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The Impact of Left Ventricular Diastolic Dysfunction on Clinical Outcomes After Transcatheter Aortic Valve Replacement

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ABSTRACT

OBJECTIVES This study sought to determine the impact of left ventricular diastolic dysfunction (LVDD) on clinical outcomes in patients undergoing transcatheter aortic valve replacement (TAVR).

BACKGROUND Left ventricular (LV) hypertrophy in response to afterload increase promotes the development of LVDD and represents an early stage in the progression to valvular heart failure.

METHODS In a consecutive cohort of 777 aortic stenosis patients undergoing TAVR, LVDD was categorized according to the latest guidelines. The primary endpoint was 1-year all-cause mortality.

RESULTS There were 545 (70.1%) patients with LVDD. Ninety-eight (18.0%), 198 (36.3%), and 104 (19.1%) patients were classified as LVDD grades I, II, and III, respectively. In 145 (26.6%) patients, LVDD grade could not be determined because of only 1 or 2 discrepant variables. One-year all-cause mortality was higher in patients with LVDD grades I (16.3%; adjusted hazard ratio [HR]$_{adj}$: 2.32; 95% confidence interval [CI]: 1.15 to 4.66), II (17.9%; HR$_{adj}$: 2.58; 95% CI: 1.43 to 4.67), and III (27.6%; HR$_{adj}$: 4.21; 95% CI: 2.25 to 7.86) than in those with normal diastolic function (6.9%). The difference in clinical outcome emerged within 30 days, was driven by cardiovascular death, and maintained in a sensitivity analysis of patients with normal systolic LV function. Furthermore, LVDD grades I (HR$_{adj}$: 2.36; 95% CI: 1.17 to 4.74), II (HR$_{adj}$: 2.58; 95% CI: 1.42 to 4.66), and III (HR$_{adj}$: 4.41; 95% CI: 2.37 to 8.20) were independent predictors of 1-year mortality.

CONCLUSIONS Advancing stages of LVDD are associated with an incremental risk of all-cause mortality after TAVR, driven by cardiovascular death and taking effect as early as 30 days after the intervention. (J Am Coll Cardiol Intv 2018;11:593–601) © 2018 by the American College of Cardiology Foundation.

Aortic valve stenosis (AS) increases left ventricular (LV) afterload and results in LV hypertrophy as a compensation mechanism to maintain cardiac output. Development of left ventricular diastolic dysfunction (LVDD) represents an early stage in the progression to valvular heart failure. Up to one-half of all patients with AS have been found to have evidence of LVDD (1,2), as a result of LV hypertrophy and myocardial fibrosis (3). LVDD in patients with AS has been identified as an independent predictor of mortality after surgical aortic valve replacement (1).

Transcatheter aortic valve replacement (TAVR) has rapidly evolved as a definitive treatment option for patients with symptomatic severe AS deemed at increased surgical risk (4-7). Hospital readmission during the first year after TAVR is associated with a significant increase in the risk of death (8). The most common reason for rehospitalization in this patient population is heart failure (9). LVDD may be an

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ABBREVIATIONS AND ACRONYMS

AR = aortic regurgitation

AS = aortic stenosis

BMI = body mass index

COPD = chronic obstructive pulmonary disease

EF = ejection fraction

LV = left ventricular

LVDD = left ventricular diastolic dysfunction

MACCE = major adverse cardiac and cerebrovascular event(s)

NYHA = New York Heart Association

TAVR = transcatheter aortic valve replacement

important factor to sustain heart failure after TAVR, because normalization of diastolic stiffness and relaxation due to regression of muscular and nonmuscular tissue may be delayed or irreversible (10).

To date, retrospective analyses found conflicting evidence on the impact of LVDD on clinical outcomes after TAVR (11-13). Thus, the aim of this study was to evaluate the impact of graded LVDD on clinical outcomes in patients undergoing TAVR.

