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# Closure of Iatrogenic Atrial Septal Defect Following Transcatheter Mitral Valve Repair: The Randomized MITHRAS Trial

**Running Title:** *Lurz et al.; Atrial Septal Defect Post Mitral Interventions*

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Transcatheter mitral valve repair (TMVR) requires transseptal access to the left atrium, which creates a persistent iatrogenic atrial septal defect (iASD) in approximately 24 to 50% of patients.[1, 2] Post-TMVR iASD has been associated with right heart volume overload, as well as increased rates of heart failure (HF) hospitalization and death in some studies.[1, 2]
In contrast, other studies have shown an association between post-TMVR iASD and improved hemodynamics[3], a concept currently investigated in large-scale clinical trials in patients with HF.[4]

The MITHRAS-trial (Closure of Iatrogenic Atrial Septal Defects following Transcatheter Mitral Valve Repair) is an investigator-initiated, single-center, randomized, open-label trial conducted at the Heart Center Leipzig at Leipzig University between January 2016 and September 2020 in patients with a relevant post-TMVR iASD comparing iASD transcatheter closure versus conservative therapy (CT) (URL:https://www.clinicaltrials.gov, NCT03024268). The trial was approved by the local ethics committee and all patients gave written informed consent. The data that support the findings of this study are available from the corresponding author upon request.

Consecutive patients underwent transthoracic and transesophageal echocardiography 30 days post TMVR and were eligible if a relevant iASD (fraction of pulmonary perfusion [Qp]/ fraction of systemic perfusion [Qs] ≥1.3 and predominantly left-to-right shunt) was present. Exclusion criteria were inter-atrial shunt before TMVR, unsuccessful TMVR (no reduction in mitral regurgitation [MR] severity), additional valvular heart disease planned for surgery or intervention, malignancy limiting survival <12 months and anatomic considerations precluding transcatheter iASD closure.

The primary endpoint was changes in the 6-minute walk test (6MWT) distance between randomization and at 5-months follow-up and was analyzed on an intention-to-treat principle using a Student's t-test. Secondary endpoints were changes in peripheral edema, New York Heart Association [NYHA] functional class, NT-proBNP and death or hospitalization for HF. Eighty patients were randomized to transcatheter closure of the iASD (n=40) or CT (n=40) (**Figure panel A**). Successful closure (Figulla Flex II, Occlutech, Jena, Germany) of the iASD was performed within 3 days after randomization.

Baseline characteristics were well balanced (iASD closure vs. CT: age 77±9 vs. 76±10 years, previous cardiac surgery 6[15%] vs. 6[15%], Euroscore 4.9[3.3-9.6] vs. 5.5[2.6-7.6], NYHA ≥III 25[62%] vs. 28[70%], functional MR 25[62%] vs. 25[62%], left ventricular ejection fraction 38±13% vs. 37±19%, tricuspid annular plane systolic excursion 14[12-17] vs. 16[13-21] mm, post-TMVR MR grade ≤II 39 [98%] vs. 39 [98%], tricuspid regurgitation grade ≥III 6[15%] vs. 6[15%], Qp/Qs 1.5[1.4–1.6] vs. 1.5[1.3–1.6], p>0.05 for all).

The 6MWT distance did not differ between patients in the iASD closure and the CT group (at randomization time point 272±124 vs. 302±124 m and at follow-up 276±119 vs. 301±118 m, Δ iASD occlusion 5±89 m vs. Δ CT -1±83 m, p=0.75, p=0.92, p=0.76, respectively) (**Figure panel B**). No significant differences in the secondary endpoints could be observed (change in NT-proBNP [iASD closure pre vs. post 3105 (IQR1902-4134) vs. 2259 (IQR1648-4804) Δ-846 CT pre vs post 3653 (IQR1746-5848) vs. 3374 (IQR1394-6065) Δ-279, p=0.44 for intergroup comparison]). Transcatheter iASD closure was successful in all patients with Qp/Qs of 1.0 at follow-up. Nineteen patients (46%) in the CT group demonstrated a reduction in Qp/Qs (<1.3), with a decrease in Qp/Qs ratio from 1.5 to 1.3 (p=0.02). There was no difference in HF rehospitalization and mortality (iASD occlusion vs. CT: 8 (21%) vs. 9 (23%), p=0.22).

In conclusion, transcatheter iASD closure following TMVR was not superior to CT alone with respect to the primary or secondary endpoints. Positive effects of iASD closure on right sided volume overload might be counterbalanced by negative implications of closure on left atrial pressures as shown by recent trials on iASD-creation in patients with HF.[4]

The inclusion criterion of Qp/Qs of ≥1.3 was based on the finding that a shunt fraction of 30% was proposed as the optimal balance between risks of right sided volume overload and left atrial pressure reduction in HF patients and previous trials on iASD creation.[5] Results might differ in patients with larger intra-atrial left-to-right shunts.

The finding of a relevant reduction in Qp/Qs in 45% in the CT group gives rise to the question whether iASD closure at 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 shunt reduction over time.

The sample size of the randomized trial is small and based on previous assumptions that might have overestimated the intrinsic effect of iASD closure. Therefore, we cannot exclude a treatment effect that would be unraveled in a larger and more specific set of patients with post-TMVR iASD or at longer follow-up. Treatment effect might depend on left atrial and left ventricular filling pressures as well as degree of right ventricular failure and volume overload, but the actual sample size is too small for informative subgroup analysis.

In this randomized controlled trial involving patients with persistent iASD one month after TMVR, iASD closure did not improve functional or clinical midterm outcomes.



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**Subject Terms**: transcatheter mitral valve edge-to-edge repair, atrial septal defect, closure, shunt, heart failure.







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## Figure Legend

**Figure: Study flow-chart and 6-minute walk test**

**Panel A:** study flow chart of the MITHRAS trial, # randomization in a 1:1 fashion stratifying for diabetes mellitus and previous cardiac surgery **Panel B:** primary endpoint 6-minute walk test distance differences between randomization and 5 months follow-up post randomization (blue: within iASD closure group, red: within conservative therapy group, asterisk: intergroup comparison of the mean change of 6MWT difference) Abbreviations: 6MWT: 6-minute walk test, iASD: iatrogenic atrial septal defect, TMVR: Transcatheter mitral valve repair