International Journal of Cardiology 288 (2019) 39–43

Contents lists available at ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard

Fate and long-term prognostic implications of mitral regurgitation in patients undergoing transcatheter aortic valve replacement

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ARTICLE INFO

Article history:
Received 23 December 2018
Received in revised form 12 March 2019
Accepted 24 March 2019
Available online 27 March 2019

Keywords:
Transcatheter aortic valve
Mitral regurgitation
Heart team
Aortic valve replacement

ABSTRACT

Background: The management of patients with mitral regurgitation (MR) undergoing transcatheter aortic valve replacement (TAVR) is challenging. We sought to investigate the evolution and long-term prognostic impact of residual post-TAVR MR.

Methods: The severity of MR was assessed at baseline and at 30 days and six months post-TAVR. Left ventricular mass and volumes were assessed by magnetic resonance imaging at two weeks and six months post-TAVR.

Results: The study included 970 patients (age, 80.6 ± 6.2 years; female, 53.2%; Society of Thoracic Surgeons score, 5.2 ± 4.6). Moderate-severe MR at baseline improved at 30-day post-TAVR in 60% of cases, and TAVR with the Medtronic CoreValve (OR: 0.44 [0.23–0.86]) was associated with a lower likelihood of improvement. Further MR improvement continued beyond 30 days post-TAVR especially in patients with a significant improvement of left ventricular volume and mass.

Stratified by the severity of MR at 30 days post-TAVR, the 5-year cumulative incidence of the composite of cardiovascular mortality or heart failure hospitalization was 37.5%, 40.0%, and 58.2% in patients with none-mild, moderate, and severe MR, respectively (log rank $p < .001$; adjusted hazard ratio of severe vs. none-mild MR: 4.83 [2.49–9.38].

Conclusions: MR improves in a majority of patients early after TAVR, and its evolution continues thereafter in line with reverse cardiac remodeling. Residual post-TAVR severe MR is associated with adverse long-term outcome. Therefore, intervention to treat severe MR persisting after TAVR should be considered by the heart team.

1. Introduction

The incidence of both aortic stenosis (AS) and mitral regurgitation (MR) increases as the age advances, and the coexistence of AS and MR is a common clinical encounter [1,2]. In patients with predominant AS referred for surgical aortic valve replacement (SAVR), the decision to surgically manage concomitant MR is always challenging as MR tends to improve after aortic valve replacement [3] and a double-valve (aortic and mitral) surgery is known to – at least – double the operative risk as compared to isolated SAVR [4]. Even though, there is a general consensus that high grade MR (especially when organic) should be routinely repaired in the setting of SAVR [5]. In the setting of transcatheter aortic valve replacement (TAVR), concomitant high grade MR continues to be a challenging clinical context.

There is a wealth of data suggesting that MR improves early after the procedure in a large proportion of patients [6–9], but whether this improvement continues thereafter is not adequately studied to date. Additionally, previous studies have documented that high grade baseline MR is associated with worse short/intermediate-term post-TAVR prognosis [6–9], but little is known on the long-term prognostic implications of residual MR persisting after TAVR. In this study, we sought to investigate further MR improvement beyond the early post-TAVR period and the long-term prognostic impact of residual MR after TAVR.

2. Methods

Since September 2007, all patients undergoing TAVR at the Heart Center, Segeberger Kliniken, Bad Segeberg, Germany are included in a prospective registry (NCT03192774) approved by the local ethics committee and conforming to the Declaration of Helsinki. Each patient has provided a written informed consent for analysis of anonymized data. Eligibility for TAVR was determined by the local heart team taking into account patient's age, operative risk (based on established operative risk scores as well as other comorbidities not included in the scores), anatomical considerations, life expectancy, and the likelihood that TAVR will lead to a significant clinical improvement. Clinical and echocardiographic follow-up are routinely scheduled at 30 days, 6 months, 1, 2 and 5 years. Patient outcomes

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https://doi.org/10.1016/j.ijcard.2019.03.048
0167-5273/

and TAVR-related adverse events are defined according to the Valve Academic Research Consortium (VARC) criteria [10].

