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Iatrogenic Atrial Septal Defects Following Transcatheter Mitral Valve Repair and Implications of Interventional Closure

Philipp Lurz, MD, PhD,[a,b,*] Matthias Unterhuber, MD,[a,*] Karl-Philipp Rommel, MD,[a] Karl-Patrik Kresoja, MD,[a,b] Tobias Kister, MD,[a] Christian Besler, MD,[a] Karl Fengler, MD,[a] Marcus Sandri, MD,[a] Ingo Daehnert, MD,[c] Holger Thiele, MD,[a,b] Stephan Blazek, MD,[a,†] Maximilian von Roeder, MD[a,†]

ABSTRACT

OBJECTIVES The authors investigated whether iatrogenic atrial septal defect (iASD) closure post-transcatheter mitral valve edge-to-edge repair (TMVR) is superior to conservative therapy (CT) and whether outcomes (death/heart failure [HF] hospitalization) differ between patients with and without an iASD post-TMVR.

BACKGROUND Transseptal access for TMVR can create an iASD, which is associated with impaired outcomes. Controversially, the creation of an iASD in HF has been linked to improved hemodynamics.

METHODS 80 patients with an iASD and relevant left-to-right shunting (Qp:Qs ≥1.3) 30 days following TMVR were randomized to CT or interventional closure of the iASD (MITHRAS [Closure of Iatrogenic Atrial Septal Defect Following Transcatheter Mitral Valve Repair] cohort), and 235 patients without an iASD served as a comparative cohort.

RESULTS All patients of the MITHRAS cohort (mean age 77 ± 9 years, 39% women) received their allocated treatment, and follow-up was completed for all MITHRAS and comparative cohort (mean age 77 ± 8 years, 47% women) patients. Twelve months post-TMVR, there was no significant difference in the combined endpoint of death or HF hospitalization within the MITHRAS cohort (iASD closure: 35% vs CT 50%; $P = 0.26$). The combined endpoint was more frequent among patients within the MITHRAS cohort as opposed to the comparative cohort (43% vs 17%; $P < 0.0001$), primarily driven by a higher rate of HF hospitalization (34% vs 8%; $P = 0.004$).

CONCLUSIONS In this randomized controlled trial, interventional closure of a relevant iASD 1 month after TMVR did not result in improved clinical outcomes at 12 months post-TMVR. Patients with an iASD are at higher risk for HF hospitalization independent of iASD management and warrant close follow-up. (Closure of Iatrogenic Atrial Septal Defect Following Transcatheter Mitral Valve Repair [MITHRAS]; NCT03024268)
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In selected patients with severe mitral regurgitation (MR) and increased surgical risk, transcatheter approaches and techniques to treat regurgitation are increasingly adopted (1-4) and have shown to reduce mortality and heart failure (HF) hospitalization rates (5).

Transcatheter treatment of mitral regurgitation (TMVR) usually requires transseptal access to the left

From the [a]Department of Internal Medicine/Cardiology, Heart Center Leipzig at Leipzig University, Leipzig, Germany; [b]Leipzig Heart Institute, Leipzig, Germany; and the [c]Department of Pediatric Cardiology, Heart Center Leipzig at Leipzig University, Leipzig, Germany. *Drs Lurz and Unterhuber contributed equally to this work as co-first authors. †Drs Blazek and von Roeder contributed equally to this work as co-senior authors.
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ABBREVIATIONS AND ACRONYMS

CT = conservative therapy

HF = heart failure

iASD = iatrogenic atrial septal defect

LV = left ventricle/ventricular

MR = mitral regurgitation

NT-proBNP = N-terminal pro-B-type natriuretic peptide

Qp = pulmonary perfusion

Qs = systemic perfusion

RV = right ventricle/ventricular

TMVR = transcatheter mitral valve edge-to-edge repair

TEE = transesophageal echocardiography

TTE = transthoracic echocardiography

atrium, and smaller studies reported a persistent iatrogenic atrial septal defect (iASD) in approximately 24% to 50% of patients (6,7).

On the one hand, postinterventional iASDs following TMVR have been associated with signs and symptoms of right heart and pulmonary circulatory volume overload, as well as increased rates of HF hospitalization and death, with recent hemodynamic data indicating that interventional closure of an iASD post-TMVR might improve biventricular function (6-9). On the other hand, left-to-right shunting across an iASD decompresses the left atrium and might be able to reduce both left atrial and left ventricular (LV) filling pressures (10,11), a concept currently applied and investigated in patients with both reduced and preserved ejection fraction (12-15). Given these controversies and lack of evidence to guide clinical management, we conducted the randomized MITHRAS trial (Closure of Iatrogenic Atrial Septal Defect Following Transcatheter Mitral Valve Repair; NCT03024268). We previously reported that interventional closure of the iASD 1 month post-TMVR did not improve exercise capacity as compared with conservative treatment (CT) at 5 months' follow-up (16). Here, we report the 11 months' outcomes of the randomized controlled MITHRAS trial and implications of iASD closure or CT on death and HF hospitalization. In addition, results of the MITHRAS cohort are compared with a comparative cohort of patients without relevant iASD 1 month post-TMVR.

