Does the Presence of Significant Mitral Regurgitation prior to Transcatheter Aortic Valve Implantation for Aortic Stenosis Impact Mortality? – Meta-Analysis and Systematic Review

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Keywords

Mitral regurgitation · Aortic stenosis · Transcatheter aortic valve implantation · Transcatheter aortic valve replacement

Abstract

Background: Mitral regurgitation (MR) is commonly encountered in patients with severe aortic stenosis (AS). However, its independent impact on mortality in patients undergoing transcatheter aortic valve implantation (TAVI) has not been established. **Methods:** We performed a systematic search for studies reporting characteristics and outcome of patients with and without significant MR and/or adjusted mortality associated with MR post-TAVI. We conducted a meta-analysis of quantitative data. **Results:** Seventeen studies with 20,717 patients compared outcomes and group characteristics. Twenty-one studies with 32,257 patients reported adjusted odds of mortality associated with MR. Patients with MR were older, had a higher Society of Thoracic Surgeons score, lower left ventricular ejection fraction, a higher incidence of prior myocardial infarction, atrial fibrillation, and a trend towards higher NYHA class III/IV, but had similar mean gradient, gender, and chronic kidney disease. The MR patients had a higher unadjusted short-term (RR =

1.46, 95% CI 1.30–1.65) and long-term mortality (RR = 1.40, 95% CI 1.18–1.65). However, 16 of 21 studies with 27,777 patients found no association between MR and mortality after adjusting for baseline variables. In greater than half of the patients (0.56, 95% CI 0.45–0.66) MR improved by at least one grade following TAVI. **Conclusion:** The patients with MR undergoing TAVI have a higher burden of risk factors which can independently impact mortality. There is a lack of robust evidence supporting an increased mortality in MR patients, after adjusting for other compounding variables. MR tends to improve in the majority of patients post-TAVI.

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Background

Aortic stenosis (AS) and mitral regurgitation (MR) are two common valve disorders that frequently coexist. Calcification of the mitral annulus, leaflets, and subvalvular apparatus, along with leaflet tethering secondary to pressure overload and concomitant coronary artery disease are factors implicated in the pathogenesis of MR in patients with severe AS [1]. Current guidelines recommend mitral valve repair or replacement in patients with severe

primary MR undergoing cardiac surgery for another indication [2]. The management of moderate MR in patients undergoing surgical aortic valve replacement (SAVR), and its mortality benefit, remains controversial [3, 4]. The advent of transcatheter aortic valve implantation (TAVI) has resulted in a paradigm shift in the management of severe AS. Patients with significant MR were largely excluded from pivotal clinical trials. However, with the wider use of TAVI, concerns have been raised regarding the management of concomitant MR, affecting up to 20% of patients with severe AS [1].

Studies in patients with severe AS and significant MR, undergoing TAVI, have yielded mixed results [5–8]. Previous meta-analyses revealed higher short- and long-term mortality in patients with significant MR [9, 10]. Considering the observational nature of the studies, we postulated that patients with significant MR may have differences in baseline characteristics as compared to a control group devoid of significant MR, which would impact mortality. Therefore, the aim of our study is to compare the baseline characteristics of patients with and without significant MR and evaluate its impact on mortality in patients with severe AS undergoing TAVI.

Methods

A systematic search of the electronic databases PubMed and EMBASE was conducted for studies in patients with severe AS and MR undergoing TAVI reporting clinical outcomes. We used the following keywords “TAVR mitral regurgitation,” “TAVI mitral regurgitation,” “mitral regurgitation transcatheter aortic valve.” We did not enforce any language restriction. We performed the last search on August 31, 2018. In addition, we searched the relevant websites acc.org and pconline.com for the abstracts presented at major national meetings in the last 10 years. The bibliography of relevant review articles and prior meta-analysis were manually searched for any additional studies.

We included the studies which reported the outcomes of patients with and without MR before TAVI for AS and described the baseline characteristics of the two groups. In the event that a study did not describe group characteristics, it was included only if the mortality risk (odds or hazard ratio) associated with significant MR was adjusted for baseline variables using a multivariable regression. We excluded studies without any description of the characteristics or adjusted outcomes.

Two investigators independently searched the electronic databases for the relevant studies. We retrieved the full manuscripts of relevant studies for a detailed independent review. The data on study population, sites/registry, time period, definition of significant MR, duration of follow-up, post-procedure change in MR and timing of evaluation, group characteristics, short- and long-term mortality and adjusted mortality were extracted from the studies meeting the inclusion criteria. We selected those reports with a description of group characteristics, larger sample size, and longer

follow-up, from the multiple reports extracted from the site or registry. A third author resolved any inconsistencies in the preliminary dataset. In the event of missing data, we contacted the corresponding author. This meta-analysis was conducted in accordance with the MOOSE (Meta-analysis of Observational Studies in Epidemiology) group recommendations [11].

