



## Impact of moderate to severe mitral stenosis in patients undergoing transcatheter aortic valve replacement

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### ARTICLE INFO

#### Article history:

Received 28 November 2018

Received in revised form 24 March 2019

Accepted 26 March 2019

Available online 28 March 2019

#### Keywords:

Mitral stenosis

Transcatheter aortic valve replacement

### ABSTRACT

**Objective:** In patients with severe aortic stenosis (AS) undergoing transcatheter aortic valve replacement (TAVR), the impact of concomitant mitral stenosis (MS) remains unknown. The aim of this study was to determine the incidence and impact of moderate to severe MS in patients undergoing TAVR.

**Methods:** The study included 2113 consecutive patients (mean age: 80 ± 9 years, mean STS: 6.4 ± 5.2%) who underwent TAVR in 2 centers. The presence of MS was defined as a mean transmitral gradient ≥ 5 mm Hg on baseline echocardiography in the absence of severe mitral regurgitation. Clinical events were prospectively collected in a dedicated TAVR database.

**Results:** A total of 157 patients (7.4%) had moderate to severe MS (mean gradient: 7.2 ± 2.8 mm Hg; degenerative origin in 88%). Patients with MS were younger, more frequently women, had a higher left ventricular ejection fraction and an increased rate of severe pulmonary hypertension ( $p < 0.02$  for all). Thirty-day mortality was similar in both groups (MS: 3.8%; no MS: 5.5%, adjusted  $p = 0.34$ ). At a mean follow-up of 3 ± 2 years, there were no differences between groups in mortality (MS: 35%, no MS: 36.2%, adjusted HR: 1.14, 95% CI: 0.86–1.51), or heart failure rehospitalization (MS: 21%, no MS: 21.7%; adjusted HR: 1.16, 95% CI: 0.81–1.67). Patients with MS exhibited a similar functional status at follow-up compared to those with no MS (NYHA I–II in 85% and 88% of patients, respectively, adjusted  $p = 0.20$ ).

**Conclusions:** About 7% of patients undergoing TAVR had concomitant moderate to severe MS. The presence of MS had no negative impact on early and mid-term clinical outcomes post-TAVR. These results suggest that TAVR is a valid alternative for treating patients with aortic stenosis in the presence of moderate to severe MS.

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### 1. Introduction

Transcatheter aortic valve replacement (TAVR) has been established as a valid alternative for the treatment of patients with aortic stenosis at intermediate to high surgical risk [1]. While the results of TAVR have constantly improved over time, some factors remain associated with poorer outcomes [2]. The presence of multivalvular disease, and particularly moderate to severe mitral regurgitation (MR), has been associated with increased early and late mortality as well as an impaired functional status following TAVR [3]. Unlike surgical candidates where significant mitral disease is addressed at the time of surgery, MR is left untreated at the time of TAVR and its severity does not improve over time in a significant proportion of patients [4].

Degenerative mitral stenosis (MS), mainly secondary to mitral annular calcification, is a disease with increasing prevalence among elderly patients [5]. This has a high clinical relevance considering the fact that the current guidelines for the management of patients with valvular heart disease recommend concomitant mitral valve surgery for patients with moderate to severe MS undergoing cardiac surgery for other indications (e.g. aortic stenosis) [6,7]. According to these recommendations, the presence of MS may have an impact on the clinical decision-making process (TAVR vs. SAVR) of patients with aortic stenosis at intermediate to high surgical risk. Therefore, it would be very important to obtain data on the prevalence and prognostic value of MS in TAVR candidates. Few data exist on the presence and impact of MS in TAVR recipients. Joseph et al. recently reported a MS rate of 12% among TAVR candidates, with MS being associated with poorer outcomes at midterm follow-up. However, the method (echocardiographic or cardiac catheterization) for determining the mitral valve area and the causes of MS were not documented, the information was limited at 1-year follow-up, and no data on functional status and exercise capacity was provided [8].

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Thus, the purpose of our study was to determine the prevalence and long-term clinical impact (clinical events, functional status) of moderate to severe MS (as determined by echocardiography) in TAVR recipients.