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METHODS

TRIAL DESIGN. The MITHRAS trial is an investigator-initiated, randomized, unblinded trial involving patients with a relevant iASD 30 days after interventional edge-to-edge TMVR. The study addressed the question whether interventional iASD closure after TMVR is superior to CT in terms of change in 6-minute walk test. The trial was performed in accordance with the principles of the Declaration of Helsinki, the protocol was approved by the local ethics committee, and all patients gave written informed consent. The trial was previously registered at Clinicaltrials.gov (NCT03024268) and is funded by the Leipzig Heart Institute (Leipzig, Germany) and Occlutech (Jena, Germany).

STUDY POPULATION. Consecutive TMVR patients underwent routine 30-day follow-up assessment including transthoracic (TTE) and transesophageal (TEE) echocardiography at our institution. Patients with an echocardiographic relevant iASD (fraction of pulmonary perfusion [Qp]/fraction of systemic perfusion [Qs] ≥1.3) and predominantly left-to-right shunt 30 days post-TMVR were eligible and included. All other patients underwent regular follow-up either within the outpatient department or by telephone assessment as part of a prospective registry. Patients were enrolled between January 2016 and October 2019, and last follow-up was completed in September 2020. Exclusion criteria included significant left-to-right shunting (>30%) before TMVR, right-to-left shunting, unsuccessful TMVR with residual MR grade ≥II, and anatomic considerations precluding interventional iASD closure. The trial ended regularly after the planned number of patients were included.

RANDOMIZATION AND INTERVENTIONS. In total, 80 patients with significant iASD 30 days following TMVR were randomized in a 1:1 fashion to percutaneous closure of the iASD (n = 40) or CT (n = 40). Randomization was performed using a time-based Java script (Oracle) computer algorithm stratifying for the presence of diabetes mellitus and previous cardiac surgery, and took place on the same day after the echocardiographic iASD evaluation. Three of the authors (C.B., S.B., and M.v.R.) enrolled the patients and performed randomization. Closure of the iASD was performed within 3 days of randomization.

ECHOCARDIOGRAPHIC PROTOCOL. TTE and TEE (Vivid E9/E95, General Electric Healthcare) were performed by experienced cardiologists (M.v.R and C.B.). The chamber sizes, origin, and degree of MR post-TMVR and the severity of tricuspid regurgitation were classified according to the recommendations of the American Society of Echocardiography (17-19). Intracardiac shunting through the iASD was quantified by calculating the fraction of Qp to the fraction of Qs (Qp:Qs) (20). Therefore, Qp was calculated by the perfusion through the shunt and Qs. Shunt flow through the iASD during TEE was measured by multiplying the area of the iASD by the velocity time integral through the iASD on continuous wave Doppler (21). The area of the iASD was measured by 3-dimensional TEE. Systemic perfusion volume was measured as the diameter of the LV outflow tract multiplied by the velocity time integral of the pulsed-wave Doppler (20). Due care was taken to acquire only the flow through the iASD. As an estimate of right ventricular (RV) systolic pressure, the RV-to-right atrium pressure gradient was calculated from the

tricuspid regurgitation jet (without addition of right atrial pressure) (22).

iASD CLOSURE PROTOCOL. Catheterization was guided by fluoroscopy and echocardiography. Either TTE guidance or, in the case of suboptimal imaging quality, TEE guidance under conscious sedation was used for iASD closure. After femoral venous access, the iASD was crossed and an Amplatzer sizing balloon (St. Jude Medical) was placed across the iASD. According to the sizing, an atrial septal defect occluder (Figulla Flex II, Occlutech) was implanted. Procedural success was assessed by echocardiography.

ENDPOINTS. The endpoint of this subanalysis was a combined endpoint of death or first incidence of HF hospitalization within 11 months post-iASD assessment (12 months post-TMVR). Safety endpoints were complications from interventional iASD closure. All patients underwent the same assessment 30 days post-TMVR (including TTE/TEE) and routine follow-up 12 months after TMVR, including TTE (11 months post-iASD assessment or randomization). All patients of the randomized cohort underwent additional TTE/TEE at 6 months post-TMVR. In the randomized cohort, N-terminal pro-B-type natriuretic peptide (NT-proBNP) was measured at 1 and 12 months post-TMVR.

STATISTICAL ANALYSIS. The trial was originally powered to detect a difference of 55 ± 91 m obtained during a 6-minute walk test between iASD closure and CT 6 months post-TMVR at a total sample size of 80 randomized patients. The current analysis was prespecified and considered hypothesis-generating because statistical power considerations were hampered by the lack of clinical outcome data at the time of study planning in 2015.