From September 2007 to February 2018, 1090 patients underwent TAVR at our institution. Out of 1046 patients who survived to 30 days post-TAVR, MR severity was documented in 970 patients (92.7%) who constitute the population of the present study. Mitral regurgitation was graded by transthoracic echocardiography (integrating the assessment of valve morphology with color and continuous-wave Doppler criteria) into none-trace (0/4+), mild (1+/4+), moderate (2+/4+), moderately-severe (3+/4+), or severe (4+/4+) [11]. For descriptive purposes, MR was deemed "none-mild" if graded as 0 or 1+, "moderate" if graded as 2+, and "severe" if graded as 3+ or 4+/4+. Assessment was performed at baseline (before TAVR), at 30 days and 6 months post-TAVR, and thereafter at the above mentioned follow up time points. In the present analysis; we investigated the fate of MR at two stages: a) from baseline to 30 days post-TAVR; and b) from 30 days to six months post-TAVR. Prosthetic valve regurgitation (PVR) was quantified based on the VARC criteria [10], and is represented as the sum of para- and trans-valvular regurgitation. In a subgroup of patients, cardiac magnetic resonance imaging (MRI) was used to assess left ventricular ejection fraction (LVEF), end-diastolic volume (LVEDV), and mass (LVM) at two weeks (median [IQR]: 13 [9–19] days) and six months (182 [177–186] days) post-TAVR.

2.1. Statistical methods

Qualitative variables are summarized as frequencies and percentages, while quantitative variables are summarized as mean ± SD or median [25th–75th quartiles], depending on variable distribution. Inter-group comparisons were conducted using Student *t*-test or ANOVA test for continuous variables, and by chi-square test for categorical variables. The comparison of MRI parameters collected at 2 weeks and 6 months was conducted using the Wilcoxon signed-rank test. Survival curves were created using the Kaplan–Meier method, and compared using log rank and Cox hazard regression analyses. For the latter, the hazard ratio (HR) and the 95% confidence interval (CI) are presented. Multivariable binary logistic regression analysis was performed using entry criteria of $p < .05$ in univariable analysis. The odds ratio (OR) and the 95% CI are presented. Data analysis was performed using SPSS V.24.0 (IBM Corp., New York, USA).

3. Results

The study included 970 patients who underwent TAVR (98.7% transfemoral) between September 2007 and January 2018 (age, 80.6 ± 6.2 years; female, 53.2%; Society of Thoracic Surgeons score, 5.2 ± 4.6).

3.1. Fate of MR in patients undergoing TAVR

The severity of MR at baseline and at 30 days and six months post-TAVR is displayed in Table S1. MR was none-mild in 71.5% and 75.4%, moderate in 22.8% and 21.4%, and severe in 5.7% and 3.2% of patients at baseline and at 30 days post-TAVR, respectively. While only 18 patients (1.9%) with non-mild or moderate MR at baseline deteriorated to severe MR at 30 days post-TAVR, 76.4% of cases with severe MR at baseline improved to non-severe MR at 30 days post-TAVR. Table S2 summarizes the baseline and periprocedural characteristics of patients in whom MR severity remained unchanged, improved, or deteriorated at 30 days post-TAVR as compared to baseline. After accounting for PVR and new left bundle branch block (LBBB) or pacemaker implantation after TAVR; TAVR with the Medtronic CoreValve (OR: 0.44 [0.23–0.86]) was independently associated with a lower likelihood of improvement of greater than mild MR.

MR evolution after TAVR continued beyond 30 days (Table S1) and -as a result- MR was none-mild in 78.6%, moderate in 17.7%, and severe in 3.7% of patients at six months post-TAVR. Prosthetic valve effective orifice area index (1.07 ± 0.36 vs. 1.12 ± 0.40 vs. 1.10 ± 0.32 cm/m^2, $p = .583$), ≥mild PVR (42.5% vs. 52.5% vs. 46.4%, $p = .220$), and permanent pacemaker implantation (27.6% vs. 32.9% vs. 27.0%, $p = .641$) were not significantly different between patients with unchanged, improved, or deteriorated MR severity from 30 days to six months post-TAVR. On the other hand, these three groups displayed differential MRI patterns of cardiac remodeling after TAVR (Table 1). While LVEF, LVEDV, and LVM have all improved in patients with improved as well as in patients with unchanged MR severity, LVEDV and LVM did not improve in patients with deteriorated MR severity.