## 2. Methods

A total of 2113 consecutive patients who underwent TAVR in 2 centers between 2007 and 2017 were included. The procedures were performed according to current TAVR standards, and the heart team of each center determined the TAVR indication, valve type, and approach. According to the EAE/ASE recommendations for clinical practice [9], we selected the mean transmitral gradient as a marker of severity because valve planimetry may be difficult and non-reliable in degenerative MS (orifice geometry and presence of calcification). All patients had a baseline (pre-procedural) transthoracic echocardiography and moderate to severe MS was defined by a mean transmitral gradient  $\geq 5$  mm Hg on baseline echocardiography in patients with no severe mitral regurgitation (effective regurgitant orifice area  $\geq 40$  mm Hg and regurgitant volume  $\geq 60$  mL/beat at PISA) in order to avoid the inclusion of functional elevated mitral gradients. Mitral valve area was determined by proximal isovelocity surface area (PISA), obtained with color flow Doppler in apical 4-chamber view. The calculation of PISA requires the measurement of several different parameters as follows: the aliasing velocity, radius of the convergence hemisphere, the peak mitral inflow velocity, and the opening angle of the leaflets relative to the flow direction. Rheumatic MS was defined according four main echocardiographic parameters: commissural fusion, thickening at the leaflet tips, chordal shortening and restricted mobility of the posterior MV leaflet.

Baseline, procedural and follow-up data were prospectively collected in a dedicated TAVR database. The functional status of the patients was determined by the NYHA class. In one participating center, a six-minute walk test (6MWT) was performed at baseline and at 12-month follow-up in order to determine the changes in exercise capacity following TAVR. Follow-up outpatient visits or telephone interviews were conducted at 30 days, 12 months, and yearly thereafter, and clinical events were recorded according to the Valve Academic Research Consortium (VARC) 2 criteria [10]. Follow-up echocardiography was performed at 12-month follow-up.

Qualitative variables were expressed as number (percentage), whereas continuous data were presented as mean  $\pm$  SD or median (interquartile range) depending on their

distribution. Qualitative variables were compared using the chi-square test and numerical variables using the *t*-test or Wilcoxon test. Comparisons of echocardiographic data between baseline and follow-up were performed with the paired *t*-test. Survival rates were summarized using Kaplan-Meier estimates, and log-rank tests were used to compare groups. Differences between groups in clinical outcomes were analyzed using a logistic regression (30-day outcomes) or proportional hazard models to adjust for baseline differences between groups. All analyses were performed using a hierarchical method in order to account for between-center variability. The multivariate models were adjusted for the baseline differences between groups ( $p < 0.05$  in the univariate analysis). All tests were two-sided at the 0.05 significance level. Statistical analyses were conducted with the statistical package SAS version 9.3 (SAS Institute, Cary, North Carolina).

## 3. Results

The main characteristics of the study population are shown in Table 1. The mean age of the study population was  $80 \pm 9$  years, 53% of the patients were males and the mean STS score was  $6.4 \pm 5.2\%$ . The presence of moderate to severe MS was diagnosed in 157 patients (7.4%) according baseline echocardiography, with a mean transvalvular gradient of  $7.2 \pm 2.8$  mm Hg and a mean mitral valve area of  $1.5 \pm 0.5$  cm<sup>2</sup>. MS was of degenerative and rheumatic origin in 139 (89%) and 18 (11%) patients, respectively. Patients with MS were younger and more frequently female, had less coronary artery disease, an increased left ventricular ejection fraction and a higher rate of severe pulmonary hypertension ( $p < 0.02$  for all). There were no differences between groups in the main procedural characteristics (Table 1).

The 30-day outcomes according to the presence of MS are shown in Table 2. There were no differences between groups in peri-procedural complications. The 30-day mortality rate in the MS group was 3.8% (vs. 5.5% in the no MS group, adjusted  $p = 0.34$ ). At a mean follow-up of  $3 \pm 2$  years, a total of 762 patients (36%) had died, 471 (22%) from

**Table 1**  
Baseline and procedural findings of the study population, according to presence of moderate to severe mitral stenosis.

