Circulation

ORIGINAL RESEARCH ARTICLE

Hemodynamics and Prognostic Impact of Concomitant Mitral Stenosis in Patients Undergoing Surgical or Transcatheter Aortic Valve Replacement for Aortic Stenosis

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BACKGROUND: Mitral stenosis frequently coexists in patients with severe aortic stenosis. Mitral stenosis severity evaluation is challenging in the setting of combined aortic stenosis and mitral stenosis because of hemodynamic interactions between the 2 valve lesions. The impact of aortic valve replacement (AVR) for severe aortic stenosis on mitral stenosis is unknown. This study aimed to assess the effect of AVR on mitral stenosis hemodynamics and the clinical outcomes of patients with severe aortic stenosis with and without mitral stenosis.

METHODS: We retrospectively investigated patients who underwent surgical AVR or transcatheter AVR for severe aortic stenosis from 2008 to 2015. Mean transmitral gradient by Doppler echocardiography ≥4 mm Hg was identified as mitral stenosis; patients were then stratified according to mitral valve area (MVA, by continuity equation) as >2.0 cm^2 or ≤2.0 cm^2. MVA before and after AVR in patients with mitral stenosis were evaluated. Clinical outcomes of patients with and without mitral stenosis were compared using 1:2 matching for age, sex, left ventricular ejection fraction, method of AVR (surgical AVR versus transcatheter AVR) and year of AVR.

RESULTS: Of 190 patients with severe aortic stenosis and mitral stenosis (age 76±9 years, 42% men), 184 were matched with 362 with severe aortic stenosis without mitral stenosis. Among all mitral stenosis patients, the mean MVA increased after AVR by 0.26±0.59 cm^2 (from 2.00±0.50 to 2.26±0.62 cm^2, $P<0.01$). MVA increased in 105 (55%) and remained unchanged in 34 (18%). Indexed stroke volume ≤45 mL/m^2 (odds ratio [OR] 2.40; 95% CI, 1.15–5.01; $P=0.020$) and transcatheter AVR (OR, 2.36; 95% CI, 1.17–4.77; $P=0.017$) were independently associated with increase in MVA. Of 107 with significant mitral stenosis (MVA ≤2.0 cm^2), MVA increased to >2.0 cm^2 after AVR in 52 (49%, pseudo mitral stenosis) and remained ≤2.0 cm^2 in 55 (51%, true mitral stenosis). During follow-up of median 2.9 (0.7–4.9) years, true mitral stenosis was an independent predictor of all-cause mortality (adjusted hazard ratio, 1.88; 95% CI, 1.20–2.94; $P<0.01$).

CONCLUSIONS: MVA improved after AVR in nearly half of patients with severe aortic stenosis and mitral stenosis. MVA remained ≤2.0 cm^2 (true mitral stenosis) in nearly half of patients with severe aortic stenosis and significant mitral stenosis; this was associated with worse survival among patients undergoing AVR for severe aortic stenosis.

Key Words: aortic stenosis ■ aortic valve replacement ■ echocardiography ■ mitral stenosis

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Clinical Perspective

What Is New?

- In half of patients with severe aortic stenosis and transmitral gradient ≥4mm Hg, mitral stenosis severity was overestimated; overestimation was more common with lower indexed stroke volume.
- Mitral valve area (MVA) increased to >2.0 cm^2 after aortic valve replacement (AVR) in half of patients with aortic stenosis and MVA ≤2.0 cm^2 before AVR (pseudo mitral stenosis), whereas MVA remained ≤2.0cm^2 after AVR in the others (true mitral stenosis).
- True mitral stenosis was associated with higher mortality compared with absence of mitral stenosis.

What Are the Clinical Implications?

- Mitral stenosis severity should be carefully assessed in the setting of severe aortic stenosis; mitral stenosis severity can be overestimated, but patients with true mitral stenosis may require more careful follow-up.
- MVA ≤1.5 cm^2, MAD ≤1 mm or extension of calcification to both anterior and posterior mitral leaflets suggested the presence of true MS.
- Future studies need to determine whether AVR with concomitant mitral valve replacement improves the prognosis in patients with severe aortic stenosis and true mitral stenosis.

Elevated transmitral gradient (TMG) is frequently observed during transthoracic echocardiography (TTE) in patients with aortic stenosis, a hint toward the likely presence of concomitant mitral stenosis. Mitral stenosis is present in about 15% of patients with aortic stenosis.[1,2] It is notable that mitral annulus calcification (MAC) coexists in about 50% of adults with severe aortic stenosis.[3–6] The prevalence of calcific mitral stenosis increases dramatically with age and aortic stenosis.[7,8] The management of combined aortic stenosis and calcific mitral stenosis is challenging because these patients are typically frail, elderly, and present with multiple comorbidities. Transcatheter interventions for valvular heart diseases have provided treatment options for patients at high risk for surgery.[9–11] Consequently, accurate preprocedural identification of the presence of a combined valve disease, such as concomitant mitral stenosis with aortic stenosis, has received increased attention.[1,12] Mitral stenosis should not be overlooked in patients with severe aortic stenosis because severe mitral stenosis is an independent predictor of 1-year adverse clinical outcomes after transcatheter aortic valve replacement (TAVR).[1]

The presence of combined aortic stenosis and mitral stenosis complicates evaluation of the severity of each individual lesion because of hemodynamic interactions between the two lesions. Alteration of mitral valve hemodynamics after isolated aortic valve replacement (AVR) can be useful for understanding the pathophysiology and prognosis of combined aortic stenosis and mitral stenosis. Thus, this study aimed to (1) assess the effects of AVR on mitral stenosis severity based on MVA calculation using the continuity equation by Doppler echocardiography; and (2) compare clinical outcomes of patients with severe aortic stenosis, with and without mitral stenosis, undergoing either surgical AVR (SAVR) or TAVR.

METHODS

The authors declare that all supporting data are available in the article and its online supplementary files.

Study Population

We retrospectively investigated patients who underwent SAVR or TAVR for severe aortic stenosis from 2008 to 2015 at 2 medical centers: Mayo Clinic, Minnesota, USA; and Tokyo Bay Urayasu/Ichikawa Medical Center, Japan. Patients with mitral stenosis, defined as an elevated TMG ≥4 mm Hg at baseline (pre-AVR) TTE, were included. Excluded were patients with prior aortic or mitral valve surgery (repair or replacement), congenital heart disease, and hypertrophic obstructive cardiomyopathy. Patients with heart rate ≥100 bpm or moderate or greater mitral regurgitation or aortic regurgitation were also excluded because of the challenges of assessing the degree of mitral stenosis in these situations.[13] Patients with severe aortic stenosis without mitral stenosis who underwent AVR were selected as a control group using 1:2 matching for age, gender, left ventricular ejection fraction, method of AVR (SAVR versus TAVR) and year of AVR. All patients underwent TTE within 30 days of AVR. Baseline demographic data and surgical and outcome data were extracted from the electronic medical record.

The Mayo Clinic Institutional Review Board approved the study, and research authorization was obtained from all patients. The Tokyo Bay Urayasu/Ichikawa Medical Center Human Ethics Committee approved the study, and informed consent regarding participation was obtained from all patients.