Data for continuous variables are presented as mean ± SD if normally distributed, or as median and IQR if non-normally distributed. Distribution was tested using Shapiro-Wilk tests. Analysis of variance or Kruskal-Wallis tests were used to compare continuous variables over multiple groups. Categorical variables were compared with chi-square tests and, if an assumption of ordinal scales was appropriate, *P* for trend is given. Kaplan-Meier analyses were used to compare the survival times in different subgroups; log-rank tests were used to test for differences. Univariate Cox regression analysis for the prediction of the combined endpoint was done including continuous and categorical variables. A confounder-adjusted multivariable Cox regression analysis accounting for age, sex, LV ejection fraction, tricuspid annular plane systolic excursion, MR grade, tricuspid regurgitation grade, echocardiography-derived pulmonary artery pressure, mean transmitral inflow gradient, NT-proBNP, EuroSCORE, and estimated glomerular filtration rate was used to identify the adjusted influence of intracardiac shunting on the combined endpoint of death or HF hospitalization 11 months post-iASD assessment. We included all variables that correlated with the combined endpoint at $P < 0.05$ at univariable analysis. All time-to-event endpoints were defined with time of randomization or 30-day follow up as time zero. A *P* value of <0.05 was considered statistically significant. Statistical analyses were performed using R version 4.0.0 (R Foundation for Statistical Computing).