Table 1
Cardiac remodeling as depicted by MRI in patients with different fates of MR at 6 months as compared to 30 days post-TAVR.

			p value[a]
MR no change ($n = 237$)			
MRI-LVEF, %	2 weeks	59.9 (51.0–64.6)	<0.001
	6 months	61.8 (54.3–67.5)	
MRI-LVEDV, ml	2 weeks	132 (112.4–156.6)	0.001
	6 months	128.9 (106.0–150.3)	
MRI-LVM, g	2 weeks	145.4 (126.3–171.5)	<0.001
	6 months	138.4 (116.1–158.4)	
MR improved ($n = 25$)			
MRI-LVEF, %	2 weeks	59.4 (47.1–65.7)	0.002
	6 months	61.2 (54.5–66.0)	
MRI-LVEDV, ml	2 weeks	125.1 (105.8–162.8)	0.032
	6 months	115.7 (100.3–136.4)	
MRI-LVM, g	2 weeks	140.3 (116.3–162.5)	<0.001
	6 months	120.6 (105.3–134.1)	
MR deteriorated ($n = 29$)			
MRI-LVEF, %	2 weeks	60.6 (49.4–64.1)	0.003
	6 months	64.1 (57.3–66.5)	
MRI-LVEDV, ml	2 weeks	118.6 (103.9–162.7)	0.837
	6 months	117.8 (108.9–147.8)	
MRI-LVM, g	2 weeks	125.6 (108.8–150.6)	0.088
	6 months	122.1 (98.2–145.0)	

[a] Wilcoxon signed-rank test.

3.2. Prognostic value of MR assessed at 30 days post-TAVR

Clinical follow up was complete for 967 patients (99.7%) and the median time to last follow up was 731 (IQR: 304–1365) days after TAVR. Stratified by the severity of MR at 30 days post-TAVR, the 5-year cumulative incidence of cardiovascular (CV) mortality and heart failure (HF) hospitalization was higher as the severity of residual (post-TAVR) MR increased (Fig. 1). The 5-year cumulative incidence of the composite endpoint of cardiovascular death or HF hospitalization was 37.5% in patients with none-mild, 40.0% in those with moderate, and 58.2% in patients with severe MR (log rank $p < .001$) (Fig. 2). Compared to patients with none-mild MR, the risk was non-significantly increased in those with moderate MR (HR: 1.32 [95% CI: 0.97–1.80], $p = .075$) while it was significantly increased in those with severe MR (HR: 2.79 [1.64–4.76], $p < .001$). Table S3 summarizes the baseline and periprocedural characteristics of patients with none-mild, moderate, and severe MR at 30 days post-TAVR. After accounting for baseline and periprocedural confounders, moderate MR was not associated with the composite of CV mortality or HF hospitalization (HR: 1.17 [0.78–1.74], $p = .450$) while severe MR was associated with a significantly higher risk (HR: 4.83 [2.49–9.38], $p < .001$). Additionally, atrial fibrillation, coronary artery disease, and tricuspid regurgitation were identified as independent predictors of the composite of CV mortality or HF hospitalization (Table 2).

To explore whether the prognostic value of severe residual MR (at 30 days post-TAVR) outweighs the prognostic value of baseline (pre-TAVR) MR, we investigated the prognostic value of baseline MR. The 5-year cumulative incidence of the composite of CV mortality or HF hospitalization was higher with increasing severity of MR at baseline only on univariable analysis (Fig. S1). After adjustment for confounders (Table S4), baseline MR severity was no longer associated with the composite of CV mortality or HF hospitalization.

4. Discussion

The main findings of the present study are that: 1) MR is prevalent among patients undergoing TAVR and improves in a large proportion of patients early after TAVR; 2) the improvement of MR severity continues thereafter especially in patients with effective reverse cardiac remodeling; and 3) severe MR at 30 days post-TAVR is a strong and independent risk factor for increased long-term CV mortality and HF hospitalization.

