Prognostic Impact of Redo Transcatheter Mitral Valve Repair for Recurrent Mitral Regurgitation

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There is little known about the prognostic impact of a redo transcatheter mitral valve repair (TMVR) for residual or recurrent mitral regurgitation (MR). From January 2011 to March 2019, we identified 43 consecutive patients who underwent a redo TMVR procedure with the MitraClip system. A control cohort was treated medically for MR ≥2+ after the first TMVR and was propensity score 1:1 matched using age, gender, MR severity, trans-mitral pressure gradient, and etiology of MR. To investigate the association of redo TMVR with 1-year mortality, we fitted a Cox proportional hazard model. The technical success rate of redo TMVR was 95%. A reduction in MR to ≤2+ was achieved in 79% of patients, with a significant decline of tricuspid regurgitation pressure gradient and improvement of the New York Heart Association class. After matching was performed, 43 well-matched pairs of patients were analyzed. Redo TMVR patients showed lower 1-year mortality (10.5% vs 37.6%, p = 0.01) compared with the control patients. Redo TMVR was associated with better survival (hazard ratio [HR] 0.26, 95% confidence interval [CI] 0.08 to 0.79, p = 0.02) and lower risk of the composite end point (mortality and rehospitalization due to HF: HR 0.34, 95% CI 0.15 to 0.78; p = 0.01) at 1-year follow-up. The association with the primary end point remained significant after accounting for the New York Heart Association class III/IV, TR ≥severe, the type of MR (i.e., recurrent or residual MR), or the type of previous implanted TMVR device. In conclusion, redo TMVR in selected patients with residual or recurrent MR may be associated with lower 1-year mortality than medical therapy alone. **(Am J Cardiol 2020;130:123−129)**

Transcatheter mitral valve repair (TMVR) has emerged as a novel, non-surgical, less invasive therapeutic option for patients with symptomatic mitral regurgitation (MR) that are at high surgical risk.[1−4] Nevertheless, approximately 30% of patients who underwent TMVR have recurrent MR, including residual MR after the procedure,[1,4] which is associated with increased risks of all-cause mortality or recurrence of heart failure (HF).[5−7] Edge-to-edge mitral valve repair using the MitraClip system (Abbott Vascular, Menlo Park, CA) is the TMVR system that is most widely used to treat MR because of its peri-procedural safety and positive effect on clinical outcomes.[3,4] Although 2 studies have reported the procedural safety and the efficacy on MR reduction of redo TMVR with the MitraClip system,[8,9] little is known about the prognostic impact of a redo TMVR. To address the knowledge gap in the literature, we tested the hypothesis that redo TMVR with the MitraClip system would be superior to medical therapy alone to improve clinical outcomes in patients with recurrent MR after the first TMVR.

Methods

From January 2011 to March 2019, consecutive patients with MR ≥2 after the first TMVR at the University of Bonn Heart Center were identified by using a dedicated institutional database for TMVR. Among these patients, we identified patients who were treated with redo TMVR with the MitraClip system (redo TMVR group) or medical therapy alone (control group). All of the patients included were considered as inoperable or at a high surgical risk according to the consensus of the institutional heart team at the time of the first TMVR. The decision to perform a redo TMVR was left to the discretion of a consensus of the institutional multidisciplinary heart team, based on severity of MR, mean trans-mitral pressure gradient (TMPG), and symptomatic status of the parient.[10−12] We excluded patients who underwent a hybrid transcatheter procedure (i.e., mitral and tricuspid valve treatment). This study was approved by the ethics committee of the University of Bonn and was conducted in concordance with the Declaration of Helsinki.

Preprocedural transthoracic echocardiograms and transesophageal echocardiograms were performed with an iE33 ultrasound system (Philips Medical Systems, Andover, Massachusetts), according to the current recommendations

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and guidelines.[13,14] MR severity was defined as follows: grade 0 indicates none, 1+ mild, 2+ moderate, 3+ moderate-to-severe, and 4+ severe MR. Residual MR was defined as MR ≥2+ upon discharge from the hospital after the first TMVR, whereas recurrent MR was defined as MR that was grade <2+ at discharge but developed to ≥2+ during the follow-up period.[15–17] Tricuspid regurgitation (TR) was graded as none to trivial, mild, moderate, severe, massive, or torrential.[18] Each evaluation was performed by cardiologists who were blinded to the procedural outcomes.

