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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

Lee Joseph, MD, MS,[a] Mohammad Bashir, MD,[b] Qun Xiang, MS,[c] Babatunde A. Yerokun, MD,[c] Roland Albert Matsouaka, PhD,[c,d] Sreekanth Vemulapalli, MD,[c] Samir Kapadia, MD,[e] Joaquin E. Cigarroa, MD,[f] Firas Zahr, MD[f]

ABSTRACT

OBJECTIVES This study sought to examine the prevalence of mitral stenosis (MS) and its impact on in-hospital and 1-year clinical outcomes among patients undergoing transcatheter aortic valve replacement (TAVR).

BACKGROUND Patients with coexisting severe aortic stenosis and MS are increasingly being considered for TAVR.

METHODS The study cohort included 44,755 patients (age ≥18 years) who underwent TAVR during November 1, 2011, to September 30, 2015, and were registered in Society of Thoracic Surgeons/American College of Cardiology Transcatheter Valve Therapies (TVT) Registry. One-year outcomes were assessed by linking TVT registry data of this cohort to patient-specific Centers for Medicare & Medicaid Services administrative claims data (n = 31,453). The primary outcome was the composite of death, stroke, heart failure–related hospitalization, and mitral valve intervention at 1 year.

RESULTS MS was present in 11.6% of cohort (mean age, 82 years; 52% males), being severe in 2.7%. Severe MS was associated with higher in-hospital mortality rates (5.6% vs. 3.9% for nonsevere MS and 4.1% for no MS; p = 0.02). In contrast to those without MS, severe MS group had significantly higher risk for the primary outcome, mortality (1 year), and heart failure–related hospitalization (1 year) (adjusted hazard ratio: 1.2 [95% confidence interval (CI): 1.1 to 1.4], 1.2 [95% CI: 1.0 to 1.4], and 1.3 [95% CI: 1.1 to 1.5], respectively; p < 0.05 for all).

CONCLUSIONS Approximately one-tenth of patients undergoing TAVR have concomitant MS. Severe MS is an independent predictor of 1-year adverse clinical outcomes following TAVR. The higher risk for long-term adverse events must be considered when evaluating patients with combined aortic stenosis and MS for TAVR. (J Am Coll Cardiol Intv 2018;11:693–702) © 2018 by the American College of Cardiology Foundation.

From the [a]Division of Cardiovascular Diseases, Department of Internal Medicine, University of Iowa Carver College of Medicine, Iowa City, Iowa; [b]Division of Cardiothoracic Surgery, Department of Surgery, University of Iowa Carver College of Medicine, Iowa City, Iowa; [c]Duke Clinical Research Institute, Durham, North Carolina; [d]Department of Biostatistics and Bioinformatics, Duke University, Durham, North Carolina; [e]Heart and Vascular Institute, Cleveland Clinic, Cleveland, Ohio; and the [f]Knight Cardiovascular Institute, Oregon Health & Sciences University, Portland, Oregon. Dr. Vemulapalli has received research grants from the American College of Cardiology (significant), Society of Thoracic Surgeons (significant), Abbott Vascular (significant), Patient Centered Outcomes Research Institute (significant), and Boston Scientific; consulted for Novella (insignificant/modest) and Boston Scientific; received travel expenses from Medtronic; and received speaker fees from Boston Scientific. Dr. Zahr is a primary investigator for clinical trials sponsored by Edwards Lifesciences and Medtronic. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose. The Society of Thoracic Surgeons/American College of Cardiology Transcatheter Valve Therapies Registry is an initiative of the Society of Thoracic Surgeons and the American College of Cardiology Foundation. The views expressed in this manuscript represent those of the authors and do not necessarily represent the official views of the American College of Cardiology or Society of Thoracic Surgeons.

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ABBREVIATIONS AND ACRONYMS

ACC = American College of Cardiology

AVR = aortic valve replacement

CMS = Centers for Medicare and Medicaid Services

ICD-9-CM = International Classification of Diseases-9th Revision-Clinical Modification

MS = mitral stenosis

NYHA = New York Heart Association

STS/ACC TVT Registry = Society of Thoracic Surgeons/American College of Cardiology Transcatheter Valve Therapies Registry

TAVR = transcatheter aortic valve replacement

Among patients who are undergoing surgical aortic valve replacement (AVR), one-tenth of patients have significant mitral stenosis (MS) (1). Although the natural history of patients with combined aortic and mitral valve disease in the current era of transcatheter interventions is not well documented, this condition has historically been associated with at least 40% to 50% mortality over a 10- to 20-year period (2–4). The 2014 American Heart Association/American College of Cardiology (ACC) 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 (5). For patients with severe aortic stenosis who are inoperable or at high risk for surgical AVR, transcatheter aortic valve replacement (TAVR) has been increasingly used following its approval by the U.S. Food and Drug Administration in 2011. Consequently, patients who have coexistent MS and severe aortic stenosis are being considered for TAVR.

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In current U.S. TAVR practice consisting of patients with high or prohibitive surgical risk, less than one-tenth of patients die during the 30 days following the procedure, whereas almost one-quarter of the patients die or experience a stroke by 1 year (6,7). Despite its importance, the prevalence of MS and its effect on clinical outcomes among patients undergoing TAVR are not established. Assessing the risk for fatal and nonfatal events is critical in counseling and selecting patients with concomitant aortic and MS for TAVR. No explicit recommendations exist regarding whether patients with combined aortic and MS should have additional periprocedural considerations during patient selection, counseling, and management, including possible MS intervention if MS is significant. Because of this lack of evidence and guidelines, evaluating patients with coexisting MS for TAVR is challenging.