Statistical Analysis

We extracted categorical and continuous characteristics to perform a quantitative meta-analysis of between-group differences in patients with and without significant MR using the mean difference and risk ratio (RR), respectively. Furthermore; a meta-analysis of unadjusted short- (30 days) and long-term mortality was performed as a function of the degree of significant MR. A subgroup analysis to assess the impact of significant MR on both the short- and long-term mortality was performed. A meta-analysis of adjusted hazard/odds ratio was planned, but not performed because of unreported effect size and confidence intervals in several studies with nonsignificant results. Because of the observational nature of the included studies and significant heterogeneity, we decided a priori to conduct a random effect meta-analysis, although heterogeneity among the studies for each outcome was assessed using the I^2 statistic. The RR was used as summary statistic, and a p value <0.05 was considered significant. Publication bias was assessed using the funnel plot and Egger method. All statistical analysis was conducted using “meta” package in the R statistical software (version 3.3.1) [12]. The quality of included studies was assessed using the Newcastle-Ottawa scale for non-randomized cohort studies [13].

Results

Seventeen studies with 20,717 patients compared the characteristics and outcomes of the groups with and without significant MR. Twenty-one studies reported the effect of significant MR on mortality adjusted for baseline variables. Figure 1 shows the flowchart depicting the search process. The characteristics of the included studies are shown in Table 1. Studies used grades as recommended by the American Society of Echocardiography/European Association of Echocardiography [14, 15] to define significant MR. Four studies used MR $\geq$ grade 3 (moderate to severe), one study used grade 4 (severe), and the rest used $\geq$ grade 2 (moderate) to define significant MR. From this point onwards in the study, we refer to patients with significant MR as MR patients and those without significant MR as patients no MR. The proportion of patients with pre-TAVI MR varied from 8 to 53% in all eligible studies, with follow-up ranging from 8 months to 5 years.

Patients with MR were: older (MR 82.4 years [81.4–83.3], without MR 81.3 years [80.7–81.93]); had higher Society of Thoracic Surgeons (STS) scores (MR [8.8, 95% CI 7.9–9.8], without MR [7.6, 95% CI 6.91–8.46]); de-

Fig. 1. Studies selection process.

Fig. 2. Forest plots showing difference between patients with and without significant MR (a), continuous variables, and categorical variables (b). AFIB, atrial fibrillation; CKD, chronic kidney disease; LVEF, left ventricle ejection fraction; MI, myocardial infarction; STS, Society of Thoracic Surgeons.