Transthoracic Echocardiography

TTE was performed using commercially available state-of-the-art ultrasound machines. Comprehensive TTE including aortic and mitral stenosis assessments were performed according to guidelines.[13–15] Aortic stenosis was evaluated using a multiwindow approach, and aortic valve area (AVA) was calculated using the continuity equation. Severe aortic stenosis was defined as an AVA ≤1.0 cm^2, indexed AVA ≤0.6 cm^2, peak velocity ≥4.0 m/s or mean gradient ≥40 mm Hg.[13] TMG and mitral valve time-velocity integral were derived from transmitral flow velocity waveform recorded by continuous

wave Doppler. MVA was calculated using the continuity equation as the ratio of stroke volume to mitral valve time-velocity integral. Significant mitral stenosis was defined as MVA ≤2.0cm^2 and mild mitral stenosis as MVA >2.0 cm^2.[7] Similarly, the severity of mitral regurgitation, aortic regurgitation, and tricuspid regurgitation were assessed using an integrated approach according to guideline recommendations.[15] Right ventricular systolic pressure was estimated from peak tricuspid valve regurgitant jet velocity, using the simplified Bernoulli equation and combining this value with an estimate of the right atrial pressure.[16]

The increase or decrease in MVA after AVR was considered significant when it changed ≥0.1 cm^2, on the basis of previous work,[17] and the increase or decrease in TMG was considered significant when it changed ≥1 mm Hg. In patients with significant mitral stenosis at pre-AVR TTE, true mitral stenosis was present if MVA remained ≤2.0 cm^2 at post-AVR TTE and pseudo mitral stenosis if MVA increased to >2.0 cm^2 at post-AVR TTE.

Rheumatic mitral stenosis was defined echocardiographically when typical features such as leaflet thickening, nodularity, commissural fusion and chordal fusion and shortening were present. Calcific mitral stenosis was defined as the presence of a bright echo-producing structure (calcification) located at the mitral annulus and mitral leaflets. MAC was defined as the presence of dense calcium deposits at the base of mitral leaflets between the left atrium and ventricle.[18,19] The extension of calcification to both anterior and posterior mitral leaflets was evaluated from parasternal long axis view.[20] Mitral annulus diameter was measured in parasternal long axis view at end diastole and end systole. Mitral annulus distension (MAD) was calculated by the difference between mitral annulus diameter at end diastole and end systole in the parasternal long axis view as a means of assessing the degree of mitral inflow obstruction from calcification. Comprehensive transthoracic echocardiography was performed by multiple sonographers according to usual clinical practice, and data were reviewed by an experienced level 3 trained echocardiographer before patient dismissal from the laboratory. Two similarly trained investigators analyzed additional data.

Follow-Up and Outcome

The endpoint was all-cause mortality during follow-up. Perioperative events occurring within the same hospitalization or 30 days after AVR (all-cause death, aortic valve reintervention, myocardial infarction, stroke, renal failure, bleeding, need for permanent pacemaker, and new onset atrial fibrillation) were recorded. The latest TTE during follow-up was selected as the follow-up TTE. If follow-up TTE was not performed, post-AVR TTE was used to assess mitral stenosis severity during follow-up. The timing of clinical follow-up assessment varied according to clinical judgment.

Statistical Analysis

Continuous data are expressed as mean±SD or median [interquartile range] and categorical data are expressed as frequency or percentage. Continuous variables were compared between groups using the Student *t* test or Wilcoxon rank-sum test whenever appropriate. Nominal variables were compared between groups using chi-square test. Pre- and postoperative measurements were compared using a paired *t* test and McNemar test. Matching was done using a greedy matching algorithm. Each patient with mitral stenosis was matched to 1–2 patients without mitral stenosis on age, gender, left ventricular ejection fraction, method of AVR, and year of AVR. Gender and method of AVR were required to be an exact match while age could differ by 5 years, left ventricular ejection fraction by 10%, and year of AVR by 2 years. Most subjects were matched much closer than these limits. Survival analysis was performed by the Kaplan–Meier method and log-rank test. Cox proportional hazards modeling was used to identify independent predictors for all-cause mortality; variables that showed statistically significant differences between groups in the univariable analysis were included in the model. Results of these analyses are shown as hazard ratios (HRs) and 95% CIs. The proportional hazard assumption was evaluated both visually by plotting residuals versus time and formally by testing for a correlation between residual and time. No violations of the proportional hazard assumption were observed. A multivariable logistic regression analysis was performed to assess independent predictors of increase in MVA after AVR; variables that showed statistically significant differences between groups in the univariable analysis were included in the model. Receiver operating characteristics curve analysis was used to assess the accuracy of variables for identifying true mitral stenosis and the area under the curve was presented. Areas under the curve were compared using the method of DeLong and DeLong. Youden index was used to assess the optimal cutoff value. Tests were 2-sided, and $P<0.05$ was considered statistically significant. All statistical analysis was performed using JMP Pro 13 and SAS version 9.4 (SAS Institute, Cary, North Carolina).

RESULTS

Patient Characteristics

We included 190 patients with severe aortic stenosis and concomitant mitral stenosis (185 from Mayo Clinic and 5 from Tokyo Bay Medical Center). Age was 76±9 years, 42% were male, 31% underwent TAVR, and 107 (56%) had significant mitral stenosis. Of 190 with mitral stenosis, 184 patients could be matched with 362 control patients with severe aortic stenosis without mitral stenosis. Characteristics of patients with severe aortic stenosis with and without mitral stenosis are shown in Table 1. Patients with concomitant mitral stenosis more frequently had a history of diabetes, dialysis, chronic lung disease, and chest irradiation compared with controls. Frequency of atrial fibrillation was similar between the 2 groups. There were no significant differences in aortic peak velocity, mean transaortic gradient, or AVA. Left atrial volume index was larger (47±14 versus 44±13 mL/m^2, $P<0.01$) and right ventricular systolic pressure was higher (41 [31–51] versus 34 [28–41] mm Hg, $P<0.01$) in patients with mitral stenosis.

Hemodynamic Assessment of Mitral Valve Before and After AVR

The hemodynamic changes after AVR in 190 patients with mitral stenosis are shown in Table 2. TTE was performed at a median of 32 [9–65] days before AVR and 4 [3–5] days after AVR. The etiology of mitral stenosis was calcific in 185 (97%) and rheumatic in 5 (3%). The mean MVA increased after AVR by 0.26±0.59 cm^2 (from 2.00±0.50 to 2.26±0.62 cm^2, P<0.01). The mean TMG decreased after AVR from 5.2±1.5 to 4.7±1.9 mm Hg (P<0.01). MVA increased after AVR in 105 (55%) patients, remained unchanged in 34 (18%) and decreased in 51 (27%). In 105 with increased MVA, the mean TMG decreased from 5.2±1.5 to 4.5±1.8 mm Hg (P<0.01). TMG decreased after AVR in 94 (49%), remained unchanged in 57 (30%), and increased in 39 (21%). Indexed stroke volume ≤45mL/m^2 (odds ratio [OR] 2.40; 95% CI,1.15–5.01; P=0.020) and TAVR (OR, 2.36; 95% CI, 1.17–4.77; P=0.017) were independently associated with increase in MVA after AVR as shown in Table 3. MVA at baseline tended to be associated with improvement in MVA (OR, 0.49; 95% CI, 0.21–1.28; P=0.088). Area under the curve of this multivariable model was 0.72.