The MitraClip procedure has been described previously.[19] During the study period, redo TMVR were only performed by 2 interventional cardiologists (GN and NW). The number and location of the clips was left to the discretion of the physician performing the procedure. Technical success was defined as the implantation of one or more devices without periprocedural mortality, according to the Mitral Valve Academic Research Consortium criteria.[20]

The primary end point was all-cause mortality within 1 year of follow-up.[4] The secondary end point was a composite of all-cause mortality and re-hospitalization due to HF. These outcomes were collected by reviewing the medical records and contacting the general practitioners of the individual patients. To complete the follow-up for survival, all patients without on-site follow-up were contacted by phone in December 2019.

Continuous variables with a normal distribution were reported as the mean ± standard deviation and were analyzed by using a *t* test, whereas non-normally distributed variables were reported as the median value with an interquartile range and analyzed by using the Mann-Whitney *U* test. Categorical variables were expressed as numbers and percentages, and were analyzed by using the chi-square test or the Fisher exact test, as appropriate.

We performed a propensity score (PS) matched analysis to overcome the differences in baseline characteristics between the redo TMVR and the control groups. PS was calculated using a logistic regression model that estimates the likelihood of redo TMVR. Age, male gender, severity of MR, etiology of MR, and TMPG were used in this PS model.[21] One-to-one matching was then conducted based on the PS with the nearest matching method. We examined the balance using the standardized mean differences between the groups. Standardized differences were reported for baseline characteristics. After PS matching, we performed a survival analysis using the Kaplan-Meier method to estimate the event probabilities at 365 days and to compare the distributions of event-free survival times among the groups by using a log-rank test. Then, we estimated the hazards ratio (HR) and 95% confidence interval (CI) of the redo TMVR for 1-year mortality using a Cox proportional hazard model. Additionally, we estimated the HRs by accounting for variables that were not included in the PS matching: New York Heart Association (NYHA) class III/IV, TR ≥severe, the type of MR (i.e., recurrent or residual MR), or the type of previous implanted TMVR device (i.e., MitraClip or non-MitraClip). As an analysis of the sensitivity, we fitted a Cox proportional hazards model using the whole study cohort to examine the consistency of the inferences. Age, male gender, severity of MR, etiology of MR, TMPG, and NYHA class were incorporated in the final model, based on previous knowledge.[4,21]

All statistical analyses were performed using EZR version 1.37 (Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria). Two-tailed p values <0.05 were considered statistically significant.

Results

During the study period, a total of 539 patients underwent an initial TMVR at the University of Bonn Heart Center. We identified 225 consecutive patients with residual or recurrent MR after the first TMVR. Of these, 43 patients underwent redo TMVR with the MitraClip system (redo TMVR group), whereas 161 patients received medical therapy alone (control group) (Supplementary Figure 1). The baseline characteristics before PS matching are summarized in Supplementary Table 1. The mean age was 77-year-old and 58% of the patients were male. The mean STS score was 4.6%. Forty-three patients were defined as recurrent MR, whereas 161 patients were categorized as residual MR. Redo TMVR patients had worse symptomatic status (NYHA III/IV: 77% vs 41%), lower mean TMPG (3.1 mm Hg vs 4.3 mm Hg), more often recurrent MR (41.9% vs 15.5%), and higher MR grades (MR ≥3+: 93% vs 42%).

After PS matching, 43 pairs of matched patients were identified. Baseline characteristics were comparable between the redo TMVR group and the control group (Table 1). The only significant difference that persisted between the matched groups was that the redo TMVR patients had higher grades of MR. In contrast, there were no significant differences in NYHA class, basal etiology of MR, mean TMPG, prevalence of recurrent MR, or type of previous implanted TMVR devices.