SEE PAGE 602

METHODS

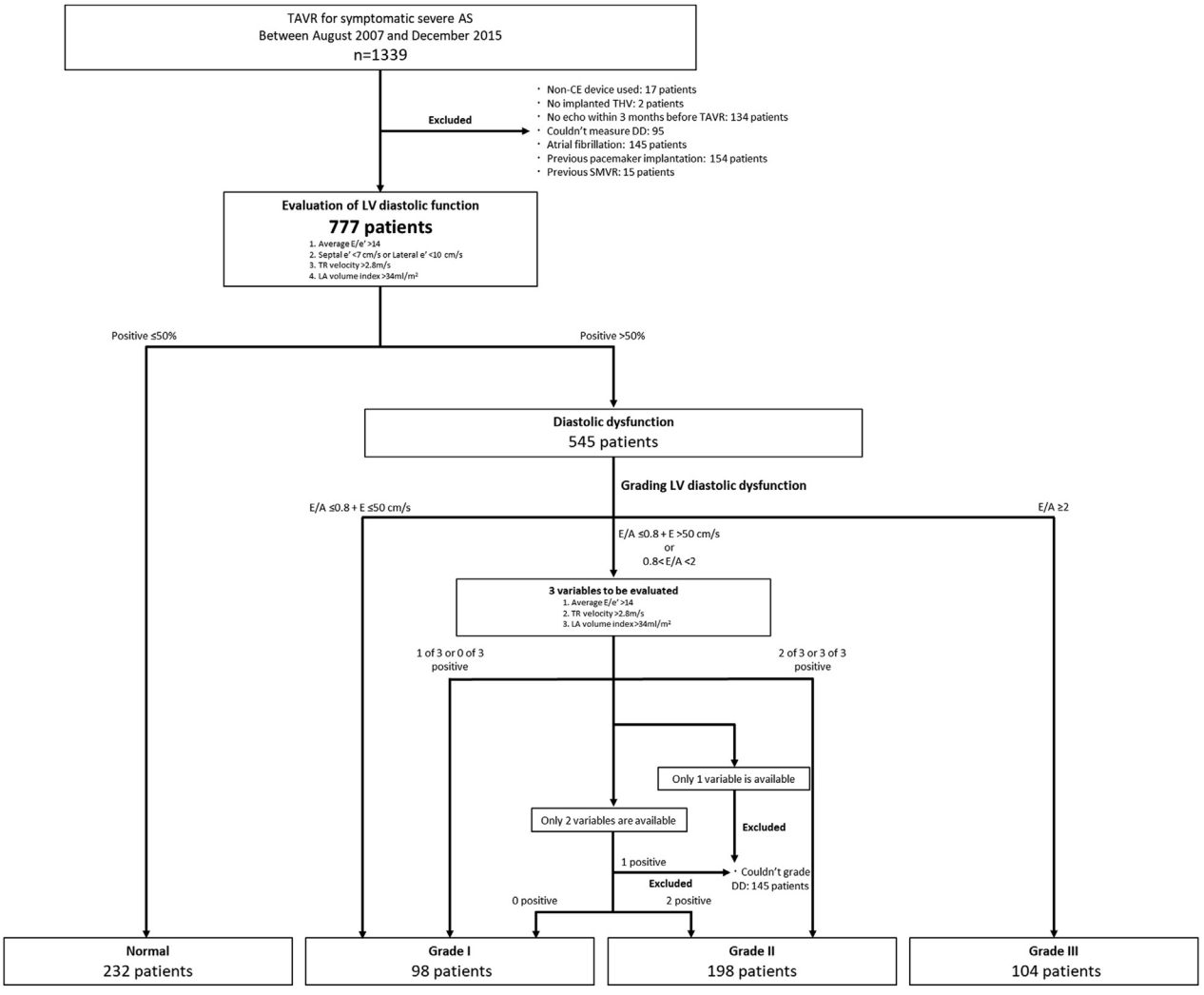
PATIENT POPULATION. All patients undergoing TAVR at our institution are consecutively enrolled into a prospective registry that is part of the Swiss TAVI Registry (NCT01368250) and were considered eligible for the present analysis. Patients with a history of atrial fibrillation, previous permanent pacemaker implantation, or status post-surgical mitral valve replacement were excluded because echocardiographic parameters for LVDD are not evaluable in these patients. A multidisciplinary heart team consisting of cardiac surgeons, interventional cardiologists, imaging, and heart failure specialists decided on treatment strategy and suitability for TAVR in all patients. The local ethics committee approved the study and all study-related procedures were carried out in accordance with the Declaration of Helsinki. All study participants gave written informed consent. Data was prospectively entered in a web-based database held at the Clinical Trial Unit at the University of Bern, Switzerland.

PROCEDURE. Standard techniques were used for TAVR as previously described (14). After the intervention, all patients were monitored for at least 48 h. Laboratory examination and a 12-lead electrocardiography were routinely performed immediately after the procedure and daily thereafter. In all patients, an echocardiographic control was performed before discharge.

ASSESSMENT OF LVDD. All subjects underwent transthoracic echocardiography within 3 months before TAVR. For the acquisition of echocardiographic parameters, at least 3 consecutive heart beats were recorded and averaged for each parameter. Echo loop and still frames were analyzed at a workstation allowing for offline analysis (Syngo Dynamics Workplace, version 9.5, Siemens Medical Solutions, Inc., Malvern, Pennsylvania). According to current American Society of Echocardiography and European Association of Cardiovascular Imaging guidelines, 4 variables are required for the assessment of LVDD (**Figure 1**) (15). The variables and respective cutoffs used for the present analysis were as follows: 1) annular e′ velocity (septal e′ <7 cm/s or lateral e′ <10 cm/s); 2) average E/e′ ratio >14; 3) left atrium maximum volume index >34 ml/m^2; and 4) peak tricuspid regurgitation velocity >2.8 m/s. LVDD is present if greater than one-half of all available parameters meet the aforementioned cutoff values. In patients with LVDD, the key variables for categorizing LVDD include mitral flow velocities (E/A ratio and peak E velocity). Grade I is defined as a mitral inflow pattern showing an E/A ratio ≤0.8 along with a peak E velocity of ≤50 cm/s. Grade III is present in case of an E/A ratio ≥2, in combination with an elevation of the left atrium mean pressure. When mitral inflow shows an E/A ratio ≤0.8 and the peak E velocity is >50 cm/s, or if the E/A ratio is >0.8 but <2, the following indicators are necessary for accurate evaluation: 1) the peak continuous-wave Doppler velocity of the tricuspid regurgitation jet obtained from multiple views; 2) E/e′ ratio; and 3) left atrium maximum volume index. If all 3 parameters are available for interpretation, and none or only 1 of the 3 meets the cutoff value, grade I DD is present. If 2 of 3, or all 3 available parameters meet the corresponding cutoff values, DD is categorized as grade II. If only 1 parameter is available, the grade of DD should not be reported. Likewise, DD is not reported if there is a discrepancy between the only 2 available parameters. However, if neither of the 2 available parameters meets the cutoff values, DD is categorized as grade I, whereas grade II DD is present if both parameters meet the cutoff values.