The hemodynamic changes according to the method of AVR are shown in Table I in the online-only Data Supplement. In 58 patients undergoing TAVR, the mean MVA increased by 0.42±0.55 cm^2 (1.96±0.50 to 2.38±0.64 cm^2, P<0.01). The mean stroke volume and indexed stroke volume markedly increased after TAVR (stroke volume: 86±15 to 97±19 mL, P<0.01; index stroke volume: 45±8.0 to 51±11 mL/m^2, P<0.01). In 132 patients undergoing SAVR, the mean MVA increased by 0.19±0.59 cm^2 (2.02±0.50 to 2.21±0.60 cm^2, P<0.01), but the mean stroke volume and indexed stroke volume did not significantly change.

Of 51 patients with decreased MVA after AVR, indexed stroke volume decreased in 40 and heart rate decreased in 11; decreases were related to the decrease in transmitral flow rate. Of 39 patients with increased TMG, heart rate increased in 34 and indexed stroke volume increased in 4; in 1 patient with normal left ventricle size and heavy calcification of the mitral valve, MVA decreased after TAVR using a 31-mm self-expandable valve.

True Mitral Stenosis

Stroke volume and indexed stroke volume were lower before AVR in patients with significant mitral stenosis (MVA ≤2 cm^2) compared with those with mild mitral stenosis (stroke volume: 82±15 versus 99±20 mL, P<0.01, indexed stroke volume: 44±8 versus 50±10 mL/m^2, P<0.01). Moreover, MVA tended to increase after AVR in patients with small MVA. We further assessed MV hemodynamics in 107 patients with significant mitral stenosis before AVR. Of these patients, MVA increased to >2.0 cm^2 after AVR in 52 (49%, pseudo mitral stenosis) and remained ≤2.0 cm^2 in 55 (51%, true mitral stenosis) as shown in Figure 1. In patients with true mitral stenosis, the mean stroke volume, MVA, and TMG did not significantly change after AVR. In patients with pseudo mitral stenosis, the mean indexed stroke volume increased (44±9 to 51±11 mL/m^2, P<0.01) and the mean MVA increased after AVR by 0.80±0.43 cm^2 (1.72±0.21 to 2.52±0.40 cm^2, P<0.01), and TMG decreased after AVR (5.2±1.4 to 4.3±1.5 mm Hg, P<0.01). Examples of true and pseudo mitral stenosis are shown in Figure 2.

To identify true mitral stenosis among patients with severe aortic stenosis and mitral stenosis, mitral valve hemodynamics and anatomical features at baseline were compared in patients with true mitral stenosis (n=55) and pseudo or mild mitral stenosis (n=135) in Table 4. TMG was higher in patients with true mitral stenosis than pseudo or mild mitral stenosis (6.0±2.0 versus 4.9±1.2 mm Hg, P<0.01). Extension of calcification to mitral leaflets was more frequently observed in patients with true mitral stenosis than pseudo or mild mitral stenosis (18% versus 6%, P<0.01). MAD tended to be smaller in patients with true mitral stenosis. Stroke volume, indexed stroke volume, and AVA were smaller in patients with true mitral stenosis than pseudo or mild mitral stenosis (82±16 versus 92±20 mL, P<0.01, 45±8 versus 48±10 mL/m^2, P=0.062, and 0.73±0.15 versus 0.82±0.16 cm^2, P<0.01, respectively). TAVR was performed in 16 (28%) of patients with true mitral stenosis and 39 (30%) of those with pseudo or mild mitral stenosis (P=0.78). The other characteristics listed in Table 1 were similar in patients with true mitral stenosis and pseudo or mild mitral stenosis

Area under the curve of MVA for identifying true mitral stenosis (0.86; 95% CI, 0.80–0.90) was higher than TMG (0.70; 95% CI, 0.61–0.77, versus MVA P<0.01) and MAD (0.57; 95% CI, 0.48–0.65, versus MVA P<0.01). MVA ≤1.9cm^2 best identified true mitral stenosis (sensitivity, 93%; specificity, 73%; accuracy, 78%). The sensitivity, specificity, and accuracy of other variables were, respectively, 36%, 95%, and 77%, for MVA ≤1.5cm^2; 80%, 50%, and 58%, for TMG ≥5mm Hg; 22%, 86%, and 65%, for MAD ≤1 mm; and 18%, 94%, and 72%, for extension of calcification to mitral leaflets.

Clinical Outcomes and Perioperative Events

Clinical outcomes were compared among the 3 groups with severe aortic stenosis: true mitral stenosis, pseudo or mild mitral stenosis, and controls. Perioperative all-cause mortality was similar (1.9%, 0.8%, and 2.2%,

Table 1. Patient Characteristics

Clinical and echocardiographic characteristics	All Mitral Stenosis (n=190)	Case-Matched Comparison		
		Mitral Stenosis (n=184)	Controls (n=362)	*P* Value
Age, y	76±9	77±9	77±9	0.96
Male	80 (42)	76 (41)	150 (41)	0.98
Body mass index, kg/m^2	30 [26–35]	30 [26–35]	29 [25–32]	<0.01*
New York Heart Association Class III or IV	134 (71)	128 (70)	220 (61)	0.043*
Diabetes mellitus	83 (44)	80 (43)	91 (25)	<0.01*
Dyslipidemia	161 (85)	155 (84)	311 (86)	0.60
Hypertension	163 (86)	159 (86)	302 (83)	0.36
Atrial fibrillation	39 (21)	38 (21)	59 (16)	0.21
Creatinine, mg/dL	1.1 [0.9–1.4]	1.1 [0.9–1.4]	1.0 [0.8–1.2]	0.12
Dialysis	9 (4.7)	9 (4.9)	5 (1.4)	0.014*
Chronic lung diseases	78 (41)	74 (40)	104 (29)	<0.01*
Cerebral vascular diseases	54 (28)	53 (29)	89 (25)	0.29
Chest irradiation	11 (5.8)	9 (4.9)	4 (1.1)	<0.01*
Previous myocardial infarction	30 (16)	28 (15)	60 (17)	0.68
Previous coronary artery bypass graft	26 (14)	25 (14)	59 (16)	0.41
Surgical details				
Transcatheter aortic valve replacement	58 (31)	55 (30)	106 (29)	0.88
Concomitant coronary artery bypass graft	43 (23)	41 (22)	87 (24)	0.65
Concomitant tricuspid valve surgery	3 (1.6)	3 (1.6)	4 (1.4)	0.86
Echocardiography at baseline				
Left ventricular ejection fraction, %	63±10	63±10	63±9	0.84
Left ventricular end diastolic diameter, mm	48±6.5	48±6.3	48±5.5	0.25
Left ventricular end systolic diameter, mm	31±6.9	30±6.8	31±5.8	0.88
Left ventricular mass, g	227±59	227±58	222±63	0.35
Left atrial volume index, mL/m^2	49±14	49±14	44±13	<0.01*
Stroke volume, mL	89±19	89±19	93±19	0.068
Indexed stroke volume, mL/m^2	47±10	47±9	49±10	0.012*
Aortic valve				
Peak velocity, m/s	4.6±0.6	4.6±0.6	4.6±0.5	0.68
Mean pressure gradient, mmHg	54±14	54±14	53±13	0.45
Aortic valve area, cm^2	0.79±0.16	0.79±0.16	0.81±0.18	0.19
Moderate or greater tricuspid regurgitation	14 (7.4)	13 (7.1)	15 (4.1)	0.14
Right ventricular systolic pressure, mmHg	41 [30–50]	41 [31–50]	34 [28–41]	<0.01*