Variables	Overall (n = 2113)	MS (n = 157)	No MS (n = 1956)	p value
<b>Baseline clinical characteristics</b>				
Age, years	80 $\pm$ 9	78 $\pm$ 11	80 $\pm$ 9	<b>0.009</b>
Male	1126 (53.3)	54 (34.4)	1072 (54.8)	<b>&lt;0.001</b>
Body mass index, kg/m <sup>2</sup>	26.7 $\pm$ 5.6	27.5 $\pm$ 6.8	26.7 $\pm$ 5.5	0.158
Diabetes mellitus	645 (69.5)	49 (31.2)	596 (30.5)	0.846
NYHA class > II	1591 (75.3)	116 (73.9)	1475 (75.4)	0.670
Atrial fibrillation	724 (34.3)	52 (33.1)	672 (34.4)	0.754
Previous pacemaker	352 (16.7)	29 (18.5)	323 (16.5)	0.526
Coronary artery disease	1081 (51.2)	66 (42.0)	1015 (51.9)	<b>0.017</b>
Chronic obstructive pulmonary disease	443 (21.0)	39 (24.8)	404 (20.7)	0.215
Chronic kidney disease (eGFR < 60 mL/min)	1139 (54.2)	81 (51.9)	1058 (54.3)	0.560
Cerebrovascular disease	288 (13.6)	18 (11.5)	270 (13.8)	0.411
Peripheral artery disease	535 (25.3)	37 (23.6)	498 (25.5)	0.600
STS score, %	6.4 $\pm$ 5.2	7.1 $\pm$ 6.0	6.3 $\pm$ 4.5	0.194
<b>Echocardiographic findings</b>				
Left ventricular ejection fraction, %	53.1 $\pm$ 12.8	56.4 $\pm$ 10.0	52.9 $\pm$ 12.9	<b>&lt;0.001</b>
Left ventricular ejection fraction $\leq$ 50%	714 (33.8)	34 (21.7)	680 (34.8)	<b>0.001</b>
Mean transaortic gradient, mm Hg	45.0 $\pm$ 17.0	49.4 $\pm$ 18.5	44.7 $\pm$ 16.7	<b>0.001</b>
Mean transmitral gradient, mm Hg	3.8 $\pm$ 2.5	7.2 $\pm$ 2.8	2.7 $\pm$ 1.1	<b>&lt;0.001</b>
Transmitral gradient $\geq$ 10 mm Hg	–	22 (14%)	–	–
Mitral valve area, cm <sup>2</sup>	–	1.5 $\pm$ 0.5	–	–
sPAP > 60 mm Hg	223 (12.5)	28 (17.8)	198 (12.1)	<b>0.017</b>
<b>Procedural findings</b>				
Primary access				0.609
Transfemoral	1443 (68.3)	113 (72.0)	1330 (68.0)	
Transapical	418 (19.8)	27 (17.2)	391 (20.0)	
Transaortic	84 (4.0)	6 (3.8)	78 (4.0)	
Transcarotid	89 (4.2)	7 (4.5)	82 (4.2)	
Valve type				0.447
Self-expandable	630 (29.8)	51 (32.5)	579 (29.6)	
Balloon-expandable	1483 (70.2)	106 (67.5)	1377 (70.4)	
Implantation success (VARC-2)	1912 (91.2)	144 (92.3)	1768 (91.1)	0.605
Median length of stay, days (IQR)	7 (5–9)	7 (5–10)	6 (5–9)	0.739

Values are n (%) or mean  $\pm$  SD.

Bold emphasis correspond to values lower than 0.05.