Accordingly, we examined the in-hospital and 1-year outcomes among the patients who underwent TAVR using the Society of Thoracic Surgeons (STS)/ACC Transcatheter Valve Therapies (TVT) Registry and the Centers for Medicare & Medicaid Services (CMS) administrative claims data to address the following questions: what is the prevalence of MS and its severity among patients undergoing TAVR?; and what is the association between severity of MS, and the in-hospital and 1-year clinical outcomes following TAVR?

METHODS

STUDY POPULATION. The design of STS/ACC TVT Registry has been previously described in detail (8). The registry includes all patients undergoing TAVR with commercially approved devices at U.S. centers per the CMS National Coverage Determination requirements. Data on demographics, comorbidities, procedural details, and outcomes (periprocedural, 30 day, and 1 year) are collected using standardized definitions to allow uniform reporting across sites and rigorous data quality programs (9,10). Information on the presence of MS including the smallest mitral valve area measured and the highest mitral valve mean gradient between 12 months before the procedure and start of the procedure are collected. Echocardiographic data are used when both echocardiographic and cardiac catheterization data were available.

From the STS/ACC TVT registry, we identified 47,721 patients aged 18 years or older who underwent TAVR as the index procedure during their initial hospitalization between November 1, 2011, and September 30, 2015. We then excluded 34 patients who underwent other cardiac valvular procedures in combination with TAVR and 2,932 patients (6.1%) with missing data for MS. Thus, our TVT registry data cohort included 44,755 patients. Subsequently, we linked clinical records for 31,453 patients in the TVT registry cohort who were not enrolled in a health maintenance organization to the patient-specific CMS administrative claims data using name and social security number to construct the CMS-linked cohort (Online Figure 1).

STUDY VARIABLES. Based on MS severity, the study population was divided into 3 groups: 1) no MS; 2) nonsevere MS; and 3) severe MS. No MS, nonsevere MS, and severe MS groups were defined by mitral valve area if >4 cm^2, between 1.51 and 4 cm^2, and 1.5 cm^2 or less, respectively, as per the 2014 American Heart Association/ACC practice guidelines for management of patients with valvular heart disease (11). We included the following covariates: age, sex, race (non-Hispanic white vs. other), body mass index (categorized as underweight, normal weight, overweight, obese I to III), left ventricular ejection fraction, hemoglobin, platelet count, estimated glomerular filtration rate, number of days from November 1, 2011, until procedure date, current dialysis, left main stenosis (≥50%), proximal left