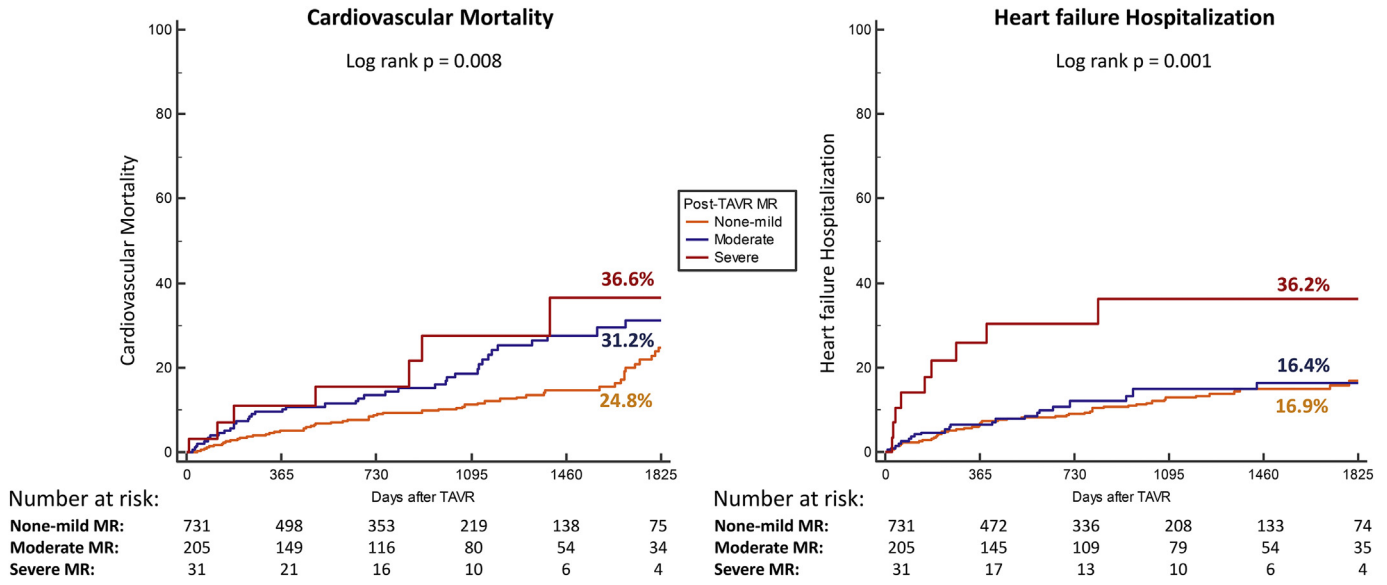

Fig. 1. Kaplan-Meier curves of cardiovascular mortality (left) and heart failure hospitalization (right) in the study population stratified according to the severity of residual post-TAVR mitral regurgitation.

4.1. The prognostic value of MR after TAVR

Previous studies [6–9,12,13] as well as our findings indicate that MR severity tends to improve after TAVR. Additionally, we found that the worse outcome in patients with higher grade of baseline MR is rather related to other conditions that typically coexist with MR (e.g. atrial fibrillation, coronary artery disease, and tricuspid regurgitation). Due to these two factors, we focused on the prognostic value of residual MR after TAVR unlike previous studies which focused on the prognostic value of baseline MR [7,8,12,13].

After accounting for confounders, severe residual MR was associated with more than four-fold increased incidence of the composite of CV mortality or HF hospitalization in the long-term after TAVR. The long-term follow up is a distinctive feature of the present analysis as compared to previous studies which were confined to one/two year outcomes [6,7]. The adverse prognostic impact of residual severe MR is calling for a more proactive management of this condition. Such a proactive approach is especially relevant in patients at intermediate/low risk whose survival and quality of life are likely better, and would thus benefit more from MR correction than the traditional high risk TAVR population. Although one previous study has suggested that only 13% of patients with residual high grade MR after TAVR are suitable candidates for percutaneous management (repair/replacement) [13], prospective studies of percutaneous management of severe MR persisting after TAVR are required given the strong adverse prognostic impact of this condition.