CLINICAL FOLLOW-UP AND ENDPOINT ASSESSMENT. Standardized clinical follow-up was performed at 30 days and 1 year after TAVR. Telephone interviews, documentation from referring physicians, and hospital discharge summaries were used to ascertain clinical endpoints. All suspected adverse events were independently adjudicated according to the criteria by the Valve Academic Research Consortium-2 (16). The primary endpoint of this study was all-cause mortality within 1 year after TAVR. Secondary endpoints included cardiovascular death, major adverse cardiac and cerebrovascular events (MACCE), disabling stroke, and myocardial infarction. A composite of all-cause death, disabling stroke, and myocardial infarction was considered as MACCE. Moreover, life-threatening and major bleeding, kidney injury (stage 3), and major access site complications at 30 days of follow-up were included in this

FIGURE 1 Study Flow Diagram



The study flow diagram illustrates the number of TAVR patients with adequate echocardiographic data, categorized according to LVDD grade before TAVR. CE = Conformité Européenne; DD = diastolic dysfunction; LA = left atrial; LV = left ventricular; SMVR = surgical mitral valve replacement; TAVR = transcatheter aortic valve replacement; THV = transcatheter heart valve; TR = tricuspid regurgitation.

analysis. New York Heart Association (NYHA) functional class was evaluated at baseline, 30 days, and 1 year after TAVR.

STATISTICAL ANALYSIS. Continuous data are reported as mean ± SD (with p values from F tests across all 4 dysfunction groups). Categorical variables are reported as number of patients and percentage (with p values from chi-square tests across all 4 dysfunction groups), comparing normal, grade I, II, and III groups.

Events are reported as counts of first occurrence per (sub)type of event within 30 days or 1 year of follow-up (percentage from lifetable estimates), comparing grade I, II, or III versus normal diastolic function (pairwise) using Cox's regressions (i.e., censoring patients at death or lost to follow-up). Reported are crude hazard ratios (HRs) (with 95% confidence intervals [CIs]) with p values from Wald chi-square tests, or continuity correct risk ratios with p values from Fisher exact tests in case of 0 events. Single imputation of missing data was performed, before any adjusted analyses, using the median or mode (missing data: 2 chronic obstructive pulmonary disease [COPD] assumed no COPD, 2 body mass index [BMI] assumed above 20 kg/m^2, 2 post-aortic regurgitation [AR] assumed mild, 1 creatinine assumed <200 μmol/l).

TABLE 1 Baseline Characteristics

	Normal (n = 232)	Diastolic Dysfunction Grade I (n = 98)	Grade II (n = 198)	Grade III (n = 104)	Overall p Value
Age, yrs	82.2 ± 5.4	82.5 ± 6.8	83.4 ± 5.1	79.3 ± 9.1	<0.001
Female	133 (57.3)	46 (46.9)	112 (56.6)	40 (38.5)	0.005
Body mass index, kg/m^2	26.3 ± 5.2	25.1 ± 4.7	26.5 ± 5.2	25.5 ± 4.8	0.12
Cardiac risk factors					
Diabetes mellitus	54 (23.3)	18 (18.4)	51 (25.8)	33 (31.7)	0.15
Hypercholesterolemia	152 (65.5)	63 (64.3)	123 (62.1)	64 (61.5)	0.86
Hypertension	193 (83.2)	81 (82.7)	167 (84.3)	82 (78.8)	0.68
Current smoker	4 (5.2)	6 (12.8)	6 (7.1)	8 (17.0)	0.11
Past medical history					
Previous myocardial infarction	19 (8.2)	22 (22.4)	36 (18.2)	28 (26.9)	<0.001
Previous PCI	59 (25.4)	30 (30.6)	55 (27.8)	32 (30.8)	0.69
Previous CABG	21 (9.2)	11 (12.1)	21 (11.1)	25 (25.5)	0.001
Previous stroke or TIA	26 (11.2)	8 (8.2)	13 (6.6)	14 (13.5)	0.19
Peripheral vascular disease	27 (11.6)	12 (12.2)	26 (13.1)	22 (21.2)	0.12
Chronic obstructive pulmonary disease	22 (9.5)	20 (20.6)	24 (12.1)	7 (6.8)	0.01
Renal failure (eGFR <60 ml/min/1.73 m^2)	160 (69.0)	72 (73.5)	147 (74.2)	77 (74.0)	0.60
Symptoms					
NYHA functional class III or IV	129 (55.6)	65 (66.3)	144 (72.7)	84 (80.8)	<0.001
CCS class III or IV	16 (6.9)	10 (10.2)	28 (14.1)	12 (11.5)	0.10
Syncope	24 (10.3)	17 (17.3)	26 (13.1)	10 (9.6)	0.26
Risk assessment					
Logistic EuroSCORE, %	14.6 ± 9.3	22.5 ± 13.0	22.4 ± 14.8	27.5 ± 16.3	<0.001
STS score, %	4.7 ± 3.3	6.4 ± 3.7	6.5 ± 3.9	7.0 ± 4.6	<0.001
Laboratory values					
Brain natriuretic peptide, pg/ml	400.9 ± 681.9	738.1 ± 945.8	775.2 ± 1,201.4	1,386.2 ± 1,282.5	<0.001

Values are mean ± SD or n (%). The p values are from F tests (continuous variables) and chi-square tests, across all 4 groups.

CABG = coronary artery bypass grafting; CCS = Canadian Cardiovascular Society; eGFR = estimated glomerular filtration rate; EuroSCORE = European System for Cardiac Operative Risk Evaluation; LV = left ventricular; NYHA = New York Heart Association; PCI = percutaneous coronary intervention; STS = Society of Thoracic Surgeons; TIA = transient ischemic attack.