Table 1. Characteristics of included studies

Study	Patient population	Sample size	Valve type	MR categories compared	Proportion with significant MR, %	Follow-up
a Studies which reported characteristics of patients with and without significant MR						
Mavromatis et al. [5]	TVT registry 2012–2013	11,104	NR	< grade 2 vs. grade ≥2	36.8	1 year
Hutter et al. [6]	German heart center 2007–2009	268	MCV 72.4%, ESV 27.6%	< grade 3 vs. ≥ grade 3	29.7	1 year
Barbanti et al. [7]	Partner Cohort A	499	ESV 100%	< grade 2 vs. grade ≥2	19.6	2 years
Cortes et al. [8]	Spanish multicenter registry 2007–2015	1,110	ESV 20.4%, MCV 79.6%	< grade 3 vs. ≥ grade 3	15.9	6 months
D'Onofrio et al. [S1]	University of Padova, Italy, 2007–2011	176	MCV 49.4%, ESV 50.6%	< grade 2 vs. grade ≥2	24.4	10 months
Khawaja et al. [S2]	St. Thomas Hospital, London, UK, 2008–2013	316	ESV 100%	< grade 3 vs. ≥ grade 3	19	1 year
Kindya et al. [28]	Emory University Hospital, Atlanta and Hadassah University Medical Center, Jerusalem, Israel, 2007–2013	260	ESV 71.7%, MCV 22.9%	< grade 2 vs. grade ≥2	41.5	2 years
Kiramijyan et al. [S3]	MedStar Washington Hospital Center, Washington DC, USA, 2007–2014	589	ESV 71%, MCV 29%	< grade 2 vs. grade ≥2	11.5	1 year
Toggweiler et al. [S4]	St. Paul Hospital, Vancouver, and Quebec Heart and Lung Institute, Quebec City, Canada, 2005–2010	451	ESV 100%	< grade 2 vs. grade ≥2	29.2	2 years
Vollenbroich et al. [29]	Bern University Hospital, Bern, Switzerland	603	MCV 51%, ESV 47%, Other 2%	< grade 2 vs. grade ≥2	24.7	2 years
Bedogni et al. [S5] and Barbanti et al. [S6]	Italian Core Valve registry, 2007–2011	1,007	MCV 100%	< grade 2 vs. ≥ grade 2	33.4	1 year, 5 years (adjusted)
Costantino et al. [S7]	Potenza-San Carlo Hospital, Potenza and Roma-San Camillo Hospital, Rome, Italy, 2010–2014	165	MCV 69%, ESV 31%	< grade 3 vs. ≥ grade 3	17	2 years
Haensig et al. [S8]	Leipzig Heart Center, Leipzig, Germany, 2006–2011	439	ESV 100%	< grade 2 vs. grade ≥2	31.6	4 years
Baumgartner [S9] and Schymik et al. [S10]	SOURCE XT registry	2,615	ESV 100%	< grade 2 vs. grade ≥2	19.6	1 year
Dijk et al. [S11]	Academic medical center, University of Amsterdam, Amsterdam, The Netherlands, 2007–2013	375	ESV 70%, MCV 30%	< grade 2 vs. grade ≥2	45.6	2 years
Silberman et al. [S12]	Shaare Zedek Medical Center, Jerusalem, Israel, 2008–2013	164	ESV 81%, MCV 19%	< grade 2 vs. grade ≥2	53	3 years
Ruck et al. [S13]	Swedish TAVI registry, 2008–2012	576	MCV 53%, ESV 47%	< grade 2 vs. ≥ grade 2	19.6	2 years
b Studies which did not report group characteristics but reported mortality associated with significant MR adjusted for baseline variables						
Zahn et al. [S14]	The German Transcatheter Aortic Valve Intervention registry, 2009–2010	1,378	MCV 81.4%, ESV 18.6%	< grade 2 vs. grade ≥2	33	5 years
Van Belle et al. [S15]	France 2 registry	3,195	ESV 66.9%, MCV 33.1%	< grade 2 vs. grade ≥2	22	1 year

Table 1 (continued)

Study	Patient population	Sample size	Valve type	MR categories compared	Proportion with significant MR, %	Follow-up
Yoon et al. [S16]	The Asian TAVR registry	848	ESV 64.7%, MCV 35.3%	< grade 2 vs. grade ≥2	13.9	1 year
Wendler et al. [S17]	SOURCE 3 registry, 2014–2015	1,946	ESV 100%	< grade 2 vs. grade ≥2	14	1 year
Gilard et al. [S18]	ESC Sentinel registry	4,571	ESV 57.3%, MCV 42.7%	< grade 2 vs. grade ≥2	20.8	1 year
Rodes-Cabau et al. [21]	Canadian multicenter registry, 2005–2009	339	ESV 100%	< grade 4 vs. > grade 4	8.5	8 months

ESV, Edwards SAPIEN valve; Grade 2: moderate mitral regurgitation (MR) as defined by the American Society of Echocardiography (ASE)/European Association of Echocardiography (EAE); Grade 3: moderate to severe MR as defined by ASE/EAE; Grade 4: severe MR as defined by ASE/EAE [references 12, 13]; MCV, Medtronic core valve; TAVI/R, transcatheter aortic valve implantation/replacement; TVT, transcatheter valve therapy.

pressed left ventricular ejection fraction (MR [48.8%, 95% CI 46.8–50.8], no MR [54.7%, 95% CI 53.4–56]); more likely to have had a myocardial infarction (MR [27%, 95% CI 21–33], no MR [23%, 95% CI 19–28]); and, a higher incidence of atrial fibrillation (MR [37%, 95% CI 30–44], no MR [24%, 95% CI 19–30]). The mean gradient across the valve was similar (MR 44.7 mm Hg [95% CI 43.2–46.1] vs. no MR 45.9 mm Hg [95% CI 45.1–46.8]). There were 43.9% (95% CI 40.7–44.6) and 45.6% (95% CI 42.5–48.7) males in the MR and no MR groups, respectively. In the MR and no MR groups, 78.9% (95% CI 70–85.4) and 76.6% (95% CI 68.5–83.2) patients, respectively, had NYHA class III or IV symptoms. There was no difference in prevalence of chronic kidney disease (38%, 95% CI 15–69 vs. 34%, 95% CI 17–56). The forest plot of differences in group characteristics is shown in Figure 2.