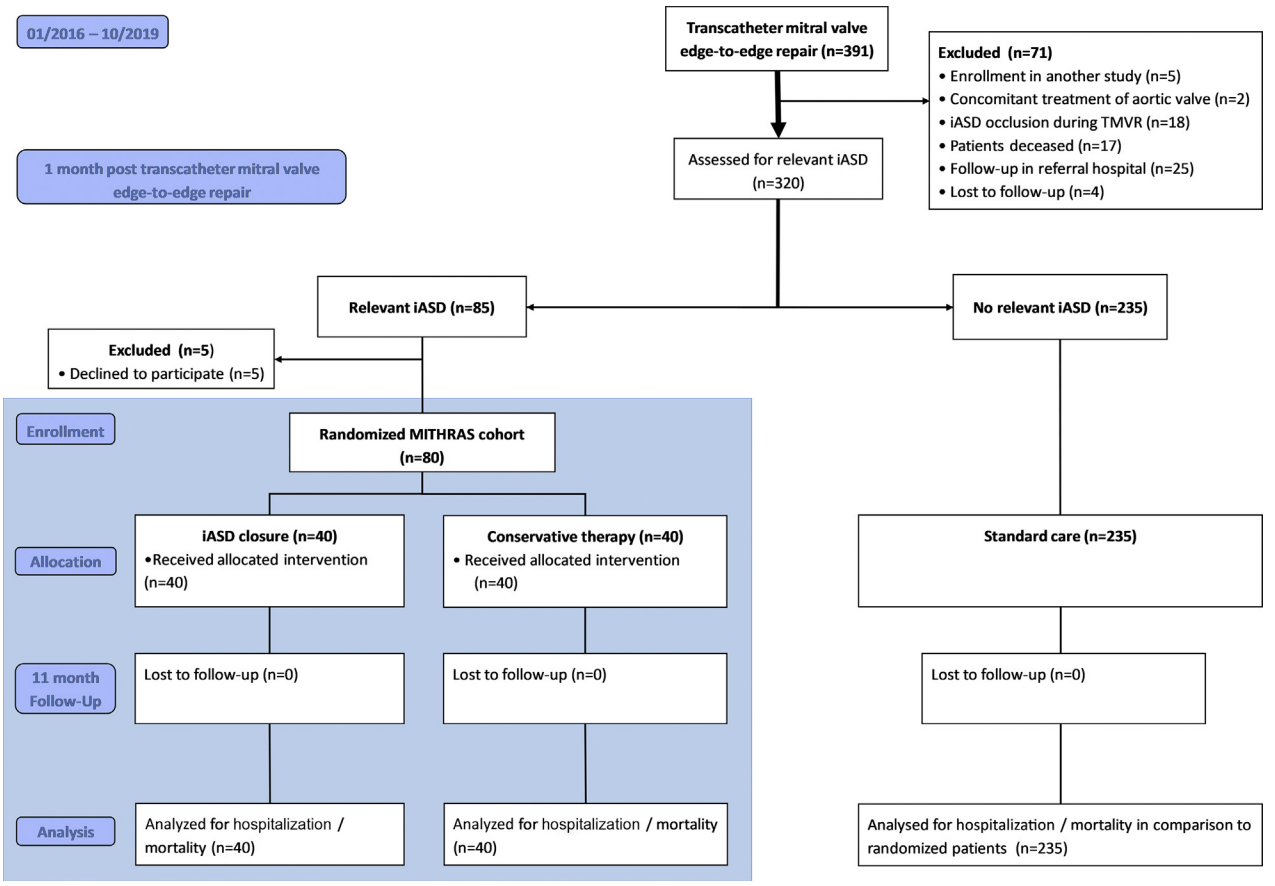
RESULTS

BASELINE CHARACTERISTICS. A total of 391 symptomatic patients received a TMVR at the Heart Center Leipzig at Leipzig University, Germany, between January 2016 and October 2019. Overall, 320 patients were screened with TTE/TEE for the persistence of a relevant iASD 30 days post-TMVR. From 85 patients with a relevant iASD, 5 patients declined study participation, the remaining 80 patients were randomized 1:1 to receive either interventional iASD closure (n = 40) or CT only (n = 40) compiling the MITHRAS cohort. Overall, 235 patients did not have a relevant iASD and were followed up as comparative cohort (**Figure 1**). As shown in **Table 1**, there were no differences in the baseline echocardiographic characteristics in the 2 randomized groups, and all patients received their allocated treatment. In a subset of patients, invasive oximetry or cardiac magnetic resonance imaging was performed before iASD closure. No significant differences in shunt fraction could be revealed between these modalities (Supplemental Table 1).

Patients in the MITHRAS cohort did not differ from the comparative cohort with regard to baseline medical history but more often had functional MR (62% versus 29%; $P < 0.001$) and exhibited impaired LV and RV function more frequently (**Table 1**).

TMVR resulted in a successful reduction of MR to grade ≤2 in 98% of the MITHRAS and 97% of the comparative cohort patients. The median MR reduction was 2 grades ($P = 0.71$ across groups). A 2-clip strategy was pursued more frequently in the MITHRAS cohort (iASD occlusion n = 23 [57%], CT n = 23 [57%]) than in the comparative group (n = 84 [36%]; $P < 0.003$) (Supplemental Table 2). In the majority of the patients, the MitraClip system (Abbott) was used for TMVR (in 38 patients [95%] in the iASD closure

FIGURE 1 Study Flow of the MITHRAS Trial



iASD = iatrogenic atrial septal defect; MITHRAS = Closure of Iatrogenic Atrial Septal Defect Following Transcatheter Mitral Valve Repair; TMVR = transcatheter mitral valve edge-to-edge repair.

group, 38 [95%] in the CT group, and in 219 patients [93%] in the comparative group; $P = 0.85$). In the remaining patients, the PASCAL system (Edwards Lifesciences) was used.

OUTCOME. All iASD closures (median occluder size 14 [IQR: 12-16] mm) were successfully performed without any adverse events.

Follow-up regarding the combined endpoint was completed in all patients and was concluded in the last patients in September 2020. Median clinical follow-up was 334 days (IQR: 324-338 days) for iASD closure, 331 days (IQR: 323-337 days) for CT, and 334 days (IQR: 326-369 days) in the comparative cohort.

Forty-four patients of the MITHRAS cohort (22 in each group) had complete NT-proBNP measurements at 1 month and 12 months post-TMVR. A numerically lower decrease in NT-proBNP could be observed in the group with iASD closure (iASD closure 1 month post-TMVR vs 12 months post-TMVR 3,132 ng/mL [IQR: 2,070-4,138 ng/mL] vs 1,958 ng/mL [IQR: 1,265-4,536 ng/mL]) and conservative therapy 1 month post-TMVR vs 12 months post-TMVR (3,738 ng/mL [IQR: 1,896-9,452 ng/mL] vs 2,211 ng/mL [IQR: 895-6,456 ng/mL], with a Δ of −1,175 vs −1,526) without reaching statistical significance ($P = 0.86$).

There was no significant difference in the combined endpoint of all-cause death or HF hospitalization between patients randomized to interventional iASD closure or CT (n = 14 [35%] vs n = 20 [50%]; $P = 0.26$). Subgroup analyses did not reveal a particular benefit in specific subgroups with regard to the combined endpoint (Figure 2).

The combined endpoint occurred more frequently in patients with a relevant iASD (MITHRAS cohort) as compared with the comparative cohort (34 [43%] vs