Reported are adjusted hazard ratio (HR) (95% confidence interval [CI]), with normal LV diastolic function as the reference category, adjusting for sex, diabetes, peripheral vascular disease, and BMI ≤20 kg/m^2 (these variables had a p value <0.10 in the multivariable model for predicting outcomes at 1 year). Adjusted analyses conducted in cases with 10 events or more were available overall. As sensitivity analyses, the above crude and adjusted analyses were repeated for the patients presenting with LV ejection fraction (EF) ≥50% as assessed by the biplane Simpson method (Online Tables 1A and 1B). Predictors of 1-year all-cause mortality, cardiovascular death, and MACCE were evaluated separately (Online Tables 2 and 3), and included LVDD as main effect, age, diabetes, peripheral vascular disease, BMI ≤20 kg/m^2, COPD, previous stroke or transient ischemic attack, logistic EuroSCORE ≥40%, moderate or severe post-AR, sex, atrial fibrillation, NYHA functional class III or IV, concomitant percutaneous coronary intervention, COPD, coronary artery disease, and creatinine >200 μmol/l (univariable Cox regressions, if p < 0.10 added to multivariable model) (17–19). Associations between baseline LVDD and NYHA functional class were tested using Kendall tau-b; between baseline LVEF (<50% vs. ≥50%) and NYHA functional class or LVDD using chi-square tests; and between LVDD and 1-year mortality using Cox's regression, controlling for post-TAVR AR (none-mild or moderate-severe) as well as LV mass index, LVEF, and stroke volume (Online Table 4). All analyses were performed with Stata version 14.2 (StataCorp, College Station, Texas). Two-sided p values <0.05 were considered statistically significant.

RESULTS

STUDY POPULATION. The patient flow chart is shown in Figure 1. Among 1,339 consecutive patients undergoing TAVR between August 2007 and December 2015, 777 patients underwent detailed echocardiographic assessment and represent the study population of the present analysis. Evidence of LVDD was objectively documented in 545 (70.1%) patients, and categorized as grade I in 98 (18.0%), grade II in 198 (36.3%), and grade III in 104 (19.1%) patients, respectively. A total of 145 (26.6%) patients were excluded from our analysis due to only 1 or 2 discrepant variables available to grade LVDD.

Baseline characteristics of the study patients are provided in Table 1. Patients with LVDD were more commonly men and more likely to have a history of myocardial infarction and coronary artery bypass grafting. Advanced stages of LVDD correlated with increased Society of Thoracic Surgeons score and logistic EuroSCORE, higher NYHA functional class (Online Figure 1A), and increased brain natriuretic peptides, respectively.

ECHOCARDIOGRAPHIC ASSESSMENT. There were no significant differences in aortic valve area or mean transvalvular gradient; however, patients with LVDD had a lower LVEF (grade I: 48 ± 15%; grade II: 53 ± 15%; grade III: 42 ± 16%) as compared with patients with normal diastolic function (63 ± 8%; p < 0.001) (Table 2). Conversely, patients with compromised LVEF <50% (n = 175 [29.4%]) more commonly had advanced LVDD and higher NYHA functional class (Online Figure 1B). Patients with LVDD more commonly had concomitant mitral or tricuspid regurgitation of at least moderate degree (Table 2). With regard to LV geometry, the proportion of

TABLE 2 Echocardiographic Characteristics

	Normal (n = 232)	Diastolic Dysfunction			Overall p Value
		Grade I (n = 98)	Grade II (n = 198)	Grade III (n = 104)	
Aortic stenosis severity					
Aortic valve area, cm^2*	0.7 ± 0.2	0.7 ± 0.2	0.7 ± 0.3	0.8 ± 0.3	0.19
Mean gradient, mm Hg*	47 ± 17	46 ± 17	43 ± 18	40 ± 21	0.16
LV systolic function					
LV ejection fraction, %*	63 ± 8	48 ± 15	53 ± 15	42 ± 16	<0.001
Stroke volume index (VTI), $ml \cdot m^{-2}$	33.8 ± 12.7	35.2 ± 12.6	33.2 ± 11.4	32.3 ± 12.3	0.47
LV diastolic dysfunction					
E/A ratio	1.03 ± 0.82	0.69 ± 0.37	1.14 ± 0.42	3.22 ± 0.99	<0.001
E-wave, $m \cdot s^{-1}$	0.77 ± 0.34	0.57 ± 0.32	1.02 ± 0.32	1.09 ± 0.31	<0.001
A-wave, $m \cdot s^{-1}$	0.90 ± 0.34	0.89 ± 0.27	0.99 ± 0.36	0.37 ± 0.15	<0.001
E/e′ ratio	12.9 ± 7.0	14.8 ± 6.4	27.0 ± 12.1	28.0 ± 11.3	<0.001
e′, $cm \cdot s^{-1}$	5.45 ± 1.85	4.21 ± 1.33	4.08 ± 1.13	4.46 ± 1.54	<0.001
Deceleration time, ms	260.3 ± 87.6	241.5 ± 92.0	231.8 ± 85.8	171.2 ± 56.7	<0.001
Isovolumic relaxation time, ms	83.6 ± 21.9	84.3 ± 22.8	78.0 ± 23.1	73.9 ± 23.1	0.001
TR velocity, m/s	2.68 ± 0.51	2.60 ± 0.45	3.10 ± 0.55	3.08 ± 0.55	<0.001
LA volume index, $ml \cdot m^2$	34.7 ± 15.4	44.6 ± 17.4	47.6 ± 15.7	52.3 ± 19.5	<0.001
LV hypertrophy					
Relative wall thickness†	0.56 ± 0.20	0.55 ± 0.21	0.53 ± 0.17	0.48 ± 0.20	0.02
LV mass index, $g \cdot m^{-2}$	132.0 ± 41.2	159.2 ± 56.2	149.6 ± 59.9	157.2 ± 51.6	<0.001
LV geometry					
Normal geometry	18 (9.8)	6 (7.3)	8 (4.6)	5 (5.6)	0.26
Concentric hypertrophy	114 (62.0)	54 (65.9)	101 (58.0)	48 (53.3)	0.34
Concentric remodeling	29 (15.8)	5 (6.1)	23 (13.2)	6 (6.7)	0.048
Eccentric hypertrophy	23 (12.5)	17 (20.7)	42 (24.1)	31 (34.4)	<0.001
Evaluation of valvular abnormality*					
Aortic regurgitation moderate or severe	6 (8.3)	4 (7.4)	7 (8.2)	4 (8.0)	1.00
Mitral regurgitation moderate or severe	14 (6.3)	16 (16.8)	40 (20.4)	37 (36.3)	<0.001
Tricuspid regurgitation moderate or severe	15 (6.7)	13 (13.7)	29 (14.8)	30 (29.4)	<0.001