MR and Mortality

The unadjusted short-term (≤ 30 days) (RR = 1.46, 95% CI 1.30–1.65) and long-term (RR = 1.40, 95% CI 1.18–1.65) mortality was higher in patients with MR compared to no MR as shown in Figures 3 and 4, respectively. There was no evidence interaction between the definition of significant MR, i.e., grade 2 versus grade 3, and unadjusted risk of mortality based on testing for subgroup difference as shown in Figures 3 and 4.

Twenty-one studies with 32,257 patients investigated an independent association between MR and mortality adjusted for other baseline variables. Twelve of the 21 studies reported effect size with a confidence interval, whereas the other 9 only commented on statistical insignificance. Sixteen of 21 studies with 27,777 patients found no association between MR and mortality, after adjusting for baseline variables (Fig. 5).

Improvement in MR Post-TAVI

Fourteen studies assessed 6,139 MR patients at follow-up with echocardiogram. The follow-up ranged from 1 month to 1 year. The improvement in MR by at least one grade was reported in 0.56 (95% CI 0.45–0.66) proportion of patients (Fig. 6). Predictors of persistent MR post-TAVI are also summarized in Figure 6.

Publication Bias and Quality Assessment

We found no evidence of publication bias on visual inspection of the funnel plot or by the Egger method (short-term mortality $p = 0.42$, long-term mortality $p = 0.67$) as shown in online supplementary Figure S1 and Figure S2 (for all online suppl. material, see www.karger.com/doi/10.1159/000506624). We did not find

Fig. 3. Forest plot showing unadjusted RR of short-term mortality (≤ 30 days).

bias in selection of subjects based on four subcategories of the Newcastle-Ottawa scale. The groups were different in two or more tested characteristics in all included studies as shown in online supplementary Table S1. We considered studies with ≥ 1 year follow-up to have been of sufficient follow-up duration, with $>90\%$ of studies meeting these criteria. The assessment of study quality using this scale is shown in online supplementary Table S1.

Discussion

We conducted a quantitative meta-analysis and systematic review of all available evidence to evaluate the association between significant preprocedural MR and the risk of mortality after TAVI, for severe AS. In addition,

we studied the baseline characteristic differences between patients with and without MR which may affect clinical outcomes. In an unadjusted analysis, MR was associated with a higher short- and long-term mortality; however, significant differences in baseline characteristics between the two groups were noted. A systematic review of prior studies assessing the presence of significant MR on mortality, adjusted for baseline characteristics, showed no association. This is in contradistinction to three prior meta-analyses, of 8–13 studies including $\leq 9,000$ patients, which found a higher short- and long-term mortality in patients with MR [9, 10, 16].

Nombela-Franco et al. [9] performed a meta-analysis ($n = 8,015$ patients) and reported a higher adjusted mortality in those patients with MR. There were several differences compared to our analysis including a smaller

Fig. 4. Forest plot showing unadjusted RR of long-term mortality.

number of patients per study while restricting inclusion to national registries and randomized clinical trials. Other investigators reported significant MR in only 63% of patients, did not include this variable as a predictor of mortality in their original manuscript [17], but, included an adjusted odds ratio in their meta-analysis [9]. We paid special attention to the site and time frame of patient recruitment to prevent data duplication. More importantly, we found that many studies with no significant relationship between MR and adjusted mortality failed to report an effect size and confidence interval (Fig. 5), introducing substantial bias. Therefore, we decided not to perform a quantitative synthesis for adjusted odds ratio and opted to report qualitative outcomes.

In contrast to prior meta-analyses, we concluded that patients with MR exhibit significant baseline differences

compared to controls, which may independently impact mortality. In a meta-analysis of 11 studies ($n > 11,000$ patients), the presence of atrial fibrillation was associated with a higher short- and long-term mortality in patients undergoing TAVI [18]. Similarly, a lower LVEF and a higher STS score were associated with a higher mortality following TAVI [19, 20]. In this analysis, patients with concomitant MR were older, had a higher STS score, lower LVEF, had higher incidence of prior MI, and atrial fibrillation. Although not reaching statistical significance, patients with MR had a higher NYHA heart failure class. There were no differences in gender, incidence of chronic kidney disease, and the mean gradient compared to the no MR group.

These variables were selected based on their uniform availability from the extracted studies. Several other

Fig. 5. Forest plot showing results adjusted odds/hazards of mortality associated with significant MR including studies which did not report effect size.