The median duration from the first TMVR to the redo procedure was 11 months [interquartile range [IQR] 4 to 28 months]. Supplementary Figure 2 shows 2 example cases of the redo TMVR. Technical success was achieved in 41 patients (95.3%) and a reduction in MR to ≤2+ was achieved in 34 patients (79.1%) (Supplementary Table 2). The mean number of clips implanted was 1.3 and the median procedural time was 58 min [IQR 41 to 103 minutes]. Neither periprocedural complications nor in-hospital death were observed in these patients. The mean TMPG increased significantly (3.1 ± 1.5 mm Hg to 3.7 ± 1.5 mm Hg, $p = 0.01$), whereas TRPG decreased (40.3 ± 13.8 mm Hg to 34.4 ± 12.5 mm Hg, $p = 0.02$), with a significant improvement of NYHA functional scale (NYHA III/IV: 77% to 39%, $p < 0.001$).

As compared with the control group, the MR grades at discharge ($p < 0.001$; Figure 1) as well as the NYHA functional scale ($p < 0.001$; Supplementary Figure 3) were significantly lower in the redo TMVR group. The mean TMPG at discharge was higher in the redo TMVR group as compared with the control group ($p = 0.02$).

The median follow-up time was 11 months [IQR: 2 to 19 months]. Overall, 17 patients died and 10 patients were re-hospitalized due to HF. At 1-year follow-up, the redo TMVR group showed a lower risk of the primary endpoint (all-cause mortality: 10.5% vs 37.6%, $p = 0.01$; Figure 2) and secondary end point (mortality or re-

Table 1
Baseline characteristics after 1:1 propensity score matching

Variable	Redo TMVR (n = 43)	Medical therapy alone (n = 43)	Standardized mean difference	p value
Age (year)	77 ± 7	76 ± 11	0.07	0.72
Men	32 (74%)	27 (63%)	0.12	0.35
Hypertension	29 (67%)	26 (61%)	0.17	0.65
Diabetes mellitus	14 (33%)	9 (21%)	0.33	0.33
Chronic kidney disease	27 (63%)	31 (72%)	-0.23	0.49
Coronary artery disease	27 (63%)	27 (63%)	0.00	0.99
Atrial fibrillation	36 (84%)	31 (72%)	0.38	0.30
Prior cardiac surgery	16 (37%)	13 (30%)	0.17	0.65
Prior CRT implantation	6 (14%)	2 (5%)	0.66	0.27
Logistic EuroSCORE	21.6 ± 13.1	21.5 ± 16.2	0.004	0.98
STS score	4.6 ± 2.4	4.7 ± 2.6	0.027	0.90
NYHA functional class III/IV	33 (77%)	22 (67%)	0.28	0.44
NT-pro-BNP (pg/mL)	3659 [1717-7616]	2885 [1458-6740]	0.11	0.67
LV end-diastolic volume (ml)	158.9 ± 74.3	156.1 ± 58.3	0.03	0.87
LV end-systolic volume (ml)	90.2 ± 54.6	93.2 ± 56.9	0.05	0.83
LV ejection fraction (%)	44.2 ± 15.3	44.4 ± 19.7	0.01	0.95
Left atrium volume (ml)	114.7 ± 60.8	93.8 ± 41.8	0.30	0.16
Mean TMPG (mmHg)	3.1 ± 1.5	2.6 ± 1.4	0.22	0.30
Tricuspid regurgitation pressure gradient (mmHg)	40.3 ± 13.8	45.1 ± 11.8	-0.32	0.14
Recurrent MR	18 (42%)	15 (35%)	0.09	0.66
Residual MR	25 (58%)	28 (65%)		
MR grade			0.82	<0.001
2+	3 (7%)	3 (7%)		
3+	16 (37%)	35 (81%)		
4+	24 (56%)	5 (12%)		
Treatment devices at initial TMVR			0.08	0.71
MitraClip	29 (67%)	33 (77%)		
Cardioband	6 (14%)	4 (9%)		
Mitralign	3 (7%)	1 (2%)		
Carillon	4 (9%)	3 (7%)		
Neochord	1 (2%)	1 (2%)		
Pascal	0	1 (2%)		
MR etiology at initial TMVR			0.15	0.52
Degenerative	18 (42%)	21 (49%)		
Functional	25 (58%)	22 (51%)		
Medications				
Beta-blocker	35 (81%)	35 (85%)	0.00	0.75
Angiotensin II receptor blocker	9 (21%)	6 (15%)	0.27	0.57
Angiotensin converting enzyme inhibitor	20 (47%)	22 (54%)	-0.10	0.45