Values are mean ± SD or n (%). The p values are from F tests (continuous variables), chi-square tests, across all 4 groups. Doppler tissue imaging (DTI) indicates pulse Doppler peak velocity at the annulus. *Transthoracic echocardiography, if missing transesophageal echocardiography used. †Relative wall thickness = 2 × posterior wall thickness diastole / left ventricular internal dimension in diastole.

LA = left atrium; TR = tricuspid regurgitation; VTI = velocity time integral; other abbreviations as in Table 1.

eccentric hypertrophy increased with advancing grades of LVDD (normal: 12.5%; grade I: 20.7%; grade II: 24.1%; grade III: 34.4%).

Echocardiographic follow-up between 6 and 18 months was available in 87 (27.1%) patients. Although individual parameters changed between baseline and follow-up, LVDD grade remained unchanged in approximately 50% of patients (Online Figure 2). Parameters to assess LVDD at baseline and during follow-up are summarized in **Table 2** and Online Table 5, respectively.

PROCEDURAL CHARACTERISTICS. Procedural characteristics are summarized in **Table 3**. Patients with LVDD grade III were more commonly treated by nontransfemoral access, and length of hospital stay tended to increase with worsening grade of LVDD. There were no significant differences across groups with regards to valve type used.

CLINICAL OUTCOMES. Event rates with crude and adjusted HR for clinical outcomes are provided in **Tables 4 and 5** and Online Table 6. Clinical follow-up at 1 year was completed in all patients. All-cause mortality at 1 year increased with worsening degrees of LVDD and was twice as high in patients with LVDD grade I (16.3%; HR_{adj}: 2.32; 95% CI: 1.15 to 4.66; p = 0.02), 2.5-fold as high in patients with LVDD grade II (17.9%; HR_{adj}: 2.58; 95% CI: 1.43 to 4.67; p = 0.002), and 4 times higher in patients with LVDD grade III (27.6%; HR_{adj}: 4.21; 95% CI: 2.25 to 7.86; p < 0.001) as compared with patients with normal diastolic function (6.9%) (**Figure 2A**). Although manifest as early as 30 days after the intervention in patients with LVDD grade III, the mortality difference continued to emerge during midterm follow-up and was strongly driven by differences in cardiovascular death (**Figure 2B**). There were no significant differences between groups with respect to the occurrence

TABLE 3 Procedural Characteristics

	Normal (n = 232)	Diastolic Dysfunction Grade I (n = 98)	Grade II (n = 198)	Grade III (n = 104)	Overall p Value
Procedural characteristics					
Procedure time, min	69.1 ± 35.4	65.4 ± 26.5	69.1 ± 31.8	66.3 ± 33.7	0.73
Length of hospital stay, days	8.1 ± 3.7	8.6 ± 3.9	9.2 ± 4.7	9.4 ± 4.0	0.047
General anesthesia	51 (22.0)	26 (26.5)	56 (28.3)	33 (31.7)	0.24
Access route					0.13
Femoral	206 (88.8)	83 (84.7)	177 (89.4)	81 (77.9)	0.03
Apical	24 (10.3)	14 (14.3)	20 (10.1)	19 (18.3)	0.14
Subclavian	1 (0.4)	1 (1.0)	1 (0.5)	3 (2.9)	0.16
Other	1 (0.4)	0 (0.0)	0 (0.0)	1 (1.0)	0.49
Type of valve					0.12
Medtronic CoreValve	67 (29.0)	35 (35.7)	78 (39.4)	41 (39.4)	0.10
Edwards SAPIEN XT	58 (25.1)	34 (34.7)	46 (23.2)	33 (31.7)	0.11
Symetis ACURATE valve	12 (5.2)	2 (2.0)	5 (2.5)	2 (1.9)	0.26
St. Jude Medical Portico	5 (2.2)	0 (0.0)	1 (0.5)	0 (0.0)	0.11
Edwards SAPIEN 3	53 (22.9)	19 (19.4)	44 (22.2)	17 (16.3)	0.53
Boston Scientific Lotus	17 (7.4)	6 (6.1)	13 (6.6)	6 (5.8)	0.95
Medtronic Evolut R	19 (8.2)	2 (2.0)	11 (5.6)	5 (4.8)	0.16
Revascularization					
Concomitant PCI	35 (15.1)	13 (13.3)	31 (15.7)	15 (14.4)	0.96
Procedural specifications					
Post-TAVR AR moderate or severe*	21 (9.1)	9 (9.2)	20 (10.2)	9 (8.7)	0.97
Post-TAVR need for PPM within 30 days	46 (19.8)	24 (24.5)	47 (23.7)	17 (16.3)	0.37
Valve in series	3 (1.3)	2 (2.0)	4 (2.0)	3 (2.9)	0.80

Values are mean ± SD or n (%). The p values are from F tests (continuous variables) and chi-square tests, across all 4 groups. *Post-TAVR or if missing before discharge.