**Table 2**  
30-day and cumulative outcomes, according to presence of moderate to severe mitral stenosis.

Variables	MS (n = 157)	No MS (n = 1956)	OR/HR (95%CI)	p value	Adjusted <sup>a</sup> OR/HR (95%CI)	p value
<b>30-day outcomes</b>						
Death	6 (3.8)	107 (5.5)	0.69 (0.30–1.59)	0.379	0.66 (0.28–1.55)	0.341
Cardiovascular death	5 (3.2)	91 (4.7)	0.67 (0.27–1.68)	0.399	0.66 (0.26–1.66)	0.374
Stroke	8 (5.1)	79 (4.0)	1.28 (0.61–2.69)	0.521	1.25 (0.58–2.68)	0.571
Myocardial infarction	1 (0.6)	36 (1.8)	0.34 (0.05–2.51)	0.291	0.28 (0.04–2.07)	0.211
New pacemaker	23 (14.6)	323 (16.5)	0.87 (0.55–1.37)	0.544	0.91 (0.57–1.46)	0.701
Major/life threatening bleeding	17 (10.8)	336 (17.2)	0.70 (0.43–1.13)	0.143	0.67 (0.41–1.10)	0.114
<b>Echo data post-TAVR</b>						
LVEF, %	56.4 ± 11.2	53.5 ± 11.7	–	0.004	–	0.557
Mean transaortic gradient, mm Hg	11.8 ± 6.6	11.4 ± 6.3	–	0.496	–	0.880
Moderate to severe AR	6 (5.9)	23 (4.9)	1.17 (0.62–2.23)	0.630	1.13 (0.75–1.50)	0.721
Mean transmitral gradient, mm Hg	7.0 ± 3.4	–	–	–	–	–
Mitral valve area, cm <sup>2</sup>	1.5 ± 0.4	–	–	–	–	–
<b>Cumulative outcomes</b>						
Death	55 (35.0)	707 (36.2)	0.95 (0.72–1.25)	0.722	1.14 (0.86–1.51)	0.372
Cardiovascular death	33 (21.0)	438 (22.4)	1.00 (0.70–1.43)	0.989	1.09 (0.76–1.57)	0.631
Heart failure death	13 (8.3)	141 (7.2)	1.22 (0.69–2.16)	0.496	1.54 (0.85–2.77)	0.151
Sudden cardiac death	2 (1.3)	76 (3.9)	0.35 (0.09–1.42)	0.142	0.38 (0.09–1.57)	0.179
Stroke	9 (5.7)	133 (6.8)	0.87 (0.44–1.71)	0.871	0.86 (0.43–1.71)	0.668
Myocardial infarction	6 (3.8)	103 (5.3)	0.74 (0.33–1.69)	0.474	0.73 (0.32–1.69)	0.733
New pacemaker	27 (17.2)	362 (18.5)	0.94 (0.64–1.39)	0.756	1.02 (0.69–1.53)	0.909
Hospitalization for heart failure	33 (21.0)	425 (21.7)	0.99 (0.69–1.41)	0.947	1.16 (0.81–1.67)	0.419

Values are n (%) or mean ± SD.

<sup>a</sup> Adjusted for baseline differences between groups.

cardiovascular causes, and 458 (21.7%) patients had at least one rehospitalization due to heart failure. Late clinical outcomes grouped according to the presence of MS are shown in Table 2. There were no differences between groups in late mortality (MS: 35.0%, no MS: 36.2%, adjusted HR: 1.14, 95% CI: 0.86–1.51), cardiovascular mortality (MS: 21.0%, no MS: 22.4%; adjusted HR: 1.09, 95% CI: 0.76–1.57) or heart failure rehospitalization (MS: 21%, no MS: 21.7%; HR: 1.16, 95% CI: 0.81–1.67). The Kaplan-Meier curves for clinical events (overall mortality, cardiovascular mortality, stroke and hospitalization for heart failure) up to 5-year follow-up are shown in Fig. 1. No patient underwent any intervention for treating MS at follow-up.

The NYHA functional class at baseline and at 1-year follow-up according to the presence of MS is shown in Fig. 2A. Most patients in both (MS and no MS) groups improved their functional class ( $p < 0.001$  for both), and there were no differences at follow-up in NYHA class between groups (NYHA I–II in 85% and 88% of patients in the MS and no MS groups, respectively, adjusted  $p = 0.20$ ). Exercise capacity data as evaluated by 6MWT was available in 723 patients at baseline and 340 patients at 6- to 12-month follow-up (23 and 317 patients with and without MS). There were no differences in baseline 6MWT distance between groups ( $p = 0.39$ ), and a similar degree of improvement in exercise capacity was observed in MS and no MS patients (adjusted  $p = 0.52$  for changes in 6MWT distance over time between groups) (Fig. 2B).