TABLE 1 Baseline Characteristics of the Overall Cohort and by MS Severity

	Overall (n = 44,755)	No MS (n = 39,554)	Nonsevere MS (n = 3,987)	Severe MS (n = 1,214)	p Value
Demographics					
Age, yrs	81.6 ± 8.5	81.6 ± 8.5	81.6 ± 8.5	82.0 ± 8.5	0.191
Males	23,385 (52.3)	21,189 (53.6)	1,759 (44.1)	437 (36.0)	<0.001
Whites	42,136 (94.7)	37,257 (94.7)	3,744 (94.5)	1,135 (94.0)	0.006
Laboratory parameters					
Platelet count (×1,000/μl)	199.3 ± 76.2	198.8 ± 76.1	203.4 ± 77.2	203.1 ± 74.2	<0.001
Estimated glomerular filtration rate, ml/min/1.73 m^2	62.1 ± 29.2	62.3 ± 28.9	60.8 ± 27.5	60.2 ± 39.9	<0.001
Hemoglobin, g/dl	11.8 ± 2.0	11.8 ± 2.0	11.7 ± 2.1	11.5 ± 2.0	<0.001
Comorbidities					
Hypertension	40,035 (89.5)	35,325 (89.4)	3,612 (90.6)	1,098 (90.4)	0.025
Diabetes mellitus	16,742 (37.4)	14,723 (37.3)	1,568 (39.4)	451 (37.1)	0.032
Current/recent smoker (within 1 yr)	2,438 (5.5)	2,188 (5.5)	196 (4.9)	54 (4.4)	0.078
Prior myocardial infarction	11,345 (25.4)	10,038 (25.4)	1,000 (25.1)	307 (25.3)	0.886
Prior stroke or transient ischemic attack	5,507 (12.3)	4,816 (12.2)	535 (13.4)	156 (12.9)	0.061
Carotid stenosis	8,428 (18.8)	7,338 (18.6)	859 (21.5)	231 (19.0)	<0.001
Peripheral arterial disease	13,883 (31.0)	12,271 (31.0)	1,250 (31.4)	362 (29.8)	0.590
Porcelain aorta	2,774 (6.2)	2,386 (6.0)	303 (7.6)	85 (7.0)	<0.001
New York Heart Association functional class IV within prior 2 weeks	9,097 (20.5)	7,959 (20.3)	868 (22.0)	270 (22.4)	0.011
Prior infectious endocarditis	428 (1.0)	366 (0.9)	52 (1.3)	10 (0.8)	0.058
Prior atrial fibrillation/flutter	18,357 (41.1)	16,239 (41.1)	1,625 (40.8)	493 (40.7)	0.873
Conduction defect	15,109 (33.9)	13,315 (33.8)	1,348 (33.9)	446 (36.9)	0.081
Prior permanent pacemaker	7,188 (16.1)	6,346 (16.0)	630 (15.8)	212 (17.5)	0.373
Previous implantable cardiac defibrillator	2,007 (4.5)	1,835 (4.6)	138 (3.5)	34 (2.8)	<0.001
Prior percutaneous coronary intervention	15,936 (35.7)	14,143 (35.8)	1,415 (35.6)	378 (31.2)	0.004
Prior coronary artery bypass graft	13,220 (29.6)	11,946 (30.2)	1,015 (25.5)	259 (21.3)	<0.001
Prior cardiac surgeries					<0.001
None	30,393 (68.8)	26,609 (68.1)	2,875 (73.0)	909 (75.4)	
1 only	11,940 (27.0)	10,748 (27.5)	930 (23.6)	262 (21.7)	
2 or more	1,861 (4.2)	1,690 (4.3)	136 (3.5)	35 (2.9)	
Prior aortic valve procedure	6,591 (14.7)	5,767 (14.6)	623 (15.6)	201 (16.6)	0.040
Prior nonaortic valve procedure	1,115 (2.5)	918 (2.3)	129 (3.2)	68 (5.6)	<0.001
Current dialysis	1,831 (4.1)	1,577 (4.0)	194 (4.9)	60 (4.9)	0.009
Severe chronic lung disease	6,128 (13.8)	5,423 (13.8)	556 (14.0)	149 (12.3)	0.031
Home oxygen	5,610 (12.6)	4,908 (12.4)	528 (13.3)	174 (14.4)	0.052
Hostile chest	3,578 (8.0)	3,186 (8.1)	294 (7.4)	98 (8.1)	0.312
Echocardiographic and cardiac catheterization parameters					
Left ventricular ejection fraction, %	53.5 ± 13.9	53.2 ± 14.0	56.0 ± 12.6	55.7 ± 13.4	<0.001
Degenerative aortic valve disease	42,289 (94.7)	37,411 (94.7)	3,756 (94.5)	1,122 (92.8)	0.012
Tricuspid aortic valve morphology	40,513 (91.2)	35,696 (90.9)	3,703 (93.5)	1,114 (92.3)	<0.001
Aortic insufficiency (moderate/severe)	8,990 (20.2)	7,791 (19.8)	915 (23.1)	284 (23.5)	<0.001
Mitral insufficiency (moderate/severe)	12,892 (28.8)	11,059 (28.0)	1,351 (33.9)	482 (39.8)	<0.001
Tricuspid insufficiency (moderate/severe)	10,661 (23.9)	9,219 (23.4)	1,083 (27.2)	359 (29.7)	<0.001
Left main stenosis (≥50%)	4,660 (10.5)	4,188 (10.7)	383 (9.7)	89 (7.4)	<0.001
Proximal left anterior descending stenosis (≥70%)	8,818 (19.9)	7,908 (20.3)	713 (18.1)	197 (16.4)	<0.001
Procedural characteristics					<0.001
Femoral access site	32,039 (72.0)	28,199 (71.7)	2,948 (74.4)	892 (73.8)	<0.001
Valve type					0.013
Core valve	9,922 (22.6)	8,704 (22.4)	914 (23.3)	304 (25.8)	
Sapien valve	34,014 (77.4)	30,133 (77.6)	3,005 (76.7)	876 (74.2)	
Elective status	39,287 (87.8)	34,696 (87.7)	3,520 (88.3)	1,071 (88.2)	0.518

Values are mean ± SD or n (%). The p values are obtained by testing for significant differences among 3 groups: no MS vs. nonsevere MS vs. severe MS.
MS = mitral stenosis.

TABLE 2 In-Hospital Outcomes by Severity of MS

	Total (n = 44,755)	No MS (n = 39,554)	Nonsevere MS (n = 3,987)	Severe MS (n = 1,214)	P Value
Composite of death and stroke	2,731 (6.1)	2,413 (6.1)	242 (6.1)	84 (6.9)	0.498
In-hospital death	1,828 (4.1)	1,604 (4.1)	156 (3.9)	68 (5.6)	0.023
In-hospital stroke	935 (2.1)	838 (2.1)	83 (2.1)	14 (1.2)	0.068
In-hospital myocardial infarction	197 (0.4)	174 (0.4)	18 (0.5)	5 (0.4)	0.983
Procedure-related death	285 (0.6)	247 (0.6)	26 (0.7)	12 (1.0)	0.289
Post-TAVR aortic paravalvular leak					
None to mild	31,964 (71.4)	28,177 (71.2)	2,923 (73.3)	864 (71.2)	<0.001
Moderate to severe	1,736 (3.9)	1,501 (3.8)	172 (4.3)	63 (5.2)	

Values are n (%). The p values are obtained by testing for significant differences among 3 groups: no MS vs. nonsevere MS vs. severe MS.