AR = aortic regurgitation; PCI = percutaneous coronary intervention; PPM = permanent pacemaker implantation; TAVR = transcatheter aortic valve replacement.

of myocardial infarctions or cerebrovascular events (Tables 4 and 5, Figure 2C). The association between LVDD and increased risk of mortality was maintained in a sensitivity analysis of patients with preserved LVEF (≥50%) (Online Tables 1A and 1B), as well as an adjusted model additionally including LVEF, LV mass index, and LV stroke volume (Online Table 4). There was no additive effect of baseline LVDD and post-TAVR more than mild AR (n = 59 [9.4%]) on 1-year mortality (Online Figure 1C).

PREDICTOR FOR ALL-CAUSE DEATH. In a multivariable model, worsening grades of LVDD were identified as independent predictors of death at 1 year (grade I, HR_{adj}: 2.36; 95% CI: 1.17 to 4.74; grade II, HR_{adj}: 2.58; 95% CI: 1.42 to 4.66; grade III, HR_{adj}: 4.41; 95% CI: 2.37 to 8.20). LVDD grade III was the strongest predictor of all-cause mortality followed by BMI ≤20 kg/m^2 (HR_{adj}: 3.13; 95% CI: 1.87 to 5.25), diabetes (HR_{adj}: 2.11; 95% CI: 1.37 to 3.27), COPD (HR_{adj}: 2.03; 95% CI: 1.18 to 3.50), and peripheral vascular disease (HR_{adj}: 1.77; 95% CI: 1.08 to 2.91) (Table 6).

DISCUSSION

The pertinent findings of the present analysis can be summarized as follows. 1) Two-thirds of all patients undergoing TAVR for severe AS were found to have objective evidence of LVDD. 2) Advanced stages of LVDD at baseline were associated with an incremental risk of all-cause mortality after TAVR irrespective of LV function. Differences in mortality emerged as early as 30 days after TAVR in patients with higher grade LVDD, and were mainly driven by cardiovascular death. 3) LVDD, lower BMI, diabetes, COPD, and peripheral vascular disease were identified as independent predictors for all-cause mortality at 1 year.

Mechanical obstruction from AS leads to LV pressure overload, prompting unfavorable remodeling by means of cardiomyocyte hypertrophy and collagen network abnormalities, which eventually results in LVDD (20). As compared with previous reports from surgical populations, we found a higher prevalence of LVDD in a consecutive cohort of patients with AS undergoing TAVR (1,2). This may be related to different stages of disease, and a high rate of cardiac comorbidities in our predominantly elderly TAVR

TABLE 4 Long-Term Clinical Outcomes According to Graded Diastolic Dysfunction With Crude HRs

		Diastolic Dysfunction			Crude HR					
					I vs. Normal		II vs. Normal		III vs. Normal	
1-Year Follow-Up	Normal (n = 232)	Grade I (n = 98)	Grade II (n = 198)	Grade III (n = 104)	HR (95% CI)	p Value	HR (95% CI)	p Value	HR (95% CI)	p Value
All-cause mortality	16 (6.9)	16 (16.3)	35 (17.9)	28 (27.6)	2.49 (1.24–4.97)	0.01	2.75 (1.52–4.96)	0.001	4.41 (2.39–8.16)	<0.001
Cardiovascular death	7 (3.1)	12 (12.4)	25 (13.2)	21 (21.0)	4.23 (1.66–10.70)	0.002	4.46 (1.93–10.3)	<0.001	7.47 (3.18–17.60)	<0.001
Myocardial infarction	5 (2.3)	1 (1.0)	6 (3.2)	5 (5.3)	0.49 (0.06–4.19)	0.51	1.47 (0.45–4.83)	0.52	2.43 (0.70–8.39)	0.16
Cerebrovascular events										
Disabling stroke	7 (3.0)	1 (1.0)	10 (5.3)	2 (2.0)	0.34 (0.04–2.78)	0.32	1.73 (0.66–4.54)	0.27	0.66 (0.14–3.19)	0.61
MACCE	24 (10.4)	17 (17.3)	44 (22.5)	30 (29.5)	1.74 (0.93–3.23)	0.08	2.31 (1.41–3.80)	0.001	3.12 (1.82–5.34)	<0.001

Values are n (%) unless otherwise indicated. Hazard ratios (HRs) with 95% confidence intervals (CIs) are from Cox regressions for time-to-event data. Single imputation with the mode for missing data: n = 2 post-aortic regurgitation, n = 2 body mass index ≤20 kg/m^2, n = 2 chronic obstructive pulmonary disease.

MACCE = major adverse cardiac and cerebrovascular event(s).

TABLE 5 Long-Term Clinical Outcomes According to Graded Diastolic Dysfunction With Adjusted HRs

		Diastolic Dysfunction			Adjusted HR*					
					I vs. Normal		II vs. Normal		III vs. Normal	
1-Year Follow-Up	Normal (n = 232)	Grade I (n = 98)	Grade II (n = 198)	Grade III (n = 104)	Adjusted HR (95% CI)	Adjusted p Value	Adjusted HR (95% CI)	Adjusted p Value	Adjusted HR (95% CI)	Adjusted p Value
All-cause mortality	16 (6.9)	16 (16.3)	35 (17.9)	28 (27.6)	2.32 (1.15–4.66)	0.02	2.58 (1.43–4.67)	0.002	4.21 (2.25–7.86)	<0.001
Cardiovascular death	7 (3.1)	12 (12.4)	25 (13.2)	21 (21.0)	3.81 (1.49–9.74)	0.005	4.11 (1.77–9.51)	0.001	7.53 (3.17–17.9)	<0.001
Myocardial infarction	5 (2.3)	1 (1.0)	6 (3.2)	5 (5.3)			1.38 (0.42–4.56)	0.60		
Cerebrovascular events										
Disabling stroke	7 (3.0)	1 (1.0)	10 (5.3)	2 (2.0)			1.65 (0.62–4.38)	0.31		
MACCE	24 (10.4)	17 (17.3)	44 (22.5)	30 (29.5)	1.60 (0.86–3.00)	0.14	2.18 (1.32–3.59)	0.002	2.85 (1.65–4.92)	<0.001

Values are n (%) unless otherwise indicated. HRs with 95% CIs are from Cox regressions for time-to-event data. Single imputation with the mode for missing data: n = 2 post-aortic regurgitation, n = 2 body mass index ≤20 kg/m^2, n = 2 chronic obstructive pulmonary disease. *Adjusted effect of diastolic dysfunction using the covariates from the multivariable model indicated in Table 6, reported in case of more than 10 events detected in both groups combined in the pairwise comparisons.