CRT = cardiac resynchronization therapy; ICD = implantable cardioverter defibrillator; LV = left ventricular; MR = mitral regurgitation; NT-pro-BNP = N terminal-pro-brain natriuretic peptide; NYHA = New York Heart Association; TMPG = trans-mitral pressure gradient; TMVR = transcatheter mitral valve repair; TTE = transthoracic echocardiography.

hospitalization due to HF: 22.3% vs 52.0%, p = 0.008; Figure 2), as compared with the control group. In the Cox proportional hazard model, redo TMVR was associated with a reduced risk of the primary end point (HR 0.26, 95% CI 0.08 to 0.79, p = 0.02) as well as a lower risk of the secondary end point (HR 0.34, 95% CI 0.15 to 0.78; p = 0.01). The association with the primary end point remained significant (adjusted-HR 0.21, 95% CI 0.06 to 0.71, p = 0.01; Supplementary Table 3) after accounting for NYHA class III/IV, TR ≥severe, the type of MR (i.e., recurrent or residual MR), or the type of previous implanted TMVR device (i.e., MitraClip or non-MitraClip). In the nonmatched cohort, redo TMVR was still significantly associated with a lower risk for the primary end point (adjusted-HR 0.21, 95% CI 0.07 to 0.69, p = 0.009) and for the secondary end point (adjusted-HR 0.30, 95% CI 0.13 to 0.72, p = 0.007).

After a median follow-up of 9 months [IQR 5 to 12 months]), the MR grade was significantly lower in the redo TMVR groups as compared with the control group (MR ≥3 +: 23.1% vs 52.6%, p = 0.001; Supplementary Figure 4).

Discussion

In this analysis of 43 PS-matched pairs of patients who had residual or recurrent MR ≥2+ after the first TMVR, we found that redo TMVR was associated with lower all-cause mortality as well as lower rates of a composite end point (mortality and rehospitalization due to HF) at 1-year follow-up. The technical success rate of redo TMVR was 95%

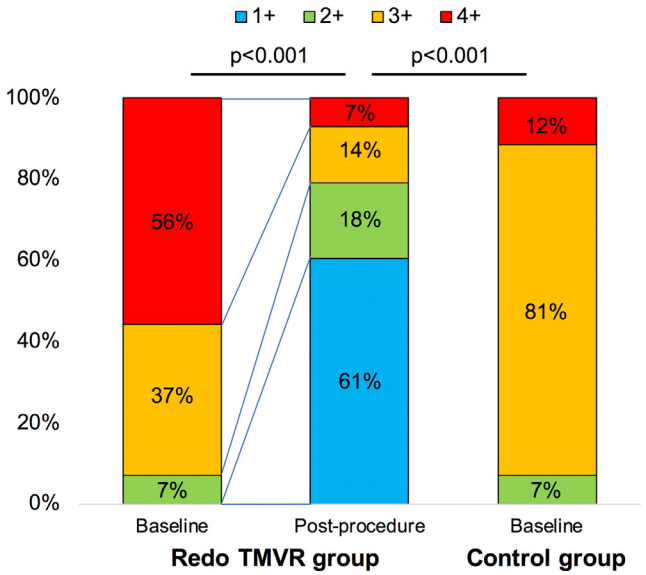

Figure 1. Severity of mitral regurgitation.
Technical success was achieved in 95% and a reduction in MR to ≤2+ was achieved in 79% of redo TMVR patients. As compared with the control group, the MR grades at discharge was significantly lower in the redo TMVR group (p <0.001).
MR = mitral regurgitation; TMVR = transcatheter mitral valve repair.

and a reduction in MR to ≤2+ was achieved in 79% of patients, with a significant decline of TRPG and improvement of the NYHA functional class.