TAVR = transcatheter aortic valve replacement; other abbreviation as in Table 1.

anterior descending stenosis (≥70%), prior myocardial infarction, prior infective endocarditis, prior stroke or transient ischemic attack, carotid stenosis, peripheral arterial disease, smoker (current/recent), diabetes mellitus, New York Heart Association (NYHA) functional class within prior 2 weeks, prior atrial fibrillation or flutter, cardiac conduction defect, chronic lung disease, requirement for home oxygen, hostile chest, porcelain aorta, access site (femoral vs. other), prior permanent pacemaker, prior implantable cardiac defibrillator, prior percutaneous coronary intervention, prior coronary artery bypass grafting, prior cardiac surgery (2 or more vs. 1 vs. none), prior aortic valve procedures, prior nonaortic valve procedure, degenerative aortic valve disease, tricuspid aortic valve morphology, moderate to severe preprocedure aortic insufficiency, moderate to severe mitral insufficiency, moderate to severe tricuspid insufficiency, and acuity. The acuity status was classified into 4 categories: 1) category 1 if TAVR was an elective procedure; 2) category 2 when it was done urgently; 3) category 3 if it was performed in a patient with circulatory shock or requiring inotropes or mechanical circulatory assist device before the procedure; and 4) category 4 if the patient experienced pre-procedure cardiac arrest or required emergent or salvage TAVR.

TABLE 3 Unadjusted and Adjusted Odds Ratios of MS Severity on In-Hospital Outcomes

	MS Group	Unadjusted Odds Ratio (95% CI)	p Value	Adjusted Odds Ratio (95% CI)	p Value
In-hospital death			0.09		0.15
	Nonsevere vs. no MS	0.95 (0.8–1.1)		0.9 (0.8–1.1)	
	Severe vs. no MS	1.4 (1.1–1.8)		1.3 (1.0–1.7)	
Composite of in-hospital death and stroke			0.54		0.74
	Nonsevere vs. no MS	1.0 (0.9–1.2)		1.0 (0.8–1.1)	
	Severe vs. no MS	1.1 (0.9–1.4)		1.1 (0.9–1.4)	

CI = confidence interval; other abbreviation as in Table 1.

We assessed in-hospital and 1-year outcomes using the TVT registry data cohort and the CMS-linked cohort, respectively. The primary outcome was the composite of all-cause mortality, stroke, hospitalization for heart failure, and mitral valve intervention at 1 year. Secondary analyses included in-hospital and 1-year outcome measures. The 1-year secondary endpoints were all-cause mortality, myocardial infarction, stroke, hospitalization for heart failure, and mitral valve intervention at 1 year. The in-hospital secondary outcomes were all-cause mortality, myocardial infarction, stroke, procedure-related death (death in operating room or cardiac catheterization laboratory), and the composite of in-hospital death and stroke during index hospitalization. In-hospital outcomes were site-reported to the TVT registry using standardized definitions (9,10). Site-reported strokes, transient ischemic attacks, and valve intervention events were centrally adjudicated. One-year mortality was identified using Medicare Denominator file and the nonfatal 1-year outcomes were obtained from inpatient Standard Analytic claims file using International Classification of Diseases-9th Revision-Clinical Modification (ICD-9-CM) diagnosis and procedure codes for stroke (ICD-9-CM codes, 434.x1, 436, 433.x1, 997.02, 437.1, 437.9, 430, 431, and 432.x), admission for heart failure (ICD-9-CM codes, 398.x, 402.x1, 404.x1, 404.x3, and 428.x), and mitral valve intervention (ICD-9-CM codes, 35.02, 35.12, 35.23, 35.24, 35.96, and 35.97). We censored patient follow-up at the end of the last available follow-up.

STATISTICAL ANALYSIS. Distribution of baseline covariates by 3 MS groups were examined. Continuous variables are presented as mean ± SD, and categorical variables are presented as counts and percentages. Differences in in-hospital and 1-year clinical outcomes by the severity of MS were assessed.

The probability of in-hospital outcomes among the 3 groups were compared using Pearson chi-square test. If the result of a global test was significant and the sample size was sufficient, post hoc analysis was applied with Bonferroni correction for pairwise comparisons. For in-hospital outcomes with adequate event rate (all-cause mortality, and a composite of all-cause mortality and stroke), we performed multivariable analysis using logistic regression with generalized estimating equations method to account for within-site correlation. We adjusted for the

TABLE 4 Outcomes at 1 Year by Severity of MS and Unadjusted Hazard Ratios

Outcomes (1 yr)	1-Year Mortality/Cumulative Incidence Probability, % (95% CI)			p Value	MS Groups	Unadjusted Hazard Ratio	
	No MS	Nonsevere MS	Severe MS			Hazard Ratio (95% CI)	p Value
The composite of mortality, stroke, heart failure-related hospitalization, reintervention for mitral valve disease	33.5 (32.8–34.1)	33.7 (31.5–35.9)	40.2 (36.2–44.1)	0.006	Nonsevere vs. no MS	1.0 (0.9–1.1)	0.945
					Severe vs. no MS	1.2 (1.1–1.4)	0.001
Mortality	21.3 (20.8–21.9)	21.0 (19.2–22.8)	24.5 (21.2–27.8)	0.093	Nonsevere vs. no MS	1.0 (0.9–1.2)	0.678
					Severe vs. no MS	1.2 (1.0–1.4)	0.039
Heart failure-related hospitalization	14.1 (13.6–14.5)	14.3 (12.8–15.9)	18.0 (15.1–21.2)	0.058	Nonsevere vs. no MS	1.0 (0.9–1.2)	0.825
					Severe vs. no MS	1.3 (1.1–1.5)	0.012
Stroke	4.0 (3.7–4.2)	3.8 (3.1–4.7)	4.3 (2.9–6.1)	0.942	Nonsevere vs. no MS	1.0 (0.8–1.2)	0.682
					Severe vs. no MS	1.0 (0.7–1.4)	0.910
Reintervention for mitral valve disease	0.4 (0.3–0.5)	0.4 (0.2–0.8)	1.4 (0.7–2.7)	0.005		–	