Echocardiographic data at 1-year follow-up were available in 79 patients among those with baseline MS (82% of the patients at risk at 1-year follow-up). In patients with baseline MS, there were no significant changes in the severity of MS at follow-up (mean transvalvular gradient:  $7.5 \pm 2.4$  mm Hg,  $p = 0.94$  vs. baseline; mitral valve area:  $1.5 \pm 0.4$  cm<sup>2</sup>,  $p = 0.68$  vs. baseline values). The pulmonary artery pressure decreased after TAVR in both groups (no MS group:  $40.9 \pm 13.8$  vs.  $44.5 \pm 14.6$  mm Hg,  $p < 0.001$  and MS group:  $44.8 \pm 13.4$  mm Hg vs.  $48.3 \pm 14.5$  mm Hg,  $p = 0.04$ ). At one-year post-TAVR, the pulmonary artery pressure continued to decrease in the no MS group ( $36.0 \pm 14.7$  vs.  $44.8 \pm 14.6$  mm Hg,  $p < 0.001$ ) but remained stable in the MS group ( $46.3 \pm 14.6$  vs.  $48.3 \pm 14.5$  mm Hg,  $p = 0.379$ ).

Twenty-two patients (14% of the patients with MS) had a mean transmitral gradient  $\geq 10$  mm Hg (mean transmitral gradient  $12.4 \pm$

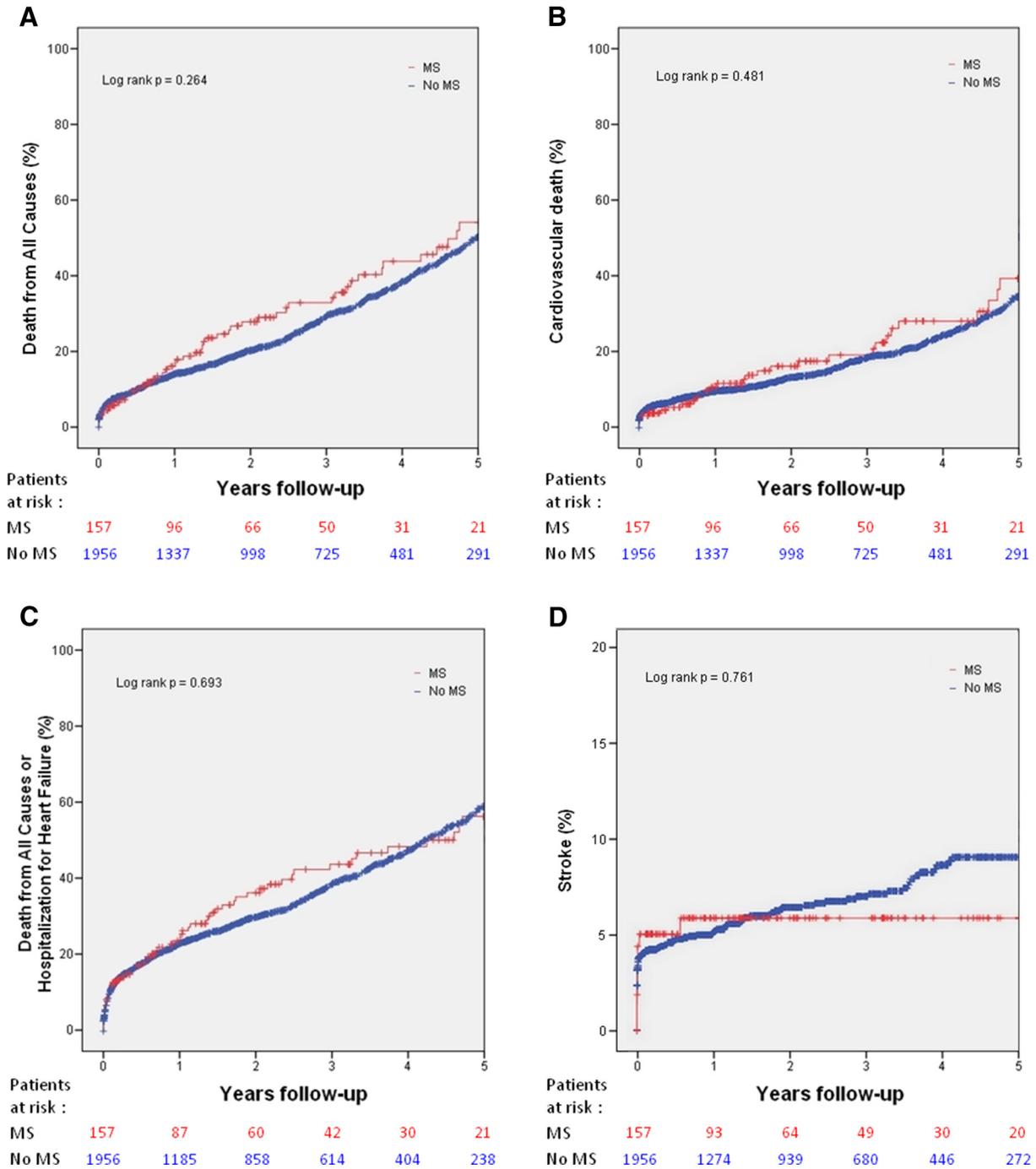
$3.5$  mm Hg; mean mitral valve area  $1.36 \pm 0.50$  cm<sup>2</sup>) without severe MR at baseline echocardiography. Despite a trend to a higher rate of rehospitalization for heart failure in patients with mean transmitral gradient  $\geq 10$  mm Hg, the main early and late outcomes of these patients compared to the rest of the study population were similar (Supplementary Table).