Data shown are mean±SD, median [interquartile range], or n (%).
*P<0.05 mitral stenosis vs controls.

respectively, P=0.40). Patients with pseudo or mild mitral stenosis more frequently needed permanent pacemaker as shown in Table 5. During the median follow-up period of 2.9 [0.7–4.9] years, 196 patients (36%) died, including 49% (n=26) with true mitral stenosis and 44% (n=58) with pseudo or mild mitral stenosis. Of 184 patients with mitral stenosis, 139 (81%) of the 171 who were alive at 1-year post-AVR TTE were still being followed. Follow-up TTE was performed in 61% of patients with mitral stenosis. Severe mitral stenosis (MVA ≤1.5cm^2) was observed in 18 (34%) of patients with true mitral stenosis (25% after AVR increasing to 34% during follow-up, P=0.025), and it was observed in 9 (7%) of those with pseudo or mild mitral stenosis during follow-up of median 0.9 years [5 days–3 years]. Transcatheter mitral valve replacement for severe mitral stenosis was performed in 2 (4%) with true mitral stenosis, and transcatheter mitral valve replacement for severe mitral regurgitation was performed in 1 (0.8%) with pseudo or mild mitral stenosis (P=0.14). True mitral stenosis and pseudo or mild mitral stenosis were associated with higher mortality compared with controls as

Table 2. Mitral Valve Hemodynamics Before and After Aortic Valve Replacement

Hemodynamic parameters	Before AVR (n=190)	After AVR (n=190)	*P* Value
Heart rate, beats per minute	72±11	75±11	<0.01*
Hemoglobin, g/dL	12.0±1.8	9.7±1.3	<0.01*
Left ventricular ejection fraction, %	63±10	62±8	0.087
Left ventricular end diastolic diameter, mm	48±6	47±7	<0.01*
Left ventricular end systolic diameter, mm	31±7	31±7	0.53
Stroke volume, mL	89±19	91±20	0.16
Indexed stroke volume, mL	47±10	48±11	0.078
Mitral valve			
Mitral valve area, cm^2	2.00±0.50	2.26±0.62	<0.01*
Indexed mitral valve area, cm^2/m^2	1.05±0.26	1.19±0.35	<0.01*
Mitral valve time-velocity integral, cm	46±11	42±10	<0.01*
Transmitral gradient, mmHg	5.2±1.5	4.7±1.9	<0.01*
Aortic valve			
Aortic valve area, cm^2	0.79±0.16	1.98±0.63	<0.01*
Peak velocity, m/s	4.6±0.6	2.5±0.5	<0.01*
Mean pressure gradient, mmHg	54±14	15±6	<0.01*
Moderate or greater tricuspid regurgitation	14 (7)	21 (11)	0.088
Right ventricular systolic pressure, mmHg	41±16	41±12	0.86

Data shown are mean±SD or n (%).
*P<0.05, before versus after aortic valve replacement.

shown in Figure 3 (true mitral stenosis: HR, 2.10; 95% CI, 1.37–3.23, P<0.01; pseudo or mild mitral stenosis: HR, 1.57; 95% CI, 1.14–2.16; P<0.01). Adjusted for variables that showed significant differences in the univariable analysis (age, New York Heart Association class III or IV, atrial fibrillation, creatinine, diabetes, hypertension, cerebrovascular diseases, chronic lung disease, TAVR, and left ventricular ejection fraction at baseline), true mitral stenosis was an independent predictor of mortality (HR, 1.88; 95% CI, 1.20–2.94; P<0.01) as shown in Table II of the online-only Data Supplement. Pseudo or mild mitral stenosis was not an independent predictor of mortality (adjusted HR, 1.38; 95% CI, 0.99–1.91; P=0.053). TAVR was not independently associated with mortality (adjusted HR, 1.19; 95% CI, 0.84–1.69; P=0.33).

DISCUSSION

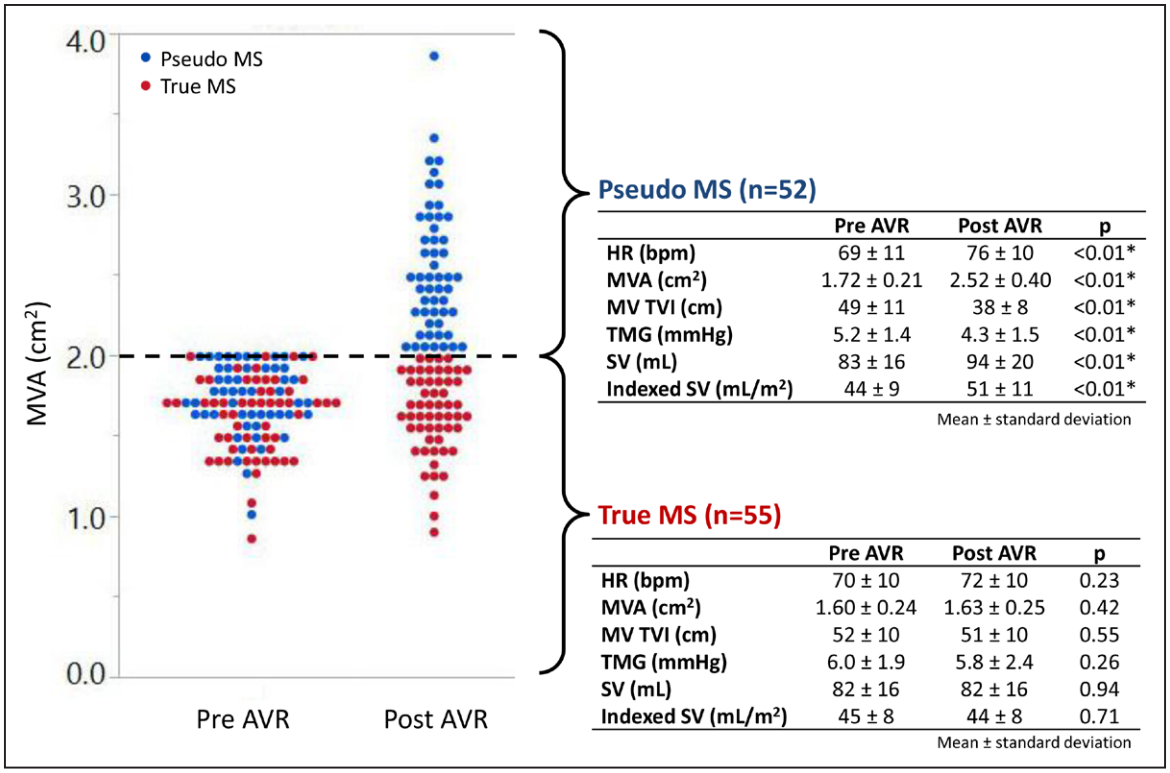
This is the first large study to quantitatively describe changes in MVA after AVR. MVA increased in half of patients with severe aortic stenosis and mitral stenosis. True mitral stenosis (MVA ≤2 cm^2 before and after AVR) was found in nearly half of patients with severe aortic stenosis and significant mitral stenosis and was associated with poorer survival after AVR compared with patients with severe aortic stenosis without mitral stenosis.