Abbreviations as in Tables 1 and 3.

following covariates in this model: age, sex, current/recent smoking status, diabetes, NYHA functional class IV, severe chronic lung disease, estimated glomerular filtration rate, current dialysis, prior percutaneous coronary intervention, prior coronary artery bypass graft surgery, prior nonaortic valve procedure, prior aortic valve procedure, acuity, aortic insufficiency (moderate/severe vs. other), mitral insufficiency (moderate/severe vs. other), access site (femoral vs. other), prior myocardial infarction, prior stroke or transient ischemic attack, prior peripheral arterial disease, carotid stenosis, prior atrial fibrillation/flutter, home oxygen, hostile chest, and porcelain aorta.

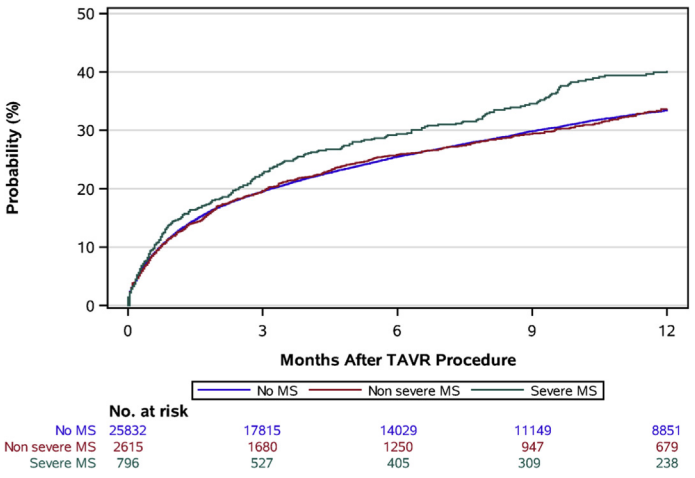
Survival analysis for mortality, heart failure-related hospitalization, mitral valve intervention, stroke, and the composite of mortality, stroke, heart failure-related hospitalization, and mitral valve intervention at 1 year were performed. To estimate the probability of primary composite outcome and mortality outcomes by MS severity over time, the Kaplan-Meier estimator was used to estimate the survival function and the log-rank test was used to compare their distributions across the MS groups. For nonfatal outcomes, a cumulative incidence method that incorporated the competing effect of death on the risk of these outcomes was used to estimate the 1-year probabilities by MS severity. The unadjusted and adjusted effects of MS severity on the 1-year outcomes with adequate event rates were estimated using the marginal Cox proportional hazard model for primary and fatal outcomes, and Fine and Gray model for nonfatal outcomes to account for death as a competing risk on such outcomes. A robust sandwich covariance estimator was used to account for the effect of patients clustering within a hospital site. The multivariable models for 1 year outcomes controlled for all the covariates listed previously under study variables based on the TAVR in-hospital mortality risk model (12). Post-TAVR paravalvular leak and residual gradients were not included in the multivariable model because these variables were candidate variables for developing the previously mentioned mortality model covariates and because of the limited number of variables that can be adjusted in the model based on the event rates.

The overall rate of missing data was <2% for all variables. Missing data were handled by imputing to the most frequent group for categorical variables and to the median for continuous variables. All analyses were performed with SAS software version 9.2 (SAS Institute, Inc., Cary, North Carolina). All tests were 2-sided, and a value of $p < 0.05$ was considered statistically significant. The institutional review board at the University of Iowa waived the requirement for its review.

RESULTS

Among 44,755 patients included in the TVT registry cohort, the mean age was 82 years, 52.3% were male, and 94.7% were white. MS was present in 5,201 patients (11.6%), being severe in 1,214 patients (2.7%) and nonsevere in the remaining 3,987 patients (8.9%). Patients with MS (severe or nonsevere), in contrast to those without MS, were more likely to have NYHA functional class IV heart failure; dialysis dependence; aortic, mitral, and tricuspid valvular insufficiencies; and prior nonaortic valve procedures. They were also less likely to have significant left main or proximal left anterior descending coronary artery disease. Overall, moderate to severe mitral insufficiency was present in 28.8% of the patients and was observed at a higher rate among the patients with

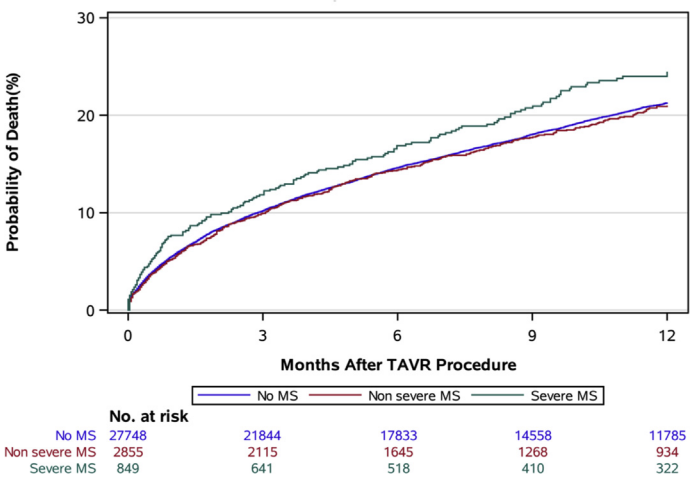
FIGURE 1 Primary Endpoint Stratified by MS Severity