Abbreviations as in Table 4.

population contributing to the development of LVDD independent of AS.

Our analysis suggests an important effect of LVDD on clinical outcome with a 2- to 44-fold increased risk of mortality with progressive stages of LVDD. The findings corroborate previous analyses from smaller patient cohorts (11,12,21). In a retrospective study of 90 patients undergoing TAVR, baseline LVDD was reported to be the most important echocardiographic factor associated with all-cause death at 1 year, whereas post-TAVR LVDD or changes in diastolic dysfunction grade were not associated with clinical outcome (11). In a prospective cohort of 166 patients with AS undergoing cardiac magnetic resonance imaging, Chin et al. (22) showed that progressive stages of LVDD correlated with increasing extent of myocardial fibrosis, and were associated with increased mortality irrespective of severity of AS. The transition from adaptive hypertrophy in response to narrowing of the aortic valve to congestive heart failure has been shown to be importantly driven by myocardial fibrosis (22,23). We observed in our cohort that the effect of LVDD was independent from systolic LV function, which underscores the applicability of LVDD as a viable tool for risk stratification in AS patients.

Differences in mortality manifested as early as 30 days after TAVR in patients with LVDD and accrued over time. The long-term effect of LVDD on survival may be related to the protracted regression of LV hypertrophy. Previous studies suggested an additive effect of LVDD and paravalvular regurgitation after TAVR. Although more than moderate AR after TAVR has been independently associated with an increased risk of mortality at 2 years (5), LV stiffness may further exacerbate the effect of persistent volume overload. In an analysis of almost 200 patients undergoing TAVR, patients with severe LVDD and evidence of at least mild AR 1 month after TAVR were found to have an almost 4 times increased risk of death at 2 years (12). The findings were corroborated by Conte et al. (21) showing an additive effect of LVDD and paravalvular regurgitation on 1-year mortality. In contrast to the these 2 studies, post-TAVR AR in patients with LVDD was not documented to further increase the risk of 1-year mortality beyond the effect of LVDD. The discrepancy in the findings may be related to the modest numbers of patients within the individual categories of LVDD and the limited duration of follow-up.

At variance with the above-mentioned studies, no association of LVDD at baseline and survival was noted in a study of 358 patients, despite documented improvement of LVDD during follow-up (13). The discrepant findings may be explained by differences in patient characteristics and ascertainment of diastolic dysfunction. In contrast to the previous report, all patients with atrial fibrillation or previous pacemaker implantation have been excluded in our analysis because mitral annular velocities and E/e′ ratios cannot be measured accurately in these patients.

STUDY LIMITATIONS. The findings of our analysis have to be interpreted in light of several limitations. First, we report on a relatively modest number of patients from a single center. However, our prospective registry is considerably larger as compared with cohorts of previous analyses, and adheres to high standards of data quality with rigorous data collection, standardized follow-up, and independent event adjudication at regular time intervals. Second, not all patients underwent detailed echocardiography for the accurate classification of diastolic function. Similarly, patients with a history of atrial fibrillation, permanent pacemaker, and surgical mitral valve

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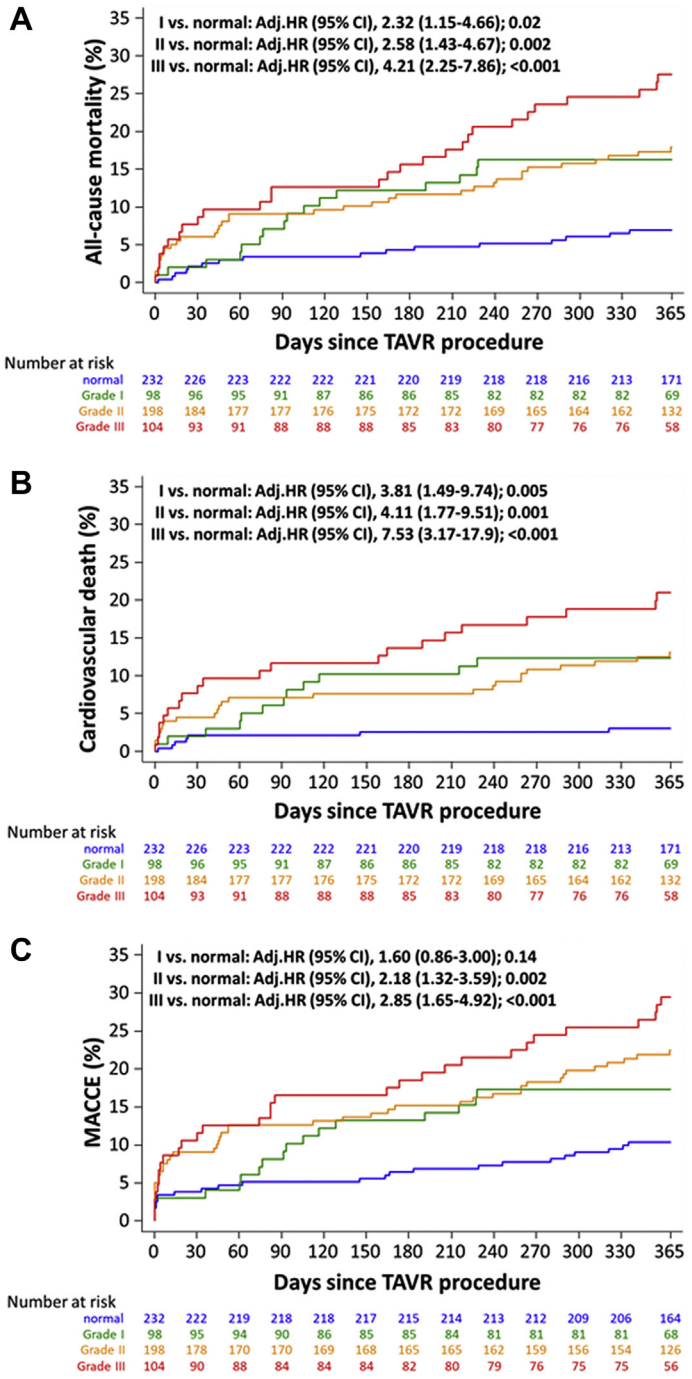
MARCH 26, 2018:593–601