Hemodynamic assessment of combined mitral stenosis and aortic stenosis is challenging. The combination of aortic stenosis and mitral stenosis results in a greater reduction of cardiac output than isolated valvular stenosis.[21] The continuity equation is a standard for measuring the effective MVA,[22] but MVA can be flow dependent when the MV is mildly stenotic[23] resulting in overestimation of mitral stenosis in the setting of severe aortic stenosis. Regarding other methods to evaluate MVA, the pressure half-time method is unreliable in the setting of severe aortic stenosis as a result of impaired left ventriclar diastolic function,[13] and the accuracy of planimetry method in calcific mitral stenosis may be impaired by heavy calcification.[2] The continuity equation was the most often performed method to measure MVA in this population. However, our results should be confirmed with an integrated approach including three-dimensional echocardiography in future studies. The postoperative improvement in MVA was mainly related to the finding of reduced indexed stroke volume at pre-AVR TTE. Some patients with low-flow aortic stenosis have been noted to normalize indexed stroke volume at discharge after TAVR;[24] relief from severe aortic stenosis

Table 3. Logistic Regression Analysis for Increase in Mitral Valve Area After Aortic Valve Replacement

	Univariable			Multivariable		
Determinants of increase in mitral valve area	Odds Ratio	95% CI	*P* Value	Odds Ratio	95% CI	*P* Value
Transcatheter aortic valve replacement	2.56	1.32–4.96	<0.01	2.36	1.17–4.77	0.017
Echocardiographic variables before aortic valve replacement						
Indexed stroke volume ≤45 mL/m^2	2.48	1.38–4.47	<0.01	2.40	1.15–5.01	0.020
Mitral valve area per 1 cm^2	0.30	0.15–0.57	<0.01	0.49	0.21–1.13	0.088
Mitral valve time-velocity integral per 1 cm	1.03	1.00–1.06	0.035	1.03	0.99–1.07	0.19

The area under the curve was 0.72. Also considered in the univariable analysis—but not significant—were age, sex, New York Heart Association class, creatinine, atrial fibrillation, chest irradiation, previous myocardial infarction, previous coronary artery bypass graft, concomitant coronary artery bypass graft, concomitant tricuspid valve surgery, heart rate, hemoglobin, left ventricular ejection fraction, left ventricular end diastolic diameter, left ventricular end systolic diameter, left atrial volume index, aortic valve area, aortic valve peak velocity, aortic valve mean pressure, transmitral gradient, mitral annulus diameter, moderate or greater tricuspid regurgitation, and right ventricular systolic pressure.



Pseudo MS (n=52)

	Pre AVR	Post AVR	p
HR (bpm)	69 ± 11	76 ± 10	<0.01*
MVA (cm²)	1.72 ± 0.21	2.52 ± 0.40	<0.01*
MV TVI (cm)	49 ± 11	38 ± 8	<0.01*
TMG (mmHg)	5.2 ± 1.4	4.3 ± 1.5	<0.01*
SV (mL)	83 ± 16	94 ± 20	<0.01*
Indexed SV (mL/m²)	44 ± 9	51 ± 11	<0.01*

Mean ± standard deviation

True MS (n=55)

	Pre AVR	Post AVR	p
HR (bpm)	70 ± 10	72 ± 10	0.23
MVA (cm²)	1.60 ± 0.24	1.63 ± 0.25	0.42
MV TVI (cm)	52 ± 10	51 ± 10	0.55
TMG (mmHg)	6.0 ± 1.9	5.8 ± 2.4	0.26
SV (mL)	82 ± 16	82 ± 16	0.94
Indexed SV (mL/m²)	45 ± 8	44 ± 8	0.71

Mean ± standard deviation

Figure 1. Hemodynamics of true mitral stenosis (MS) and pseudo MS.
In 107 patients with mitral valve area (MVA) ≤2.0 cm² at baseline, MVA increased to >2.0 cm² after aortic valve replacement (AVR) in 52 patients (pseudo MS), whereas it remained ≤2.0 cm² in 55 patients (true MS). *P<0.05 before AVR vs after AVR. HR indicates heart rate; MV TVI, mitral valve time-velocity integral; SV, stroke volume; and TMG, transmitral gradient.

can contribute to increased stroke volume after AVR. Our study included predominantly patients with calcific mitral stenosis, who have prominent calcification at the base of the leaflets without commissural fusion as seen in rheumatic mitral stenosis.[8] These features may lead to more significant flow-related changes in mitral valve opening.

In patients with true mitral stenosis, the mean MVA and stroke volume did not change after AVR. In advanced stages of mitral stenosis, calcification extends to the mitral leaflets and the mitral annulus fails to dilate during diastole.[25,26] Calcification reduces mitral leaflet mobility;[20,27] the rigid annulus and leaflets might limit the increase in stroke volume. In this study, true mitral stenosis was associated with poorer all-cause mortality in patients with severe aortic stenosis. Thus, there is a need to identify true mitral stenosis at pre-AVR TTE. In our study, MVA ≤1.9 cm² best identified patients with true mitral stenosis. However, MVA ≤1.5 cm², MAD ≤1 mm and extension of calcification to mitral leaflets were also useful to distinguish true from pseudo mitral stenosis.

TAVR was an independent predictor of improvement in MVA. This might be related to increase in stroke volume after TAVR. Previous papers have reported that stroke volume was larger at discharge in patients undergoing TAVR than SAVR.[28,29] The prevalence of true mitral stenosis was similar in patients undergoing TAVR and SAVR, and TAVR did not affect all-cause mortality. TAVR was associated with an advantage in hemodynamics immediately after TAVR.[30]

Our results showed that patients with true mitral stenosis had substantial mortality. However, pseudo or mild mitral stenosis was also associated with poorer survival compared with controls (patients with severe aortic stenosis without mitral stenosis). MAC was prevalent in this study; in a previous paper, patients with elevated TMG as a result of MAC were found to have worse outcomes compared with the general population even when TMG were only mildly elevated.[31] MAC appears to be a marker for multiple comorbidities associated with worse prognosis rather than being the direct cause of increased mortality.[31,32] Moreover, the postoperative mortality and morbidity of simultaneous double valve replacement is much higher than the risk of either AVR or MVR alone.[33,34] Future studies are needed to determine whether concomitant MVR improves the prognosis in patients with severe aortic stenosis and mitral stenosis.

