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Evolution and Prognostic Impact of Cardiac Damage After Aortic Valve Replacement

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ABSTRACT

BACKGROUND The impact of aortic valve replacement (AVR) on progression/regression of extravalvular cardiac damage and its association with subsequent prognosis is unknown.

OBJECTIVES The purpose of this study was to describe the evolution of cardiac damage post-AVR and its association with outcomes.

METHODS Patients undergoing transcatheter or surgical AVR from the PARTNER (Placement of Aortic Transcatheter Valves) 2 and 3 trials were pooled and classified by cardiac damage stage at baseline and 1 year (stage 0, no damage; stage 1, left ventricular damage; stage 2, left atrial or mitral valve damage; stage 3, pulmonary vasculature or tricuspid valve damage; and stage 4, right ventricular damage). Proportional hazards models determined association between change in cardiac damage post-AVR and 2-year outcomes.

RESULTS Among 1,974 patients, 121 (6.1%) were stage 0, 287 (14.5%) stage 1, 1,014 (51.4%) stage 2, 412 (20.9%) stage 3, and 140 (7.1%) stage 4 pre-AVR. Two-year mortality was associated with extent of cardiac damage at baseline and 1 year. Compared with baseline, cardiac damage improved in ~15%, remained unchanged in ~60%, and worsened in ~25% of patients at 1 year. The 1-year change in cardiac damage stage was independently associated with mortality (adjusted HR for improvement: 0.49; no change: 1.00; worsening: 1.95; $P = 0.023$) and composite of death or heart failure hospitalization (adjusted HR for improvement: 0.60; no change: 1.00; worsening: 2.25; $P < 0.001$) at 2 years.

CONCLUSIONS In patients undergoing AVR, extent of extravalvular cardiac damage at baseline and its change at 1 year have important prognostic implications. These findings suggest that earlier detection of aortic stenosis and intervention before development of irreversible cardiac damage may improve global cardiac function and prognosis. (PARTNER II Trial: Placement of AoRTic TraNscathetER Valves II - XT Intermediate and High Risk [PII A], NCT01314313; The PARTNER II Trial: Placement of AoRTic TraNscathetER Valves - PII B [PARTNERII B], NCT02184442; and PARTNER 3 Trial: Safety and Effectiveness of the SAPIEN 3 Transcatheter Heart Valve in Low Risk Patients With Aortic Stenosis [P3], NCT02675114) (J Am Coll Cardiol 2022;80:783–800) © 2022 by the American College of Cardiology Foundation.

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ABBREVIATIONS AND ACRONYMS

AS = aortic stenosis

AVR = aortic valve replacement

COPD = chronic obstructive pulmonary disease

LA = left atrial

LV = left ventricular

RV = right ventricular

SAVR = surgical aortic valve replacement

STS = Society of Thoracic Surgeons

TAVR = transcatheter aortic valve replacement

In patients with aortic stenosis (AS), risk stratification for aortic valve replacement (AVR) relies mainly on valve-related factors, symptoms, and comorbidities.[1,2] In 2017, we described for the first time a novel AS staging classification based on the extent of cardiac damage before AVR.[3] The aim of this stratification scheme was to provide a standardized approach to assessing the extent of cardiac damage beyond the simple grading of the valve disease itself (ie, extravalvular damage). Using specific and well-validated parameters for each stage, patients were stratified into 5 different disease stages based on the extent of cardiac damage (stage 0: no extravalvular damage; stage 1: left ventricular [LV] damage; stage 2: left atrial [LA]/mitral valve damage; stage 3: pulmonary vasculature/tricuspid valve damage; and stage 4: right ventricular [RV] damage) (**Figure 1**). These stages were designed to reflect the natural consequences and progressive damage that an untreated diseased aortic valve can have on cardiac structures. As expected, the extent of cardiac damage was strongly and positively associated with mortality and adverse events at 1-year post-AVR. Since the initial publication, the prognostic impact of this classification has been validated in multiple cohorts of patients with severe[4-14] and moderate AS[15] and among patients with and without symptoms.[16,17]

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Although the prognostic importance of extravalvular cardiac damage before AVR is thus well-established, the impact of AVR on progression or regression of cardiac damage and its association with subsequent prognosis is unknown. Therefore, in the current study, we sought to describe and characterize the natural evolution of cardiac damage 1 year after AVR and its association with subsequent outcomes.