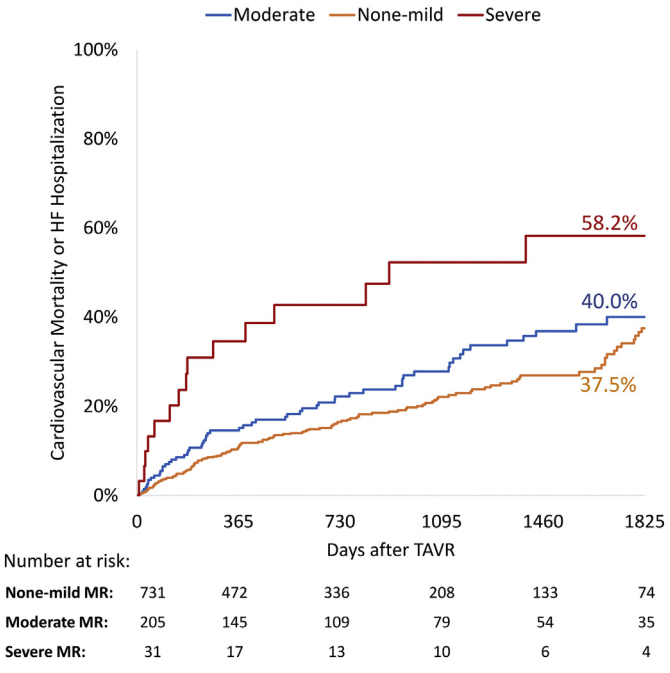

Fig. 2. Kaplan-Meier curves of the composite of cardiovascular mortality or heart failure (HF) hospitalization in the study population stratified according to the severity of residual post-TAVR mitral regurgitation.

4.2. The mechanism of MR severity change after TAVR

In patients with predominant AS, the severity of MR increases as the pressure gradient (PG) rises in the course of AS progression [14]. This progression of MR severity is secondary to the increase of the left ventricle-to-left atrium PG and to progressive LV adverse remodeling which involves the mitral valve apparatus [2]. After aortic valve replacement, two processes act together contributing to MR regression: a) the reduction of LV cavity pressure leading to reduction of the ventricle-to-left atrium PG, and b) the reduction of LV diastolic volume and change of LV shape and geometry resulting in a decrease in mitral tethering [2]. In the early post-operative phase, the reduction in mitral regurgitation volume is greater than the decrease in the effective regurgitant orifice [15], denoting that the hemodynamic – rather than the geometric – changes are the basic determinant of MR improvement early after aortic valve replacement. Thereafter, LV remodeling is likely the main factor governing further MR improvement/deterioration. This pattern of interactions which has been suggested by previous studies is further supported by our findings. We observed an impressive improvement of MR severity early after TAVR, with 76% of those with severe MR improving to lesser severity. The likelihood of improvement was lower in patients who received a CoreValve. The association between TAVR with the CoreValve and a lower likelihood of MR improvement remained significant after accounting for two important confounders; PVR and new LBBB/pacemaker implantation. These two factors are known to occur more frequently after CoreValve implantation and are also known to impair LV performance and hemodynamics, possibly hindering MR improvement. The notion that TAVR with the CoreValve is associated with

Table 2
Predictors of cardiovascular mortality or after TAVR.