Clinical Implication

Mitral stenosis severity should be carefully assessed in the setting of severe aortic stenosis because mitral ste-

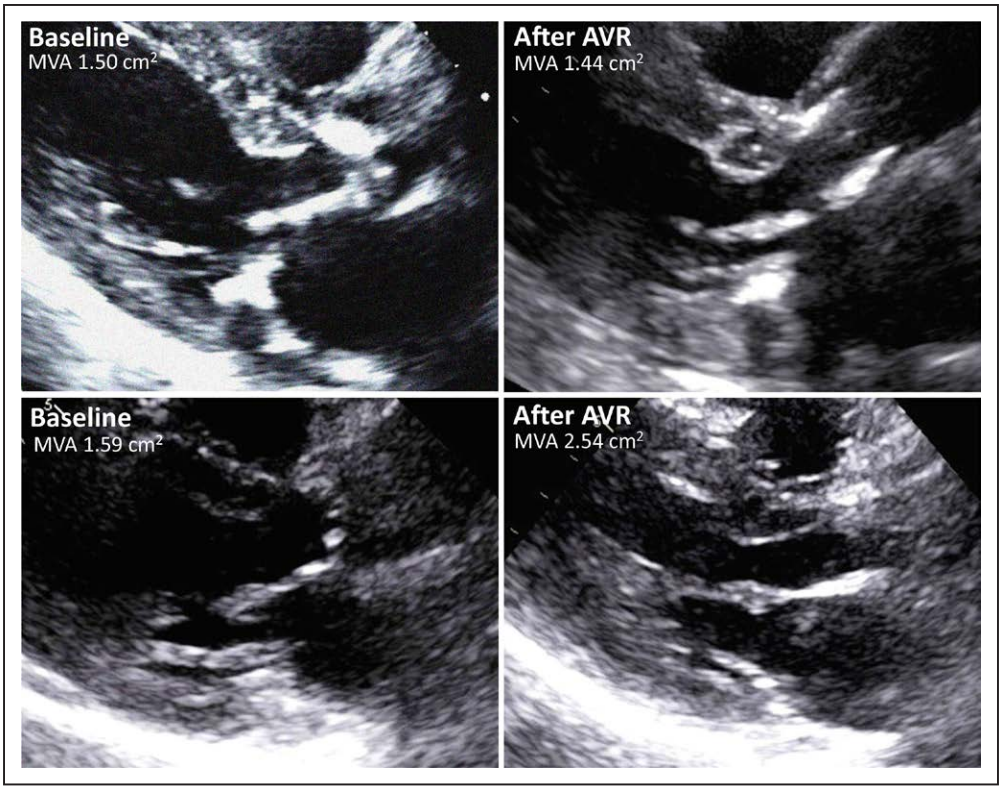


Figure 2. Examples of true mitral stenosis (MS) and pseudo MS.
Upper images show an example of true MS at diastole. Mitral annulus calcification and extension of calcification to mitral valve leaflets were observed at baseline (upper left). The mobility of mitral valve leaflets was severely reduced and mitral valve area (MVA) did not change after aortic valve replacement (AVR) (upper right). Lower images show an example of pseudo MS at diastole with limited leaflet opening (lower left). The mobility of leaflets improved after AVR (lower right).

nosis severity can be overestimated. On the other hand, patients with true mitral stenosis may require more careful follow-up. The presence of true mitral stenosis was rare when MVA was >1.9 cm² at pre-AVR TTE and it was likely with MVA ≤1.5 cm², MAD ≤1 mm, or extension of calcification to both anterior and posterior mitral leaflets. Perioperative outcomes were similar among true mitral stenosis, pseudo or mild mitral stenosis, and controls. Moreover, most patients with combined severe aortic stenosis and mitral stenosis are at high risk for surgery as a result of advanced age, comorbidities, and MAC. Thus, it might be reasonable to leave mitral stenosis untreated at the time of AVR and consider a staged procedure for mitral stenosis in symptomatic patients. Transcatheter interventions, such as staged transcatheter MVR or simultaneous transatrial MVR at the time of AVR, may be optimal treatment options in patients with severe aortic stenosis and mitral stenosis.[11,35]

Limitations

We focused on the management in patients with severe aortic stenosis and elevated TMG. Many patients with mild mitral stenosis were included in this study. The sample size was inadequate to assess the clinical outcomes in patients with severe mitral stenosis. Because this was a retrospective study, MVA and TMG were not systemically measured in the control group; however, it would be unlikely that significant mitral stenosis was missed in these patients because, in our laboratories, continuous wave Doppler is typically obtained

Table 4. Mitral Valve Hemodynamics and Anatomical Features Before Aortic Valve Replacement in Patients With Mitral Stenosis

Mitral valve features	True Mitral Stenosis (n=55)	Pseudo or Mild Mitral Stenosis (n=135)	*P* Value
Mitral valve area, cm²	1.60±0.24	2.16±0.49	<0.01*
Mitral valve time-velocity integral, cm	52±10	44±11	<0.01*
Transmitral gradient, mmHg	6.0±2.0	4.9±1.2	<0.01*
Rheumatic mitral stenosis	1 (1.8)	4 (3.0)	0.65
Chest irradiation	3 (5.5)	8 (5.9)	0.90
Mitral annulus calcification	52 (96)	120 (94)	0.49
Extension of calcification to leaflets	10 (18)	8 (6.0)	<0.01*
Mitral annulus diameter at end diastole, mm	24±3.6	25±3.5	0.16
Mitral annulus diameter at end systole, mm	22±3.6	22±3.4	0.49
Mitral annulus distension, mm	2.3±1.3	2.8±1.2	0.057

Data shown are mean±SD or n (%).
*P<0.05, significant differences between two groups.

Table 5. Perioperative Outcomes According to the Presence of Mitral Stenosis

Perioperative outcomes	True Mitral Stenosis (n=53)	Pseudo or Mild Mitral Stenosis (n=131)	Controls (n=362)	*P* Value
All-cause death	1 (1.9)	1 (0.8)	8 (2.2)	0.57
Aortic valve reintervention	1 (1.9)	0 (0)	1 (0.3)	0.14
Myocardial infarction	0 (0)	0 (0)	3 (0.8)	0.46
Stroke	2 (3.8)	1 (0.8)	5 (1.4)	0.30
Renal failure	1 (1.9)	1 (0.8)	11 (3.0)	0.33
Bleeding	1 (1.9)	3 (2.3)	5 (1.7)	0.90
Need for permanent pacemaker	3 (5.7)	17 (13)	22 (6.1)	0.034
New onset atrial fibrillation	21 (40)	42 (32)	115 (32)	0.52

Data shown are n (%).

in patients with evidence of aliasing across the mitral valve or significantly elevated pulsed-waved Doppler velocities. Although we evaluated mitral regurgitation severity with an integrated approach, it is possible that some patients with moderate or greater mitral regurgitation were not recognized because of the difficulty in assessing mitral regurgitation severity in the presence of MAC. MAC was not quantified. Patients with atrial fibrillation were included in the study and multiple values were averaged, according to our usual clinical practice. Measurement errors resulting from thoracotomy or cardiotomy might be present. Investigators were not blinded. A longer follow-up period is needed to appreciate the full impact of our findings. This study provides limited insight into the mechanisms of increased mortality because the cause of death was not known. Follow-up TTE was not performed in all patients with mitral stenosis, and the frequency of severe mitral stenosis during follow-up might be underestimated. Last, true mitral stenosis was diagnosed with only hemodynamics shortly after AVR in this study. Preoperative assessment of hemodynamics using exercise stress echocardiography and quantitation of MAC using cardiac computed tomography may be beneficial to classify true or pseudo mitral stenosis in future studies.