FIGURE 2 Kaplan-Meier Analysis of Endpoints After TAVR



(A) Cumulative incidence of all-cause mortality, **(B)** cardiovascular death, and **(C)** major adverse cardiac and cerebrovascular events (MACCE) at 1-year post-TAVR, according to severity of LV diastolic dysfunction. CI = confidence interval; HR = hazard ratio; other abbreviations as in Figure 1.

TABLE 6 Predictive Factors of All-Cause Mortality at 1 Year

	Univariable Analysis		Multivariable Analysis	
	HR (95% CI)	p Value	Adjusted HR (95% CI)	p Value
Diastolic dysfunction		<0.001		<0.001
Normal	Ref.		Ref.	
Grade I	2.49 (1.24–4.97)	0.01	2.36 (1.17–4.74)	0.02
Grade II	2.75 (1.52–4.96)	0.001	2.58 (1.42–4.66)	0.002
Grade III	4.41 (2.39–8.16)	<0.001	4.41 (2.37–8.20)	<0.001
BMI ≤20 kg/m^2	2.56 (1.55–4.24)	<0.001	3.13 (1.87–5.25)	<0.001
Diabetes	1.94 (1.28–2.93)	0.002	2.11 (1.37–3.27)	0.001
COPD	1.77 (1.05–2.98)	0.03	2.03 (1.18–3.50)	0.01
Peripheral vascular disease	1.92 (1.19–3.10)	0.007	1.77 (1.08–2.91)	0.02
Age	1.00 (0.97–1.04)	0.92	1.03 (1.00–1.07)	0.08
NYHA functional class III or IV	1.81 (1.11–2.93)	0.02		0.37*
Log EuroSCORE ≥40%	2.15 (1.29–3.59)	0.003		0.36*
Post-AR ≥ moderate	0.91 (0.44–1.88)	0.80		0.78*

Multivariable model includes variables after stepwise inclusion using $p < 0.10$. There were 95 deaths in 632 patients. *The p value if added to multivariable model. Single imputation with the mode for missing data: n = 2 post-aortic regurgitation (AR), n = 2 body mass index (BMI) ≤20 kg/m^2, n = 2 chronic obstructive pulmonary disease (COPD).

Ref. = reference; other abbreviations as in Table 1.

replacement were excluded from the study cohort. Third, the etiology of LVDD is multifactorial. However, the shared different factors contributed to LVDD was difficult to assess on an individual basis in the present cohort of patients with AS. For example, previous myocardial infarction of the septum may have affected the measurement of septal e′. Although 16.6% of patients in our analysis had a history of previous myocardial infarction, we did not have detailed information on the location of myocardial necrosis. Furthermore, annular e′ velocity was only 1 of 4 variables used to assess diastolic function. Outcomes of the present analysis have therefore not been stratified according to contributing etiology of LVDD. Along the same line, diagnosing and grading of LVDD according to the algorithm suggested by American Society of Echocardiography and European Association of Cardiovascular Imaging guidelines does not apply to all patients with heart disease because the etiology of LVDD is multifactorial. Finally, we relied on echocardiographic parameters for the assessment of diastolic function. The time constant represented by the isovolumic-pressure decline (Tau), measured via

a catheter with a manometer is a more accurate method for diagnosing LVDD (24).

CONCLUSIONS

LVDD was documented in two-thirds of patients undergoing TAVR. We found an incremental risk of all-cause mortality after TAVR with advancing stages of LVDD at baseline, which took effect as early as 30 days after the intervention and was driven by cardiovascular death. Thus, treatment of AS before LVDD has developed may be beneficial. However, optimal timing of TAVR in patients with AS needs to be investigated in prospective clinical studies.

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PERSPECTIVES

WHAT IS KNOWN? LV hypertrophy in response to aortic valve stenosis and afterload increase results in LVDD and eventually heart failure. LVDD is associated with increased risk of all-cause death after surgical aortic valve replacement. The importance of LVDD on clinical outcomes after TAVR is unclear.

WHAT IS NEW? We found an incremental risk of all-cause death after TAVR with advancing stages of LVDD at baseline, which took effect as early as 30 days and was driven by cardiovascular death.

WHAT IS NEXT? Larger prospective studies are required to corroborate our findings and evaluate the predictive value of LVDD categories on short- and long-term clinical outcomes.

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KEY WORDS aortic stenosis, clinical outcomes, diastolic dysfunction, echocardiography, transcatheter aortic valve replacement

APPENDIX For supplemental tables and figures, please see the online version of this paper.