	Univariable analysis		Multivariable analysis	
	HR (95% CI)	*p*	HR (95% CI)	*p*
Baseline characteristics				
Atrial fibrillation	1.89 (1.44–2.48)	<0.001	1.49 (1.04–2.12)	0.028
Coronary artery disease	1.34 (0.99–1.82)	0.061	1.70 (1.16–2.49)	0.007
Tricuspid regurgitation				
Moderate	1.67 (1.18–2.35)	0.170	1.35 (0.88–2.08)	0.004
Severe	2.63 (1.68–4.11)	<0.001	2.82 (1.63–4.85)	<0.001
Left ventricular ejection fraction, %	1.00 (0.99–1.01)	0.323	1.01 (0.99–1.02)	0.383
Systolic pulmonary artery pressure, mm Hg	1.02 (1.01–1.02)	0.001	1.01 (0.99–1.02)	0.322
Post-TAVR characteristics				
Prosthetic valve regurgitation				
Mild	1.00 (0.76–1.33)	0.982	0.87 (0.61–1.24)	0.432
≥Moderate	0.58 (0.24–1.42)	0.234	0.54 (0.16–1.77)	0.305
Pacemaker implantation	0.97 (0.71–1.33)	0.856	0.93 (0.64–1.35)	0.696
Mitral regurgitation				
Moderate	1.32 (0.97–1.80)	0.075	1.17 (0.78–1.74)	0.450
Severe	2.79 (1.64–4.76)	<0.001	4.83 (2.49–9.38)	<0.001

lower extent of MR improvement has been previously suggested by a large meta-analysis [7] as well as by smaller studies [16–20], some of them have documented a mechanical interference with the mitral valve by the CoreValve. It should, however, be noted that this association should not be extrapolated to the next generations of the Medtronic self-expanding transcatheter aortic valves. Compared to the older generation, those next generation devices have a shorter and more conformable frame and are usually implanted at a shallower depth than the older generation CoreValve [21,22].

Some previous studies have reported a differential pattern of MR regression after TAVR depending on the etiology/mechanism of MR (organic vs. functional) [23–25]. On the other hand, some other studies did not confirm such a difference [13,26]. Notwithstanding, the mechanism of MR (functional vs. organic) does not predict whether the regurgitant orifice is fixed or dynamic [27], and –therefore– even organic MR can significantly change in severity in response to the changes in LV hemodynamics. In our analysis, we did not explore whether the etiology/mechanism of MR would influence the change in MR severity. Specification of the mechanism of MR in TAVR patients is challenging and a "mixed" etiology (e.g. LV remodeling/dysfunction, coronary disease, annular calcification, etc.) is common especially in an elderly population.

We also explored the fate of MR beyond 30 days after TAVR, a point seldom addressed in previous studies. We hypothesized that further MR regression/deterioration after establishment of the acute hemodynamic changes that follow TAVR would be part of the gradual process of reverse cardiac remodeling ensuing over the months/years after TAVR. Although available only in a subgroup of patients, MRI provided important insights into this process. Patients with deteriorating MR severity have also displayed no effective reduction in LV volume and mass, denoting that lack of reverse cardiac remodeling after TAVR may herald progressive cardiac deterioration; a hypothesis that should be further tested in future studies. The association between MR deterioration and lack of reverse cardiac remodeling can, however, be seen the other way around, as MR deterioration per se may lead to adverse cardiac remodeling. Concluding upon the direction of causality of this relationship can be reached only through larger scale studies, which should focus on the pattern and determinants of cardiac remodeling after TAVR.

5. Limitations

The main limitation of the present study is that it did not include information on the etiology/mechanism of MR, which could be one of the factors influencing the fate of MR after TAVR. Additionally, this is a retrospective single center study -bearing the limitations inherent to such a study design- and imaging data were not core lab adjudicated. MRI was not available in all patients due to the common presence of contraindications (e.g. pacemakers). Finally, our study did not include data on mitral stenosis. Severe mitral stenosis affects <3% of patients undergoing TAVR and portends adverse clinical outcomes [28–30].

6. Conclusions

MR improves in a majority of patients after TAVR, and its evolution continues thereafter in line with reverse cardiac remodeling. Residual severe MR after TAVR is associated with significantly worse long-term outcomes. Therefore, intervention to treat severe MR persisting after TAVR should be considered by the heart team.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcard.2019.03.048.

Acknowledgements

None.

Competing interests

Drs. Abdel-Wahab and Richardt have received institutional research grants from St. Jude Medical, Biotronik and Medtronic. Dr. Abdel-Wahab is a proctor for Boston Scientific and a consultant for Medtronic. The other authors have no conflicts of interest to declare.

Funding sources

None.

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