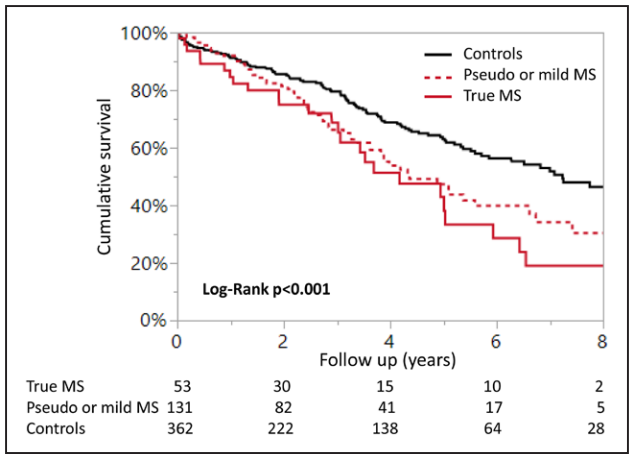


Figure 3. Kaplan–Meier curves for all-cause mortality in patients with severe aortic stenosis with and without mitral stenosis (MS). True MS and pseudo or mild MS were associated with higher overall mortality compared with the absence of MS.

CONCLUSION

Mitral stenosis severity was overestimated in half of patients with severe aortic stenosis and concomitant TMG ≥4 mm Hg, especially in those with lower indexed stroke volume. However, in nearly half of patients with severe aortic stenosis and significant mitral stenosis (MVA ≤2.0 cm^2), true mitral stenosis was present and associated with higher mortality compared with those without mitral stenosis. MVA ≤1.5 cm^2, MAD ≤1 mm or extension of calcification to both anterior and posterior mitral leaflets suggested the presence of true mitral stenosis.

ARTICLE INFORMATION

Received March 7, 2019; accepted August 23, 2019.

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The online-only Data Supplement is available with this article at https://www.ahajournals.org/doi/suppl/10.1161/circulationaha.119.040679.

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Sources of Funding

Dr Pellikka is supported as the Betty Knight Scripps Professor in Cardiovascular Disease Clinical Research.

Disclosures

None.

REFERENCES

1. Joseph L, Bashir M, Xiang Q, Yerokun BA, Matsouaka RA, Vemulapalli S, Kapadia S, Cigarroa JE, Zahr F. Prevalence and outcomes of mitral stenosis in patients undergoing transcatheter aortic valve replacement: findings from the Society of Thoracic Surgeons/American College of Cardiology transcatheter valve therapies registry. *JACC Cardiovasc Interv.* 2018;11:693–702. doi: 10.1016/j.jcin.2018.01.245
2. Unger P, Lancellotti P, de Cannière D. The clinical challenge of concomitant aortic and mitral valve stenosis. *Acta Cardiol.* 2016;71:3–6. doi: 10.2143/AC.71.1.3132091
3. Yong G, Ali A, Feldman T. Diastolic transmitral valve pressure gradients in patients with severe calcific aortic stenosis. *Catheter Cardiovasc Interv.* 2009;74:957–964. doi: 10.1002/ccd.22195
4. Abramowitz Y, Kazuno Y, Chakravarty T, Kawamori H, Maeno Y, Anderson D, Allison Z, Mangat G, Cheng W, Gopal A, et al. Concomitant mitral annular calcification and severe aortic stenosis: prevalence, charac-