TABLE 1 Baseline Characteristics

	iASD Closure (n = 40)	iASD CT (n = 40)	No Relevant iASD (n = 235)	*P* Value
Age, y	77 ± 9	76 ± 10	77 ± 8	0.12
Female	16 (40)	15 (38)	110 (47)	0.43
Diabetes	16 (40)	16 (40)	83 (35)	0.75
Hypertension	38 (95)	36 (90)	215 (91)	0.69
Hypercholesterolemia	30 (75)	31 (78)	159 (68)	0.34
Previous myocardial infarction	13 (32)	10 (25)	43 (18)	0.10
Previous coronary-artery bypass grafting	6 (15)	6 (15)	29 (12)	0.83
Previous stroke or transient ischemic attack	3 (8)	4 (10)	15 (6)	0.70
Peripheral vascular disease	2 (5)	4 (10)	27 (11)	0.46
Chronic obstructive pulmonary disease	6 (15)	6 (15)	28 (12)	0.77
History of atrial fibrillation of flutter	29 (72)	28 (70)	169 (72)	0.97
Body mass index, kg/m^2	28 ± 4	27 ± 4	27 ± 5	0.35
Creatinine clearance				
Mean, mL/min/m^2	63 ± 29	59 ± 24	60 ± 25	0.87
≤60 mL/min	20 (50)	19 (48)	128 (54)	0.75
Anemia	20 (50)	15 (38)	94 (40)	0.44
EuroSCORE II	4.9 (3.3-9.6)	5.5 (2.6-7.6)	6.4 (3.9-9.6)	0.15
NYHA functional class				0.07
I	7 (18)	5 (13)	75 (32)	
II	22 (55)	16 (40)	86 (37)	
III	10 (25)	18 (45)	68 (29)	
IV	1 (2)	1 (2)	6 (2)	
RV lead	16 (40)	18 (45)	83 (38)	0.66
Single-chamber ICD device	8 (20)	8 (20)	53 (23)	0.89
CRT-D device	5 (12)	4 (10)	23 (10)	0.87
NT-proBNP, ng/L	3,138 (2,009-5,001)	3,077 (1,830-5,657)	2,515 (1,257-5,774)	0.40
Peripheral edema	22 (55)	25 (62)	121 (51)	0.40
LVEF, %	38 ± 13	37 ± 19	47 ± 16	<0.001
LVEDV, mL	147 (124-200)	152 (121-206)	132 (92-180)	0.06
LVESV, mL	92 (63-130)	96 (56-151)	71 (38-121)	0.009
Functional MR	25 (62)	25 (62)	67 (29)	<0.001
Qp:Qs	1.5 (1.4-1.6)	1.5 (1.3-1.6)	1.0 (1.0-1.2)	<0.001
TAPSE, mm	14 (12-17)	16 (13-21)	17 (15-21)	0.010
MV mean gradient, mm Hg	4.0 (3.2-5.0)	3.8 (2.6-4.5)	4.0 (2.8-5.0)	0.34
ePAP, mm Hg	47 ± 14	45 ± 14	39 ± 12	0.59
MR grade				
0-I	31 (78)	31 (78)	168 (71)	0.35
II	8 (20)	8 (20)	61 (26)	0.25
III	1 (2)	1 (2)	6 (3)	0.97
IV	0 (0)	0 (0)	0 (0)	1.00
TR grade				
0-I	19 (48)	22 (55)	103 (44)	0.13
II	15 (38)	12 (30)	58 (25)	0.45
≥III	6 (15)	6 (15)	74 (31)	0.11

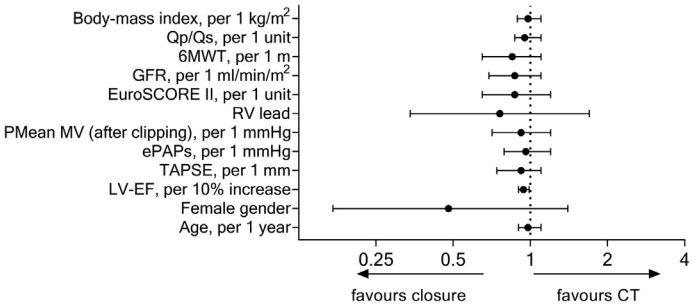
Values are mean ± SD, n (%), or median (IQR). Indicated *P* values are derived from Kruskal-Wallis tests across all groups.

CRT = cardiac resynchronization therapy; CT = conservative therapy; ePAP = estimated systolic pulmonary artery pressure; iASD = iatrogenic atrial septal defect; ICD = implantable cardioverter defibrillator; LVEDV = left ventricular end-diastolic volume; LVEF = left ventricular ejection fraction; LVESV = left ventricular end-systolic volume; MR = mitral regurgitation; MV = mitral valve; NT-proBNP = N-terminal pro–B-type natriuretic peptide; NYHA = New York Heart Association functional; Qp = fraction of pulmonary perfusion; Qs = fraction of systemic perfusion; RV = right ventricular; TAPSE = tricuspid annular plane systolic excursion; TR = tricuspid regurgitation.

41 [17%]; $P < 0.0001$). Survival free from death or HF hospitalization was significantly longer in patients of the comparative cohort without relevant iASD 30 days post-TMVR; the Kaplan-Meier estimates of event-free survival are depicted in the **Central Illustration** ($P = 0.0043$, log-rank).

Between patients randomized to interventional iASD closure or CT, there were no significant

FIGURE 2 HRs for the Combined Endpoint Death or HF Hospitalization in the Randomized Cohort



Forest plot with HR per unit increase for the combined endpoint of death or heart failure (HF) hospitalization in the randomized cohort is shown. The circles indicate the HRs and the error bars the 95% CIs. 6MWT = 6-minute walk test distance; CT = conservative therapy; ePAP = echocardiographic derived pulmonary artery pressure; GFR = glomerular filtration rate; LV-EF = left ventricular ejection fraction; PMean MV = mean transmitral inflow gradient; Qp/Qs = fraction of pulmonary to systemic perfusion; RV lead = presence of a right ventricular lead due to an intracardiac device; TAPSE = tricuspid annular plane systolic excursion.

differences regarding all-cause death (n = 2 [5%] vs n = 5 [12.5%]; $P = 0.43$) or HF hospitalization (n = 12 [30%] vs n = 15 [37.5%]; $P = 0.64$).