Kaplan-Meier plot of the composite of 1-year mortality, stroke, heart failure-related hospitalization, and mitral valve intervention by mitral stenosis severity.
MS = mitral stenosis; TAVR = transcatheter aortic valve replacement.

severe MS (28.0% in no MS group, 33.9% in nonsevere MS group, and 39.8% in severe MS group; $p < 0.001$). Similarly, 23.9% of the overall study population had moderate to severe tricuspid valvular insufficiency, a marker of advanced myocardial and valvular heart disease; its frequency increased significantly with the severity of MS (23.4% in no MS group, 27.2% in nonsevere MS group, and 29.7% in severe MS group; $p < 0.001$). The baseline characteristics of the overall cohort by MS groups and by CMS linkage are shown in **Table 1 and** Online Table 1, respectively.

FIGURE 2 All-cause Mortality Outcomes Stratified by MS Severity



Kaplan-Meier plot of the 1-year all-cause mortality across mitral stenosis groups.
Abbreviations as in **Figure 1**.

IN-HOSPITAL OUTCOMES. Severe MS was associated with higher rates of in-hospital mortality (5.6% vs. 4.1% for the no MS group vs. 3.9% for the nonsevere MS group; $p = 0.02$ for overall, $p = 0.002$ for severe MS vs. no MS, and $p = 0.0004$ for severe MS vs. nonsevere MS). The rates of post-TAVR aortic regurgitation (moderate to severe) were also significantly higher among patients with severe MS. The severity of MS, however, was not associated with a higher rate of stroke during hospitalization and the composite of death and stroke incidence during hospitalization did not differ among the 3 groups. Additionally, the rates of myocardial infarction and procedure-related death were comparable among the 3 groups. After adjusting for baseline characteristics, the presence of MS did not significantly increase the risk of in-hospital death or a composite of in-hospital death and stroke among patients undergoing TAVR. In-hospital outcomes by the MS severity are summarized in **Tables 2 and 3**.

OUTCOMES AT 1 YEAR. In contrast to patients with no MS, patients with severe MS were more likely to experience the primary composite outcome of mortality, stroke, heart failure-related hospitalization, and mitral valve intervention at 1 year after TAVR (40.2% vs. 33.5% vs. 33.7% for severe MS, no MS, and nonsevere MS groups, respectively; $p = 0.006$) (**Table 4, Figure 1**). Patients with severe MS were also at higher risk for mortality and hospitalization for heart failure at 1 year than patients with no MS (**Figures 2 and 3**). There were no differences in the rates of stroke at 1 year based on the severity of MS (**Figure 4**). Patients in the severe MS group had a greater chance of requiring mitral valve intervention in the year following TAVR (1.4% vs. 0.4% vs. 0.4% for severe MS, no MS, and nonsevere MS groups, respectively; $p = 0.005$) (**Figure 5**).

After adjusting for baseline covariates, patients with severe MS remained at elevated risk for the primary composite outcome at 1 year (adjusted hazard ratio: 1.2 [95% confidence interval: 1.1 to 1.4]; $p = 0.001$ for severe MS vs. no MS groups) (**Table 5**). Similarly, risk-adjusted hazards of mortality and hospitalization for heart failure at 1 year continued to be higher in patients with severe MS when compared with those without MS.

DISCUSSION

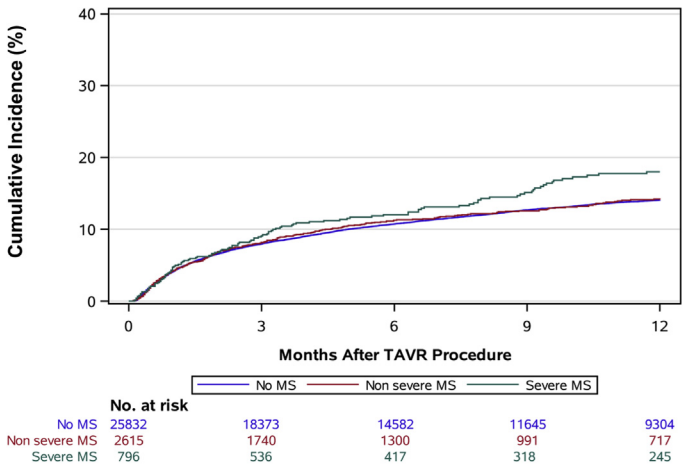
Our study provides important novel insights to the current understanding on the impact of MS among

patients undergoing TAVR by establishing its prevalence in this study population and its effect on the clinical outcomes. In this study, about one-tenth of patients undergoing TAVR have MS, classified as nonsevere in most of cases and severe in ~3% of patients. These rates are similar to the prevalence of combined aortic and mitral valve stenoses in patients undergoing surgical AVR (1). Patients with combined valve disease have an ominous natural course once they develop symptoms (13). If patients who are undergoing surgical AVR have moderate to severe MS, they are routinely managed with mitral valve surgery (5). Even though there is a net improvement in survival following double valve surgery among patients with combined aortic and mitral valve disease, this surgery has a markedly greater operative risk compared with isolated aortic or mitral valve surgery alone (14–16). Given the increased operative risk of double valve surgery, there is rising use of TAVR in patients with severe aortic stenosis with concomitant MS. The prognostic impact of MS in patients undergoing TAVR and strategies for risk-stratifying patients with combined mitral and aortic valve disease for TAVR need to be established. Our analyses suggest that TAVR patients with MS are characterized by a higher risk profile, as evidenced by greater rates of NYHA functional class IV heart failure, dialysis dependence, and multiple valvular insufficiencies. Importantly, our study highlights that the patients undergoing TAVR with concurrent severe MS had higher rates of 2 post-TAVR mortality indicators, preoperative mitral and tricuspid valvular insufficiencies (17,18). The principal finding of this study is that severe MS is independently associated with adverse outcomes in this large national registry of patients undergoing TAVR including increased 1-year mortality as compared with patients with no MS or nonsevere MS. The increased baseline risk profile for patients with severe MS undergoing TAVR could potentially explain the increased rates of 1-year adverse events.

