843.6±7260	3901.9±4077.6	0.27
eGFR (ml/min)	51.6±20.5	51.9±19.8	50.7±22.4	0.72
Systolic BP (mmHg)	126.5±20.1	126.6±20.7	126.1±19.1	0.88
Diastolic BP (mmHg)	72.6±11.0	72.6±10.7	72.4±12.0	0.9

Values are mean ± standard deviation, or number (%). p-values in parentheses refer to one-sided testing.

BMI = Body Mass Index (kg/m^2); COPD = Chronic Obstructive Pulmonary Disease, AF = Atrial Fibrillation, LBBB = Left Bundle Branch Block, CRT = Cardiac Resynchronization Therapy, FMR = functional mitral regurgitation, DCM = Dilatative Cardiomyopathy, NYHA = New York Heart Association, STS = Society of Thoracic Surgeons; NT-proBNP = N-terminal pro hormone brain natriuretic peptide, eGFR = estimated glomerular filtration rate; BP = Blood Pressure

Supplemental Table 3 – Baseline Echocardiography of Non-participating and Participating Patients

Parameter	Total	Non-Participating	Participating	p-value
LVEF (%)	44.7±18.5	46.4±18.9	40.9±16.9	0.09
LVEDd (mm)	59.6±11.3	59.3±11.0	60.2±12.1	0.63
LVESd (mm)	45.2±14.3	44.6±14.9	46.7±14.7	0.4
IVSd (mm)	11.0±2.2	11.3±2.3	10.1±1.8	**<0.01**
PWd (mm)	10.9±2.0	11.2±2.1	10.4±1.6	**0.02**
LA diameter (mm)	55.7±9.1	55.9±9.5	55.3±8.2	0.7
Grade of MR preprocedural	3.67±0.5	3.64±0.5	3.73±0.4	0.43
Severe MR (IV) pre, N (%)	93 (56.0)	58 (49.2)	35 (72.9)	**<0.01**
Grade of MR postprocedural	1.5±0.6	1.5±0.6	1.44±0.6	0.43
Grade of TR	1.8±0.8	1.8±0.8	1.58±0.7	0.04
Severe TR (Grade 3), N (%)	30 (18.1)	24 (20.3)	6 (12.5)	0.27
sPAP (mmHg)	57.0±16.9	58.7±16.7	54.2±17.2	0.15

Values are mean ± standard deviation, or number (%). p-values in parentheses refer to one-sided testing.

LVEF = Left Ventricular Ejection Fraction, LVEDd= Left Ventricular End-Diastolic diameter; LVESd= Left Ventricular End-Systolic diameter; LA= Left Atrium; IVSd= Septum diameter; PWd= Posterior Wall diameter; MR = Mitral Regurgitation; TR = Tricuspid Regurgitation; sPAP = Systolic Pulmonary Artery Pressure

Supplemental Table 4 - Procedural Details of Non-participating and Participating Patients				
Parameter	**Total**	**Non-Participating**	**Participating**	**p-value**
Fluoroscopy time (min)	25.3±11.0	22.6±8.1	29.1±13.3	**0.04**
No. of clips implanted	1.2±0.5	1.2±0.5	1.1±0.6	0.58
mPG preprocedural (mmHg)	1.6±1.0	1.6±1.0	1.6±1.1	0.99
mPG postprocedural (mmHg)	3.4±1.6	3.5±1.6	3.3±1.6	0.41
mean change in mPG (mmHg)	1.7±1.5	1.9±1.4	1.6±1.6	0.25
p-value	**<0.01**	**<0.01**	**<0.01**	
mean LA pressure preprocedural (mmHg)	21.8±7.4	23.9±6.9	20.6±7.5	**0.02**
mean LA pressure postprocedural (mmHg)	16.7±5.9	17.6±5.3	16.0±6.1	0.15
mean change in LA pressure (mmHg)	-5.5±5.1	-6.0±5.3	-5.1±5.0	0.37
p-Value	**<0.01**	**<0.01**	**<0.01**	
LA v-wave preprocedural (mmHg)	34.3±14.6	34.2±11.5	34.3±16.3	0.98
LA v-wave postprocedural (mmHg)	24.7±10.0	25.8±9.2	23.9±10.4	0.31

mean chance in LA v-wave (mmHg)	-9.6±10.5	-8.6±9.4	-10.2±11.2	0.44
p-value	**<0.01**	**<0.01**	**<0.01**	

Values are mean ± standard deviation, or number (%). p-values in parentheses refer to one-sided testing.

No.= Number; mPG= Mean Pressure Gradient; LA= Left Atrium