The higher frequency of the occurrence of the combined endpoint in the MITHRAS as compared with the comparative cohort was primarily driven by a higher rate of HF hospitalizations (27 [34%] vs 19 [8%]; $P = 0.004$). No significant difference in all-cause death was observed between patients in the MITHRAS or the comparative cohort (n = 7 [8.8%] vs n = 22 [9.4%]; $P = 0.99$).

Univariable and confounder-adjusted Cox regression analyses are depicted in **Table 2**. When adjusting for confounders, the adjusted regression analysis revealed Qp:Qs as a strong predictor of the combined endpoint (adjusted HR: 1.64; 95% CI: 1.12-2.41; $P = 0.011$) (**Table 2**).

To elucidate the effect of a mild iASD in the comparative cohort, patients were stratified according to their shunt fraction into 3 subgroups (Qp:Qs 1.0 vs 1.01-1.3; Qp:Qs <1.1 vs ≥1.1-1.3, Qp:Qs <1.2 vs ≥1.2-1.3): no significant differences in hospitalization for HF, all-cause death, or the combined endpoint between any groups could be observed (Supplemental Table 3).

At 12 months' follow-up, TTE was performed. The results were as follows: 21 patients had persistence of the iASD; in 8 patients no shunt was observed with good image quality; in 2 patients, the persistence could not be assured on TTE due to a concomitant TR jet; 5 patients died; and 4 patients were not able to undergo follow-up echocardiography due to hospitalization at other hospitals. In 21 patients with paired measurements, no increase in echocardiographic-derived systolic pulmonary artery pressure could be observed: 40 mm Hg (IQR: 30-44 mm Hg) vs 38 mm Hg (IQR: 31-49 mm Hg); $P = 0.601$.

DISCUSSION

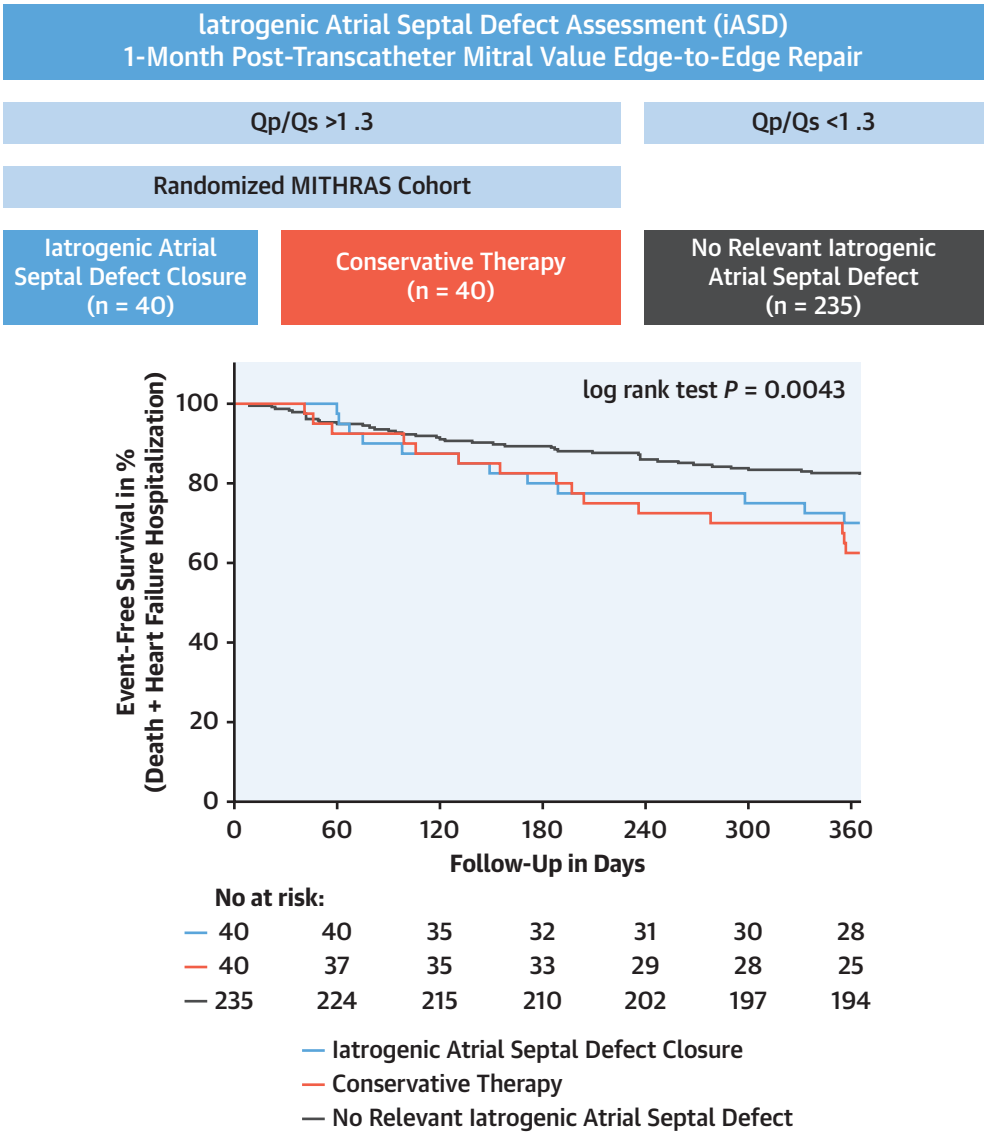
In this randomized single-center trial, iASD closure as compared with CT alone did not lead to a reduction of the combined endpoint of death or HF hospitalization within 11 months. As compared with a contemporaneous cohort of patients without iASD, patients with an iASD after TMVR experienced worse clinical outcomes, irrespective of iASD management. This finding was mainly driven by higher rates of hospitalizations for HF in iASD patients.