Although several studies have examined the risk profile of patients undergoing TAVR, the association of MS with TAVR outcomes has not been assessed in these studies (6,7,12,19–22). Previous studies from the TVT registry have reported that most fatal events following TAVR occur at a later time point, with mortality rates of 7%, 17%, and 24% at 30 days, 6 months, and 1 year, respectively, thus suggesting that these events are less likely representative of periprocedural complications and emphasizing the need for better risk stratification of patients being considered for TAVR (6,7). In this study combining STS/ACC TVT registry data with CMS administrative claims data, we identified the negative impact of MS severity on fatal and nonfatal outcomes. Although severe MS was not an independent predictor of poor in-hospital outcomes, it independently increased the risk for death, mitral valve intervention, and heart failure-related hospitalization at 1 year. Thus, the adverse outcomes were predominantly a late effect.

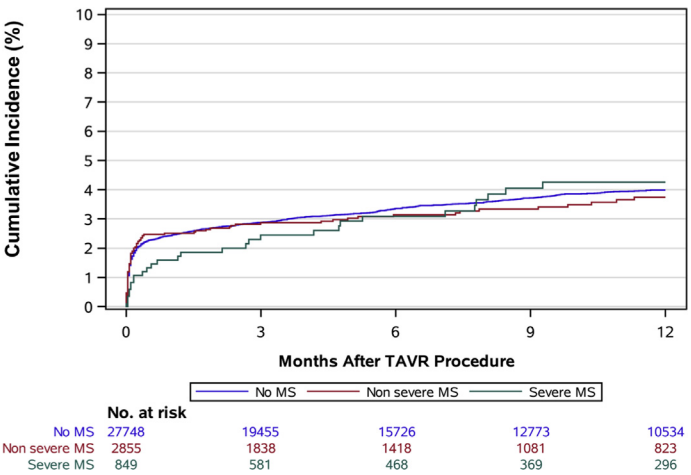
Although the mechanisms of the late adverse outcomes were not directly examined in this study,

FIGURE 3 Heart Failure-Related Hospitalization Outcomes Across Mitral Stenosis Groups



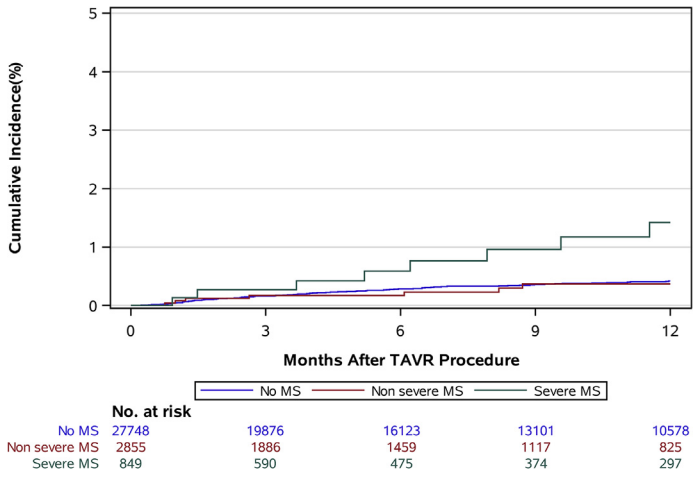
The plot of cumulative incidence curves of 1-year heart failure–related hospitalization by mitral stenosis severity. Abbreviations as in Figure 1.

FIGURE 4 Stroke Outcomes by Mitral Stenosis Severity



The plot of cumulative incidence curves of 1-year stroke across mitral stenosis groups. Abbreviations as in Figure 1.

FIGURE 5 Mitral Valve Intervention Outcomes Across Mitral Stenosis Groups



The plot of cumulative incidence curves of 1-year mitral valve intervention by mitral stenosis severity. Abbreviations as in Figure 1.

the study provides few vital clues to this effect. Given the older age of the study population, the etiology of MS in this study is more likely to be degenerative, a condition often associated with leaflet, mitral annular, and left ventricular outflow calcification, and coincident atherosclerosis. Prior research has shown that calcification of the aortic annulus and left ventricular outflow tract independently predict post-TAVR aortic regurgitation (23). Significant post-TAVR paravalvular aortic regurgitation has an independent negative impact on long-term survival after the procedure (24). In this study, there were no significant differences in the presence of atherosclerotic events at baseline. However, the incidence of in-hospital post-TAVR aortic regurgitation was significantly higher among those with severe MS, thus suggesting paravalvular leak as 1 of the potential mechanisms explaining the higher risk of adverse outcomes after TAVR among those patients with severe MS. Future investigations to prove the direct association of aortic annulus and left ventricular outflow tract calcification with long-term adverse events in the severe MS group should be considered.