#### 4. Discussion

About 7% of patients undergoing TAVR had concomitant moderate to severe MS, mainly of degenerative origin. Moderate to severe MS was not associated with poorer early and late outcomes in TAVR recipients, and patients with MS exhibited similar rates of global and cardiac mortality and heart failure rehospitalization after a mean follow-up of 3 years. In addition, significant improvements in functional status and exercise capacity were observed among patients with MS, similar to those seen in non-MS patients. These data support TAVR without mitral valve intervention as a safe and effective therapy in intermediate-to-high risk aortic stenosis patients with MS. In elderly patients with AS, some degree of mitral annular calcification is frequent, and this may explain the relatively high rate of moderate to severe MS (close to 1 out of 10 patients) observed in our study. Abramowitz et al. [11] showed that about half of the TAVR recipients exhibited some degree of mitral annular calcification, which in turn may lead to some degree of MS. This would also explain the fact that MS was of degenerative origin in the vast majority of patients, with only a minority of patients exhibiting MS of rheumatic etiology.

In a study of 101 patients with degenerative aortic stenosis, 24% were reported to have a mitral valve area (MVA)  $< 1.5$  cm<sup>2</sup> on 3D transoesophageal echocardiography [12]. Thus, the prevalence of mitral stenosis in our population does not appear to be overestimated.

The echocardiographic diagnosis of degenerative mitral stenosis can be challenging, due to calcification of the mitral annulus that extends into the leaflets causing both a narrowing of the annulus and rigidity of the leaflets without commissural fusion [13,14]. Although the choice of mean transmitral gradient as screening criteria (rather than mitral valve area) can be criticized, accurately calculating mitral valve area by transthoracic echocardiography is technically challenging in degenerative mitral valve disease because of the orifice geometry and the presence of calcification,