Although recurrent MR after the first TMVR is associated with a worse prognosis,[5–7] there has been no clear evidence whether recurrent MR should be treated conservatively, surgically, or with a redo TMVR. A small previous study (n = 21) reported that both redo MitraClip and also mitral valve surgery were feasible and safe alternatives in patients with recurrent MR.[22] Recently, 2 studies have reported the procedural safety and the efficacy on MR reduction by redo TMVR with the MitraClip.[8,9] As patients who underwent an initial TMVR are at high surgical risk, residual or recurrent MR after the first TMVR is more likely to be treated conservatively or with a redo TMVR, rather than with surgery. Furthermore, the rate of a reduction in MR to ≤2+ (79%) was comparable with two earlier studies (62% to 73%).[8,9] Therefore, the observed findings are clinically relevant and extend our previous knowledge by demonstrating the prognostic benefit of redo TMVR for residual or recurrent MR.

The potential mechanisms of the association of redo TMVR with the clinical outcomes are likely multifactorial. One plausible mechanism is related to the reduction in MR. In this study, redo TMVR significantly reduced MR severity, and the lower MR grade was maintained during the 1-year follow-up period. Previous studies of TMVR have shown a survival benefit by reducing MR severity over medical therapy alone.[1,4,21] Additionally, in the present study, the difference in the proportion of MR to LV volumes between the groups may contribute to the benefit of redo TMVR.[3,4] Another possible explanation is related to procedural safety.[23] We did not see any procedural death nor life-threatening complications in the present study, which is in line with earlier studies.[20] Alternatively, considering the difference in the TMPG at baseline between the groups (Supplementary Table 1), patients in the medical therapy group might have been withheld from having a redo TMVR due to a higher mean TMPG, despite the potential prognostic benefits of the procedure. After redo TMVR, whereas there was significant reduction in MR, the post-procedural mean TMPG was even higher at discharge compared with the PS-matched control group. Given the association between a higher mean TMPG and an increased risk of mortality,[24] our findings - patients treated with redo TMVR had better survival compared with the control group—suggest that there is a potential benefit of MR reduction on the outcomes over the elevation of mean TMPG in patients with recurrent MR.

Coupled with lower mortality rate in the redo TMVR group, the improvements in the functional capacity among patients with redo TMVR supports the validity of our findings. This improvement is consistent with the results of the COAPT trial, which showed that the functional capacity after the first TMVR was significantly better compared with medical therapy alone.[4] In agreement with this previous knowledge, our findings suggest that patients with residual or recurrent MR could benefit from redo TMVR.

There are several limitations in the present study. First, the limited sample size and the retrospective design of the study may affect the estimation of the association of redo TMVR with clinical outcomes. Yet, consistent findings between the analysis using whole cohort and those using a PS-matched cohort support the validity of our finding. In addition, the sample size is relatively small but, to our knowledge, one of the largest database in this area.[8,9] Third, central Core-Lab adjudication was not available in the present study.[11] Fourth, in the present study, multiple different devices had been used for the initial TMVR. Although the prognostic benefit of redo TMVR remained significant after accounting for the type of previous-implanted TMVR device, we did not perform a stratified analysis, due to the small sample size. Last, the long-term durability of redo TMVR was not investigated. In the present study, the median duration from the first TMVR to the redo procedure was 11 months, which was comparable to those in earlier studies (6.3 to 14.7 months).[8,9] Nevertheless, during the 9 months follow-up period, the observed rate of recurrent MR (23.1%) was relatively higher compared with previous studies evaluating first TMVR (18% to 23% at 12 months),[1,7] which may indicate the need for further studies to evaluate the durability of redo TMVR.

In conclusion, redo TMVR in selected patients with recurrent MR was feasible and safe, with a relatively high rate of technical success and no periprocedural complications. The PS-matched analysis suggests that redo TMVR might be associated with lower mortality at 1 year, as compared with medical therapy alone. Our findings should facilitate further well-conducted randomized controlled trials to confirm these preliminary findings.