TMVR is a safe alternative for MV surgery and has gained widespread use in selected patients with high or prohibitive risk for MV surgery, especially among patients with progressive left-sided HF (23,24). One-year mortality rates following TMVR vary between 15% and 20%, and various predictors of morbidity and mortality have been identified in large registries, including tricuspid regurgitation and LV dysfunction (24). In addition, patients with persistent iASD following TMVR have consistently shown worse clinical outcomes (6,7). However, the retrospective nature and the baseline differences in analyzed cohorts, including more RV enlargement and a higher incidence of severe tricuspid regurgitation in iASD patients, imply a selection bias and preclude definite conclusions on the intrinsic clinical role of an iASD in these patients (25,26).

Currently, there is no guideline-based recommendation on whether or when to close a postinterventional iASD following TMVR.

This study is the first to our knowledge to prospectively investigate the clinical effect of an interventional iASD closure in a randomized, controlled fashion. We previously have shown that iASD closure does not result in improved 6-minute walk test at 5 months and could now demonstrate the lack of benefit with respect to HF hospitalization or death at 11 months' follow-up (16). This seems surprising, given the unfavorable clinical course associated with the presence of an iASD and the beneficial effect on biventricular physiology in selected patients undergoing iASD closure (8,9). However, these effects might be counterbalanced by the implications of closure versus no closure on left atrial pressures: severity of HF symptoms and eventually cardiac decompensation are associated with higher cardiac

CENTRAL ILLUSTRATION **Kaplan-Meier Survival Curves for Combined Endpoint All-Cause Death or Heart Failure Hospitalization at 12-Months Follow-Up Post-Transcatheter Mitral Valve Edge-to-Edge Repair**



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Kaplan-Meier estimated event rates in the MITHRAS cohort and the no iASD comparative cohort for the time to the endpoint of all-cause death or heart failure hospitalization. iASD = iatrogenic atrial septal defect; MITHRAS = Closure of Iatrogenic Atrial Septal Defect Following Transcatheter Mitral Valve Repair; Qp/Qs = fraction of pulmonary to systemic perfusion.

filling pressures in patients with HF irrespective of LV ejection fraction (27,28). Reducing left atrial pressure by an intentionally created iASD has therefore been investigated as a treatment strategy in HF with reduced or preserved ejection fraction with first promising results for both entities (14,15). The attenuation of left atrial decompression by iASD closure in these patients might have been unfavorable and may have equalized the positive effects on RV function. We could not observe a beneficial effect of a mild iASD in our comparative cohort within 12 months post-TMVR. Given the nonrandomized creation of the iASD, the data should be interpreted with caution.

TABLE 2 Univariable and Confounder-Adjusted Predictors of the Combined Endpoint

	Univariable Analysis			Confounder-Adjusted Analysis	
	β	HR (95% CI)	*P* Value	HR (95% CI)	
Age, per 1 y	0.0054	1.00 (0.98-1.00)	0.62		
Male	0.41	1.50 (0.98-2.30)	0.059		
LVEDV, per 10% increase[a]	0.06	1.10 (1.00-1.10)	0.008		
LVESV, per 10% increase[a]	0.045	1.05 (1.01-1.08)	0.005		
LVEF, per 10% increase	−0.061	0.94 (0.90-0.99)	0.028		
TAPSE ≤16 mm	0.00057	0.76 (0.37-1.54)	0.445		
MR >2°	0.036	1.00 (0.69-1.60)	0.86		
Functional MR	0.50	1.65 (1.10-2.47)	0.015		
TR >2°	0.087	2.37 (0.82-6.84)	0.110		
Qp:Qs per 1 U	1.30	1.65 (1.10-2.47)	0.001	1.64 (1.12-2.41)	0.011
ePAP per 1 mm Hg	−0.012	0.99 (0.97-1.00)	0.55		
MV Pmean per 1 mm Hg	0.24	1.30 (0.66-2.40)	0.48		
MR regurgitant volume per 1 mL[a]	0.0037	1.00 (0.99-1.00)	0.55		
NT proBNP per 1 pg/mL	0.01	1.00 (1.00-1.00)	0.60		
EuroSCORE II, per 1 U	0.026	1.00 (0.99-1.10)	0.19		
eGFR ≥30 per 1 mL/min/m^2	0.0001	0.86 (0.36-2.01)	0.72		