teristics and outcome following transcatheter aortic valve replacement. *Eur Heart J.* 2017;38:1194–1203. doi: 10.1093/eurheartj/ehw594
5. Ancona MB, Giannini F, Mangieri A, Regazzoli D, Jabbour RJ, Tanaka A, Testa L, Romano V, Longoni M, Giglio M, et al. Impact of mitral annular calcium on outcomes after transcatheter aortic valve implantation. *Am J Cardiol.* 2017;120:2233–2240. doi: 10.1016/j.amjcard.2017.09.006
6. Mejean S, Bouvier E, Bataille V, Seknadji P, Fourchy D, Tabet JY, Lairez O, Cormier B. Mitral annular calcium and mitral stenosis determined by multidetector computed tomography in patients referred for aortic stenosis. *Am J Cardiol.* 2016;118:1251–1257. doi: 10.1016/j.amjcard.2016.07.044
7. Nishimura RA, Otto CM, Bonow RO, Carabello BA, Erwin JP 3rd, Guyton RA, O'Gara PT, Ruiz CE, Skubas NJ, Sorajja P, et al; ACC/AHA Task Force Members. 2014 AHA/ACC guideline for the management of patients with valvular heart disease: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation.* 2014;129:2440–2492. doi: 10.1161/CIR.0000000000000029
8. Sud K, Agarwal S, Parashar A, Raza MQ, Patel K, Min D, Rodriguez LL, Krishnaswamy A, Mick SL, Gillinov AM, et al. Degenerative mitral stenosis: unmet need for percutaneous interventions. *Circulation.* 2016;133:1594–1604. doi: 10.1161/CIRCULATIONAHA.115.020185
9. Kodali SK, Williams MR, Smith CR, Svensson LG, Webb JG, Makkar RR, Fontana GP, Dewey TM, Thourani VH, Pichard AD, et al; PARTNER Trial Investigators. Two-year outcomes after transcatheter or surgical aortic-valve replacement. *N Engl J Med.* 2012;366:1686–1695. doi: 10.1056/NEJMoa1200384
10. Stone GW, Lindenfeld J, Abraham WT, Kar S, Lim DS, Mishell JM, Whisenant B, Grayburn PA, Rinaldi M, Kapadia SR, et al; COAPT Investigators. Transcatheter mitral-valve repair in patients with heart failure. *N Engl J Med.* 2018;379:2307–2318. doi: 10.1056/NEJMoa1806640
11. Guerrero M, Urena M, Himbert D, Wang DD, Eleid M, Kodali S, George I, Chakravarty T, Mathur M, Holzhey D, et al. 1-Year outcomes of transcatheter mitral valve replacement in patients with severe mitral annular calcification. *J Am Coll Cardiol.* 2018;71:1841–1853. doi: 10.1016/j.jacc.2018.02.054
12. Fanari Z, Mahmaljy H, Nandish S, Goswami NJ. Simultaneous transcatheter transfemoral aortic and transeptal mitral valve replacement using Edward SAPIEN S3. *Catheter Cardiovasc Interv.* 2018;92:988–992. doi: 10.1002/ccd.27410
13. Baumgartner H, Hung J, Bermejo J, Chambers JB, Evangelista A, Griffin BP, Iung B, Otto CM, Pellikka PA, Quiñones M; American Society of Echocardiography; European Association of Echocardiography. Echocardiographic assessment of valve stenosis: EAE/ASE recommendations for clinical practice. *J Am Soc Echocardiogr.* 2009;22:1–23; quiz 101. doi: 10.1016/j.echo.2008.11.029
14. Lang RM, Badano LP, Mor-Avi V, Afilalo J, Armstrong A, Ernande L, Flachskampf FA, Foster E, Goldstein SA, Kuznetsova T, et al. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *J Am Soc Echocardiogr.* 2015;28:1–39.e14. doi: 10.1016/j.echo.2014.10.003
15. Zoghbi WA, Adams D, Bonow RO, Enriquez-Sarano M, Foster E, Grayburn PA, Hahn RT, Han Y, Hung J, Lang RM, et al. Recommendations for noninvasive evaluation of native valvular regurgitation: a report from the American Society of Echocardiography developed in collaboration with the Society for Cardiovascular Magnetic Resonance. *J Am Soc Echocardiogr.* 2017;30:303–371. doi: 10.1016/j.echo.2017.01.007
16. Rudski LG, Lai WW, Afilalo J, Hua L, Handschumacher MD, Chandrasekaran K, Solomon SD, Louie EK, Schiller NB. Guidelines for the echocardiographic assessment of the right heart in adults: a report from the American Society of Echocardiography endorsed by the European Association of Echocardiography, a registered branch of the European Society of Cardiology, and the Canadian Society of Echocardiography. *J Am Soc Echocardiogr.* 2010;23:685–713; quiz 786. doi: 10.1016/j.echo.2010.05.010
17. Mohan JC, Patel AR, Passey R, Gupta D, Kumar M, Arora R, Pandian NG. Is the mitral valve area flow-dependent in mitral stenosis? A dobutamine stress echocardiographic study. *J Am Coll Cardiol.* 2002;40:1809–1815. doi: 10.1016/s0735-1097(02)02487-7
18. Eleid MF, Foley TA, Said SM, Pislaru SV, Rihal CS. Severe mitral annular calcification: multimodality imaging for therapeutic strategies and interventions. *JACC Cardiovasc Imaging.* 2016;9:1318–1337. doi: 10.1016/j.jcmg.2016.09.001
19. Jassal DS, Tam JW, Bhagirath KM, Gaboury I, Sochowski RA, Dumesnil JG, Giannoccaro PJ, Jue J, Pandey AS, Joyner CD, et al. Association of mitral annular calcification and aortic valve morphology: a substudy of the aortic stenosis progression observation measuring effects of rosuvastatin (ASTRONOMER) study. *Eur Heart J.* 2008;29:1542–1547. doi: 10.1093/eurheartj/ehn172
20. Movva R, Murthy K, Romero-Corral A, Seetha Rammohan HR, Fumo P, Pressman GS. Calcification of the mitral valve and annulus: systematic evaluation of effects on valve anatomy and function. *J Am Soc Echocardiogr.* 2013;26:1135–1142. doi: 10.1016/j.echo.2013.06.014
21. Honey M. Clinical and haemodynamic observations on combined mitral and aortic stenosis. *Br Heart J.* 1961;23:545–555. doi: 10.1136/hrt.23.5.545
22. Braverman AC, Thomas JD, Lee RT. Doppler echocardiographic estimation of mitral valve area during changing hemodynamic conditions. *Am J Cardiol.* 1991;68:1485–1490. doi: 10.1016/0002-9149(91)90283-q
23. Dahan M, Paillole C, Martin D, Gourgon R. Determinants of stroke volume response to exercise in patients with mitral stenosis: a Doppler echocardiographic study. *J Am Coll Cardiol.* 1993;21:384–389. doi: 10.1016/0735-1097(93)90679-u
24. Anjan VY, Herrmann HC, Pibarot P, Stewart WJ, Kapadia S, Tuzcu EM, Babaliaros V, Thourani VH, Szeto WY, Bavaria JE, et al. Evaluation of flow after transcatheter aortic valve replacement in patients with low-flow aortic stenosis: a secondary analysis of the PARTNER randomized clinical trial. *JAMA Cardiol.* 2016;1:584–592. doi: 10.1001/jamacardio.2016.0759
25. Osterberger LE, Goldstein S, Khaja F, Lakier JB. Functional mitral stenosis in patients with massive mitral annular calcification. *Circulation.* 1981;64:472–476. doi: 10.1161/01.cir.64.3.472
26. Nishimura RA, Vahanian A, Eleid MF, Mack MJ. Mitral valve disease–current management and future challenges. *Lancet.* 2016;387:1324–1334. doi: 10.1016/S0140-6736(16)00558-4
27. Carpentier AF, Pellerin M, Fuzellier JF, Relland JY. Extensive calcification of the mitral valve anulus: pathology and surgical management. *J Thorac Cardiovasc Surg.* 1996;111:718–29; discussion 729.
28. Hahn RT, Pibarot P, Stewart WJ, Weissman NJ, Gopalakrishnan D, Keane MG, Anwaruddin S, Wang Z, Bilsker M, Lindman BR, et al. Comparison of transcatheter and surgical aortic valve replacement in severe aortic stenosis: a longitudinal study of echocardiography parameters in cohort A of the PARTNER trial (placement of aortic transcatheter valves). *J Am Coll Cardiol.* 2013;61:2514–2521. doi: 10.1016/j.jacc.2013.02.087
29. Daubert MA, Weissman NJ, Hahn RT, Pibarot P, Parvataneni R, Mack MJ, Svensson LG, Gopal D, Kapadia S, Siegel RJ, et al. Long-term valve performance of TAVR and SAVR: a report from the PARTNER I trial. *JACC Cardiovasc Imaging*. 2017;10:15-25. doi: 10.1016/j.jcmg.2016.11.004
30. Smith CR, Leon MB, Mack MJ, Miller DC, Moses JW, Svensson LG, Tuzcu EM, Webb JG, Fontana GP, Makkar RR, et al; PARTNER Trial Investigators. Transcatheter versus surgical aortic-valve replacement in high-risk patients. *N Engl J Med.* 2011;364:2187–2198. doi: 10.1056/NEJMoa1103510
31. Pasca I, Dang P, Tyagi G, Pai RG. Survival in patients with degenerative mitral stenosis: results from a large retrospective cohort study. *J Am Soc Echocardiogr.* 2016;29:461–469. doi: 10.1016/j.echo.2015.12.012
32. Baumgartner H, Falk V, Bax JJ, De Bonis M, Hamm C, Holm PJ, Iung B, Lancellotti P, Lansac E, Munoz DR, et al. 2017 ESC/EACTS Guidelines for the management of valvular heart disease: The Task Force for the Management of Valvular Heart Disease of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS). *Eur Heart J*. 2017;38:2739-2791.
33. Litmathe J, Boeken U, Kurt M, Feindt P, Gams E. Predictive risk factors in double-valve replacement (AVR and MVR) compared to isolated aortic valve replacement. *Thorac Cardiovasc Surg.* 2006;54:459–463. doi: 10.1055/s-2006-924247
34. Maleszka A, Kleikamp G, Zittermann A, Serrano MR, Koerfer R. Simultaneous aortic and mitral valve replacement in octogenarians: a viable option? *Ann Thorac Surg.* 2008;86:1804–1808. doi: 10.1016/j.athoracsur.2008.07.116
35. Russell HM, Guerrero ME, Salinger MH, Manzuk MA, Pursnani AK, Wang D, Nemeh H, Sakhuja R, Melnitchouk S, Pershad A, et al. Open atrial transcatheter mitral valve replacement in patients with mitral annular calcification. *J Am Coll Cardiol.* 2018;72:1437–1448. doi: 10.1016/j.jacc.2018.07.033