CRediT Author Statement

Atsushi Sugiura: Investigation, Formal analysis, Writing-original draft

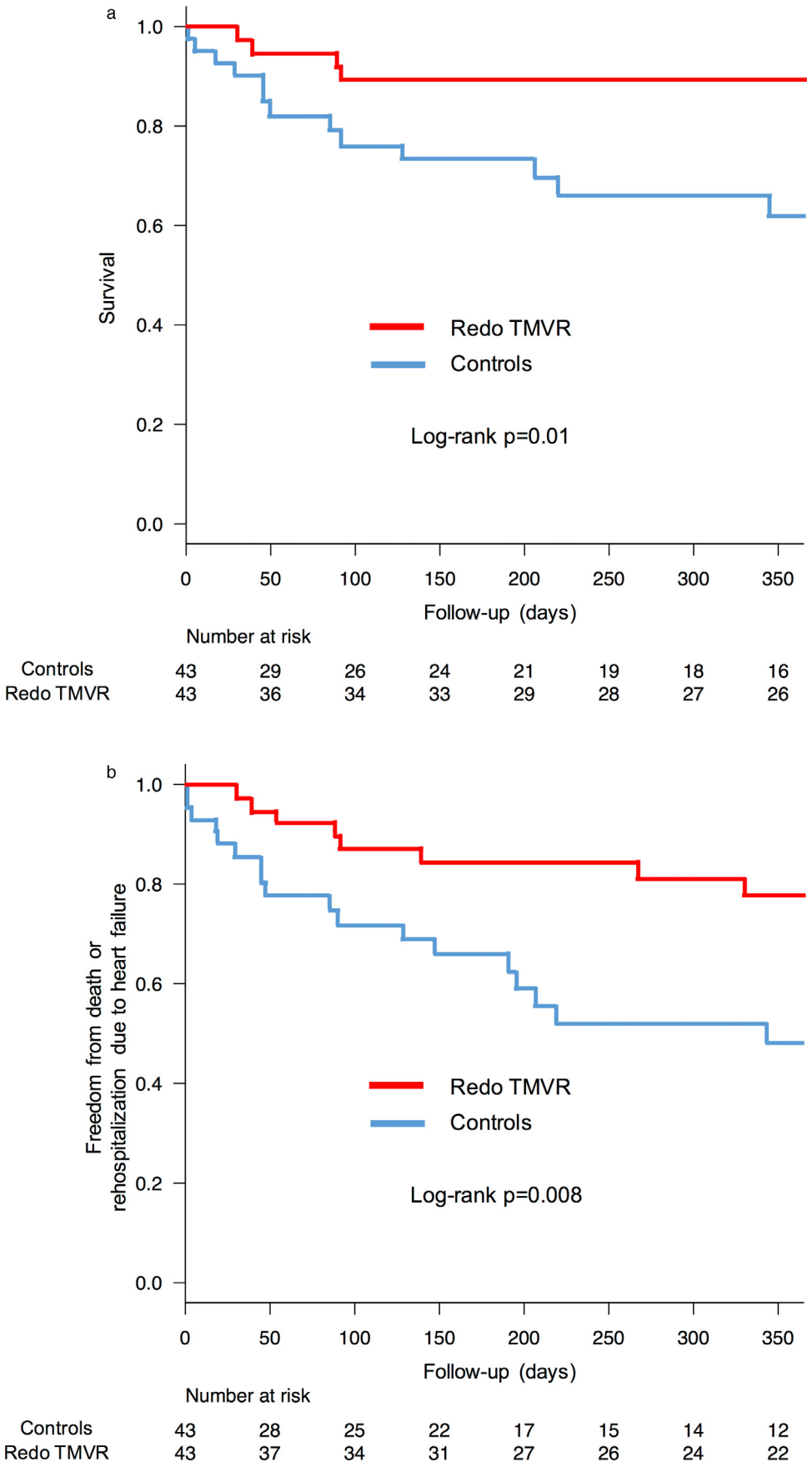

Figure 2. Kaplan-Meier analysis of the redo TMVR versus control groups.
At 1-year follow-up, the redo TMVR group showed lower mortality ***(A)*** all-cause mortality and composite outcomes *(B)* all-cause mortality or re-hospitalization due to heart failure, as compared with the control group.
TMVR = transcatheter mitral valve repair.

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Declaration of Interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Disclosures

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Supplementary materials

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