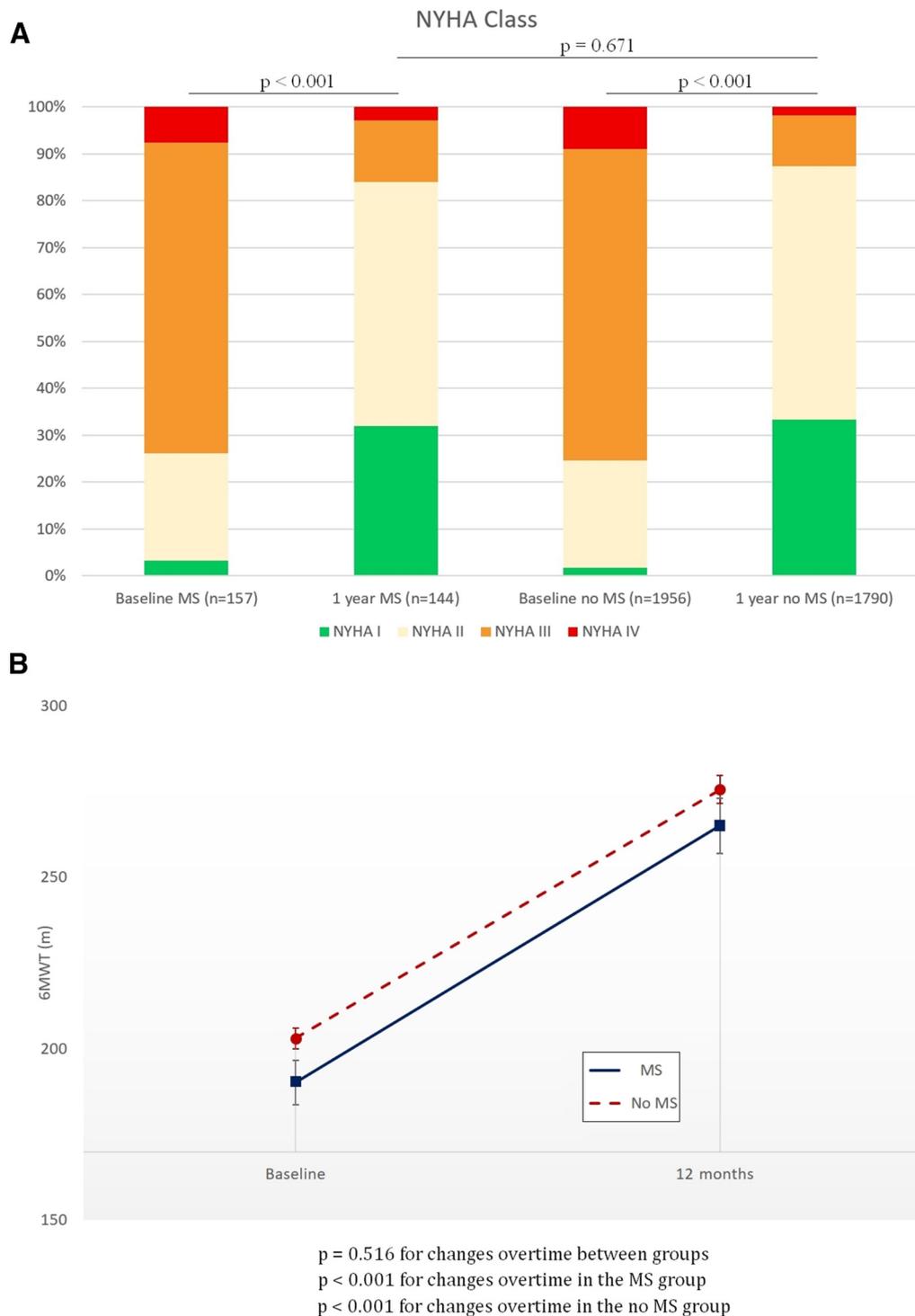


**Fig. 1.** Clinical events at 5-year follow-up, according to moderate to severe MS. (A) Kaplan-Meier curves at 5-year follow-up for overall mortality according to the presence of moderate to severe mitral stenosis (MS). (B) Kaplan-Meier curves at 5-year follow-up for cardiovascular mortality according to the presence of moderate to severe mitral stenosis (MS). (C) Kaplan-Meier curves at 5-year follow-up for overall mortality or hospitalization for heart failure according to the presence of moderate to severe mitral stenosis (MS). (D) Kaplan-Meier curves at 5-year follow-up for stroke according to the presence of moderate to severe mitral stenosis (MS).

whereas the mean gradient can be directly measured with less chance of error. Also, Bouleti et al. found that, in patients with MS undergoing percutaneous commissurotomy for mitral restenosis, the only independent postprocedural variable predicting late functional results was the residual mitral gradient, whereas the prognostic impact of mitral valve area decreased in older patients and was no longer significant after 70 years of age [15]. Likewise, several studies confirmed superior prognostic value of mitral gradient in patients with rheumatic MS [16,17].

The presence of significant multivalvular disease remains an unresolved issue among TAVR candidates. The fact that significant disease

in other valves (particularly mitral, tricuspid) remains untreated at the time of the TAVR procedure highlights the dilemma about whether a surgical approach should be the preferred strategy in multivalvular disease patients without prohibitive surgical risk. In the recent European Society of Cardiology Guidelines [7], TAVR is the recommended treatment for intermediate and high surgical risk patients with severe AS, but a surgical approach is still recommended among those patients with significant mitral disease. While this approach has been frequently evaluated among patients with concomitant MR, data on patients with AS and MS are scarce. Vassileva et al. [18] showed that among patients



**Fig. 2.** Functional status and changes in the 6MWT distance following TAVR, according to the presence of concomitant MS. (A) Functional status as evaluated by NYHA class. (B) Changes in the 6MWT distance following TAVR.