[a]Not included in the adjusted model to account for multicollinearity. The confounder-adjusted model included age, sex, LVEF, TAPSE, MR grade, TR grade, ePAP, MVmean, NT-proBNP, EuroSCORE, and eGFR.

eGFR = estimated glomerular filtration rate; MV Pmean = mean transmitral inflow gradient; other abbreviations as in Table 1.

Importantly, the combined endpoint of death or HF hospitalizations was more frequent in patients with iASD independent of treatment allocation as compared with the comparative cohort. The randomized patients differ from the comparative cohort particularly with regard to MR etiology: whereas in the comparative cohort 71% were treated with degenerative MR, patients with iASD predominantly had functional MR with more impaired LV and RV function—known predictors of impaired outcome in patients undergoing TMVR (24,29). We did not find a significant impact of renal function or tricuspid regurgitation severity on outcomes, whereas functional MR, enlarged LV, impaired function, and an increase in shunt fraction were associated with HF hospitalization and death. These parameters are indicative of increased LV filling and left atrial pressures, probably best reflecting a persistent and significant left-to-right shunt across the interatrial septum. This should explain the finding of an iASD as the only significant predictor for impaired outcomes in the confounder-adjusted model and nourishes the theory that the presence of an iASD is a prognostically relevant surrogate in these patients, but not necessarily causative for inferior outcomes. Consequently, although closure might not convey clinical benefits, the diagnosis of an iASD 1 month post-TMVR is of prognostic importance and warrants close surveillance and monitoring in these patients.

STUDY LIMITATIONS. The sample size of the randomized trial is powered to detect differences in 6-minute walk test based on historical data. We cannot exclude that a treatment effect on clinical endpoints might be unraveled in a larger and more specific set of patients with iASD post TMVR: for example, randomizing only patients with functional or degenerative MR might reveal treatment effects within these specific groups of patients. The same holds true for patients with various degrees of concomitant tricuspid regurgitation and/or RV dysfunction. A shunt fraction of 30% has been proposed as a cutoff to balance the risk of RV distension due to volume overload to the benefit of alleviating left atrial pressure by an intentionally created ASD in patients with HF and was therefore chosen as inclusion criterion in this randomized trial (30). However, the results of this study might have been different in patients with larger intra-atrial left-to-right shunting.

Additionally, left-to-right shunting across the iASD might reduce over time even without interventional closure as seen and described before (16). Inclusion and closure of iASD 1 month post-TMVR might have been too early to differentiate patients who might benefit from closure as opposed to those patients with a certain likelihood of irrelevant or no shunting

across the iASD over time. Systematic assessment of the iASD was done using TTE/TEE only and without systematic TEE follow-up beyond 6 months post-TMVR. Due to the lack of documentation of HF admissions before TMVR, no conclusions of the effect of iASDs or iASD closure on the frequency of HF hospitalization in general can be drawn.

CONCLUSIONS

In this randomized controlled trial involving patients with persistent iASD 30 days after TMVR, iASD closure did not improve clinical outcomes within 11-months' follow-up. The presence of an iASD is associated with a higher rate of HF hospitalization irrespective of its management when compared with patients without relevant iASD following TMVR.

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ADDRESS FOR CORRESPONDENCE: Dr Philipp Lurz, Department of Internal Medicine/Cardiology, Heart Center Leipzig at Leipzig University, Struempellstrasse 39, D-04289 Leipzig, Germany. E-mail: Philipp.Lurz@medizin.uni-leipzig.de. Twitter: @m_unterhuber, @mvonroeder, @thiele_holger, @PhilippLurz, @KP_Kresoja, @RommelPhilipp, @BlazekStephan.

PERSPECTIVES

WHAT IS KNOWN? TMVR provides clinical benefit; however, the clinical role of iASD and its management remain uncertain.

WHAT IS NEW? Patients with an iASD 30 days after TMVR have worse outcomes (all-cause mortality or heart failure hospitalization rate) 12 months post-TMVR in comparison to patients without an iASD, irrespective of management (interventional closure versus conservative therapy).

WHAT IS NEXT? A multicenter trial with a greater number of patients and longer follow-up should determine whether there is a viable strategy to improve outcomes for patients with relevant iASD after TMVR.

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KEY WORDS **atrial septal defect, closure, shunt, heart failure, transcatheter mitral valve edge-to-edge repair**

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