There was increased risk of needing a separate mitral valve intervention in the severe MS group. Although the type of intervention could not be accurately identified in the TVT registry, we suspect given the high surgical risk for this patient population that the majority might have been transcatheter therapy. The effect of mitral intervention on 1-year outcomes is difficult to assess in this cohort given the small sample size but it illustrates the possibility of transcatheter mitral therapy to influence the outcome of this patient population in the future. With only 29 stroke cases in the severe MS group (2.4%), the results did not provide evidence of an association between stroke and MS in contrast to the increased stroke risk seen in the natural course of MS. Although the prevalence of atrial fibrillation was similar across the MS severity groups, we did not examine the use of anticoagulation in our analyses.

Because TAVR is being performed with increasing frequency, careful patient selection is imperative to realize the potential benefits of the procedure and the potential risks. Findings from this study offer important insights into identifying patients with severe MS as a higher-risk population during TAVR evaluation. The greater risk for adverse composite outcomes at 1 year in the severe MS group was mostly driven by reintervention for mitral valve disease, mortality, and heart failure-related hospitalization. These data highlight that patients with combined severe aortic stenosis and MS being considered for TAVR should be regarded as high-risk patients. Additional periprocedural measures, particularly, aggressive heart failure management and weighing the benefits of TAVR alone versus combined aortic and mitral valve intervention, should be considered in these patients. With advances in transcatheter valve therapies, transcatheter aortic and mitral valve implantation may become a viable alternative to conventional open heart surgery in selected high-risk patients with concomitant severe aortic stenosis and MS (25). The findings of this study should not persuade against TAVR in patients with concomitant severe aortic stenosis and MS but it illustrates the increased risk of late adverse outcomes in patients with severe MS and underscores the importance

TABLE 5 Adjusted Hazard Ratios of MS Severity on 1-Year Outcomes

Outcomes (1 yr)	MS Groups	Adjusted Hazard Ratio: Hazard Ratio (95% CI)	Adjusted Hazard Ratio: p Value
The composite of mortality, stroke, heart failure–related hospitalization, reintervention for mitral valve disease	Nonsevere vs. no MS	1.0 (1.0–1.1)	0.227
	Severe vs. no MS	1.2 (1.1–1.4)	0.001
Mortality	Nonsevere vs. no MS	1.0 (1.0–1.1)	0.364
	Severe vs. no MS	1.2 (1.0–1.4)	0.046
Heart failure–related hospitalization	Nonsevere vs. no MS	1.1 (0.9–1.2)	0.360
	Severe vs. no MS	1.3 (1.1–1.5)	0.009
Stroke	Nonsevere vs. no MS	0.9 (0.7–1.2)	0.464
	Severe vs. no MS	0.9 (0.6–1.3)	0.637

Abbreviations as in Tables 1 and 3.

of appropriate risk stratification, periprocedural management, and the possibility of additional procedural consideration, such as mitral valve intervention.

STUDY LIMITATIONS. First, in addition to the limitations of registry and administrative data, CMS-linked data were not available in 29.7% patients and 6.1% patients had missing data regarding MS in the TVT registry. Although information on the exact etiology of MS is not available, MS group patients were elderly and more likely to be female suggesting that degenerative or calcific MS is the likely etiology. Second, this study provides limited insight into the mechanisms of increased mortality, because the cause of death is not known. Third, despite the TVT registry capturing the current U.S. TAVR practice in its entirety, our study sample size may still be inadequate to detect differences in some outcomes and for performing a highly detailed stratified analysis of no versus mild versus moderate versus severe MS. Finally, because mitral valve area is recorded either from echocardiographic or cardiac catheterization data and the method of measurement is not documented in the TVT Registry, it is not feasible to evaluate the effect of these methods.

CONCLUSIONS

In a large national registry of patients undergoing TAVR, approximately one-tenth of patients have concomitant MS and aortic stenosis, and severe MS is associated with adverse fatal and nonfatal clinical outcomes following TAVR, especially at 1 year. The higher risk for adverse events must be carefully considered when evaluating patients with combined aortic and MS for TAVR. Future studies should explore the uses of transcatheter mitral valve intervention in this population.

ADDRESS FOR CORRESPONDENCE: Dr. Firas Zahr, Knight Cardiovascular Institute, Oregon Health & Science University, 3181 SW Sam Jackson Park Road, Portland, Oregon 97239. E-mail: zahr@ohsu.edu.

PERSPECTIVES

WHAT IS KNOWN? Although patients with combined severe aortic stenosis and MS are frequently considered for TAVR, the prevalence of MS and its impact on clinical outcomes among patients undergoing TAVR are not known.

WHAT IS NEW? This study found one-tenth of patients undergoing TAVR had concomitant MS. Importantly, severe MS independently increased the risk for 1-year adverse clinical outcomes after TAVR. Although the findings of this study should not persuade against TAVR in patients with concomitant severe aortic stenosis and MS, it illustrates the increased risk of late adverse outcomes in patients with severe MS and underscores the importance of appropriate risk stratification, periprocedural management, and the possibility of additional procedural consideration, such as mitral valve intervention.

WHAT IS NEXT? Future investigation into reducing the risk profile of this study population is warranted. Such investigations must explore the uses of additional procedures including mitral valve intervention.

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KEY WORDS combined aortic and mitral stenoses, mitral stenosis, transcatheter aortic valve replacement

APPENDIX For a supplemental table and figure, please see the online version of this paper.