with moderate to severe MS undergoing SAVR, those who had mitral valve replacement at the time of surgery exhibited improved long-term outcomes, despite a much higher perioperative mortality as compared to isolated SAVR. However, the fact that degenerative MS in the elderly is frequently associated with significant calcification of the mitral annulus may indeed complicate the surgical treatment and further increase the perioperative risk of these patients [19–21]. This also applies to transcatheter mitral therapies. The progressive calcification from the leaflet base without commissural fusion, unlike rheumatismal MS, significantly contra-indicates percutaneous mitral valve

commissurotomy [7]. More recently, transcatheter mitral valve replacement using transcatheter aortic valve platforms has emerged as an alternative therapy in such patients, but the periprocedural complications and mortality rates remain very high [22], precluding the systematic application of this treatment to patients with MS undergoing TAVR. Therefore, the results of the present study showing the lack of negative clinical impact of moderate to severe MS on early and late clinical outcomes post-TAVR are of high clinical relevance. Also, the severity of MS remained stable following TAVR, and most patients improved their functional status and exercise capacity post-TAVR,

similarly to their non-MS counterparts. These patients however, should undergo a systematic clinical and echocardiographic follow-up evaluation, and percutaneous treatment considered in the absence of functional status improvement and/or progression of MS.

There is few information about the natural history of degenerative mitral stenosis. However, prior data suggested a slow evolution of degenerative mitral stenosis outside the TAVR field. A small study of 32 patients with severe MAC [23] demonstrated progression in mean mitral valve gradient in only half of the subjects after a mean follow-up of about 3 years. Although a fast progression was found in younger patients, mean mitral valve gradient progressed on average by 0.6 mm Hg/year in this population. Conversely, Bouleti et al. showed that valve calcification was strongly associated with poor late results and lower rate survival after percutaneous mitral commissurotomy compared to noncalcified valves in patients with rheumatic MS. However, survival rate was close to 50% at 20-year follow-up in the cohort of patients remaining with residual moderate to severe MS over the follow-up period [24]. Amat-Santos et al. [25] assessed outcomes of 91 patients with previous prosthetic mitral valves undergoing TAVR. In this population, mean mitral transprosthetic gradient was about 5 mm Hg, and several patients had moderate to severe MS on baseline echocardiography. No differences in cumulative mortality rate were found according to the presence of a prosthetic mitral valve after a median follow-up period of 5 years. These cohorts showing good evolution of patients with moderate to severe mitral stenosis and mean mitral gradient  $\geq 5$  mm Hg support and reinforce our results.

#### 4.1. Limitations

Given the nonrandomized nature of the study, and despite the adjusted analyses for comparing MS and no MS patients, the presence of unmeasured confounders that may have influenced the results cannot be completely rule out. Three-dimensional planimetry using transesophageal echocardiography (TEE) in order to further confirm the diagnosis of MS was not systematically performed. Echocardiographic findings were interpreted at each center, without core laboratory evaluation. Finally, the number of patients with transmitral gradient  $\geq 10$  mm Hg was limited, and future studies will be needed to further determine the clinical outcomes post-TAVR in this subgroup of patients.

In conclusion, close to 1 out of 10 patients undergoing TAVR had concomitant moderate to severe MS, mainly of degenerative origin. However, this entity was not associated with poorer clinical outcomes at mid-term follow-up, and MS patients experienced similar improvements in functional status and exercise capacity. These results support TAVR as the treatment of these patients and should be considered in the clinical decision-making process of intermediate or high-risk patients with severe AS and concomitant MS. Future studies will have to determine the role of transcatheter mitral valve interventions in those patients remaining highly symptomatic post-TAVR.

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.ijcard.2019.03.053>.

#### Acknowledgments

Dr. Rodés-Cabau holds the Research Chair “Fondation Famille Jacques Larivière” for the Development of Structural Heart Disease Interventions.

#### Funding

There was no specific funding for this work.

#### Conflict of interest

Dr. Rodés-Cabau has received research grants from Edwards Lifesciences and Medtronic. Dr. Himbert is a consultant for Edwards

Lifesciences; and has served as a proctor for Edwards Lifesciences and Medtronic. Pr. Lung received speaker's fees from Edwards Lifesciences. Other authors report no relationships that could be construed as a conflict of interest.

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