Fig. 6. Forest plot showing improvement in MR by at least 1 grade among the included studies.

variables which may impact mortality were unbalanced and not incorporated in the analysis (see online suppl. Table S1). Considering the observational nature of all available evidence, we focused on studies which adjusted for baseline variables, when assessing the association between MR and mortality. As shown in Figure 5, most studies did not show an association between MR and mortality when adjusted for other variables. There are

several possible explanations for this observation: with the exception of the study conducted by Rodés-Cabau et al. [21], which only included patients with severe MR, only 1 of 3 patients enrolled had severe MR; only four studies had a follow-up period >2 years, with only an 8-month follow-up in the Rodés-Cabau study [21]. The mortality in the TAVR groups at 2 years in Partner 1A and 1B were 33.9 and 43.3%, respectively, with a signifi-

cant proportion of death attributed to noncardiac causes [22, 23]. Therefore, it was not surprising that MR had no impact on mortality in patients with moderate MR, during short-term follow-up, and with other high-risk cardiovascular as well as noncardiovascular comorbidities. Secondly, in the majority of patients, the MR improved by at least a grade on the follow-up, supporting the hypothesis of significant MR being a risk marker, as unadjusted mortality was higher in both short and long term. Finally, it is interesting to note that MR is not an independent predictor of mortality in commonly used risk scores, which adjust for multiple variables, like STS score and EuroScore II after SAVR [24, 25] or TAVR specific risk scores [26, 27].

We found that MR improved post-TAVI at follow-up in 56% of patients (Fig. 6), consistent with previous studies [9, 10]. The reduction in gradient across the mitral valve due to the instantaneous decrease in left ventricle pressure after resolution of AS post-TAVI and continuous reverse remodeling of the left ventricle has been postulated to promote MR improvement acutely and upon follow-up [1]. Interestingly, measures of left ventricle size, severe pulmonary hypertension, presence of organic MR, atrial fibrillation, and lower aortic valve gradient were associated with persistence of MR in several studies. This may be a consequence of a severely dilated left ventricle and lower aortic valve gradient representing primary myocardial disease; thus, the afterload reduction post-TAVI may not significantly improve MR, similar to patients with underlying organic mitral valve pathology like prolapse or a flailed leaflet. Likewise, the presence of atrial fibrillation and severe pulmonary hypertension may represent a more advanced stage of mitral valve dysfunction, as well as, persistent pulmonary vascular remodeling. Further characterization of predictors of persistence of MR post-TAVI in future studies may help with decision-making and counselling of patients with MR and severe AS referred for TAVI.

There are several unresolved issues. The impact of functional versus organic MR on outcomes is not well understood. Two studies in the analysis compared outcomes of patients with these two entities [28, 29]. Kindya et al. [28] reported that patients with moderate to severe organic MR were less likely to have a survival free of death or hospitalization on multivariable analysis, whereas functional MR was not an independent predictor. Vollebrouch et al. [29] found organic MR to be independently associated with cardiovascular mortality at 2 years and not the functional MR. On the other hand, Kiramijyan et al. [30] found no difference in mortality between

organic and functional MR at 30 days and 1 year; although there was a larger improvement in the severity of MR, LVEF, and symptoms in patients with functional MR. Previous meta-analyses did not find any difference on the impact of MR and mortality as a function of the type of TAVI valve used (e.g., balloon expandable versus self-expanding) [9, 10]. These studies were not randomized; therefore, the role of prosthesis selection and patient specific variables could not be analyzed.

Limitations

This was an analysis based on observational studies, a prospective study analyzing prospectively gathered data would have allowed for adjustment of all confounders. There was significant heterogeneity across the studies, as shown by I^2 statistic; therefore, random effect analysis was performed. As noted above, only a limited number of patients had severe MR, consequently, more information on this group of patients is needed. In addition, the impact of the etiology of MR, functional, organic or mixed, on outcomes remains unclear. In only three studies, MR was evaluated by an independent core laboratory or echocardiographer, and only four studies have outcomes adjudicated by an independent committee. The impact of blind adjudication committee on mortality, an unambiguous outcome, is probably minimal. On the other hand, echocardiographic assessment of MR severity is challenging not only due to calcification, but also large color Doppler jet secondary to high trans-mitral driving velocity frequently seen in severe AS [1, 31]. Therefore, a blinded core lab assessment of MR severity both preprocedure and on follow-up may significantly affect the results.

Conclusion

In a comprehensive meta-analysis of observational studies, we found that patients with greater than moderate MR in severity exhibited a higher mortality post-TAVI. However, we found significant differences in the baseline characteristics of the two groups which may independently contribute to this difference in mortality. Current evidence does not support moderate MR as an independent mortality risk factor post-TAVI. We conclude from this analysis that, at the present time, moderate to severe MR may not be a contraindication for TAVI in an otherwise appropriate patient with severe AS, since the majority of patients exhibit improvement in MR at follow-up.

Disclosure Statement

We do not have any conflicts of interest related to this study.

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