METHODS

STUDY POPULATION. Patients with severe AS across the surgical risk spectrum who underwent either transcatheter aortic valve replacement (TAVR) or surgical aortic valve replacement (SAVR) as part of the PARTNER (Placement of Aortic Transcatheter Valves) 2A (N = 1,910), PARTNER 2B (N = 543), or PARTNER 3 trials (N = 948) were pooled and classified according to the extent of cardiac damage detected by echocardiography before AVR and at 1-year post-AVR as previously described (**Figure 1**).[3] The designs of the 3 trials have been described previously, including a detailed description of eligibility criteria and procedural methods.[18-20] Each trial was registered before the start of enrollment (NCT01314313 [P2A], NCT02184442 [P2B], NCT02675114 [P3]) and was approved by the institutional review board of each participating site. All patients provided written informed consent.

ECHOCARDIOGRAPHIC AND CLINICAL FOLLOW-UP. All patients underwent transthoracic echocardiography at baseline and 1-year follow-up using a uniform image acquisition protocol. All studies were analyzed by a central core laboratory with quality and measurement methodology previously reported.[21,22] In addition, all patients underwent clinical follow-up at 1, 6, 12, and 24 months after AVR, and all adverse events were adjudicated by an independent committee blinded to treatment assignment.

DEFINITIONS. At both baseline and 1-year follow-up, patients were categorized into 5 stages depending on the presence or absence of extravalvular cardiac damage as detected by transthoracic echocardiography. Stages ranged from 0 to 4, where 0 represents no cardiac damage and 4 represents the most severe cardiac damage. If patients met criteria for multiple stages, they were assigned to the highest (worst) stage. The classification algorithm as well as the statistical models were defined fully a priori.

STATISTICAL ANALYSIS. Continuous data are presented as mean ± SD and were compared between groups using the Student's *t*-test or the Wilcoxon rank sum test, as appropriate. Categorical variables are presented as count and percentage and were compared using the chi-square or the Fisher exact test. We estimated time-to-event data using Kaplan-Meier techniques. The association between baseline cardiac damage stage and 2-year outcomes (death; cardiovascular death; death or heart failure hospitalization; and death, heart failure hospitalization, or stroke) was assessed by means of multivariable Cox proportional hazards analysis with stratification by study and treatment assignment. Covariates for this analysis were selected a priori based on their known association with the outcomes of interest or clinical

The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

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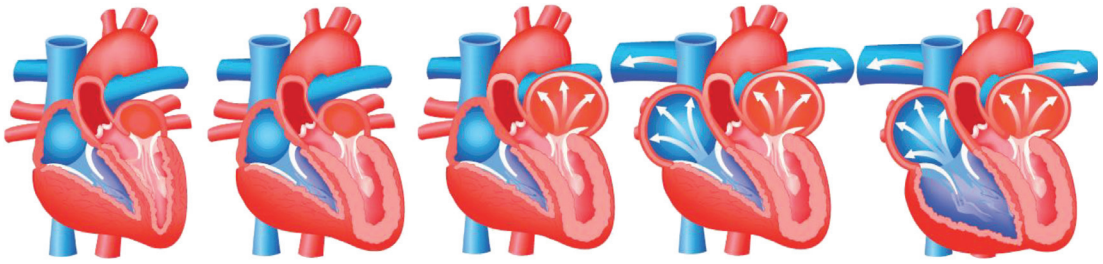
FIGURE 1 **Aortic Stenosis Staging Classification Based on Extent of Cardiac Damage**



Stages/Criteria	Stage 0	Stage 1	Stage 2	Stage 3	Stage 4
	No Cardiac Damage	LV Damage	LA or Mitral Damage	Pulmonary Vasculature or Tricuspid Damage	RV Damage
Echocardiogram		Increased LV Mass Index >115 g/m^2 (Male) >95 g/m^2 (Female)	Indexed LA Volume >35 mL/m^2	Systolic Pulmonary Hypertension >60 mm Hg	Moderate-Severe Right Ventricular Dysfunction
		E/e' >14	Moderate-Severe Mitral Regurgitation	Moderate-Severe Tricuspid Regurgitation	
		LV Ejection Fraction <50%	Atrial Fibrillation		

Stage 0: No other cardiac damage detected; Stage 1: left ventricular (LV) damage as defined by the presence of LV hypertrophy (LV mass index >95 g/m^2 for women, >115 g/m^2 for men),[42] severe LV diastolic dysfunction (E/e' >14),[43] or LV systolic dysfunction (LV ejection fraction <50%); Stage 2: left atrial (LA) or mitral valve damage or dysfunction as defined by the presence of an enlarged LA (>34 mL/m^2), the presence of atrial fibrillation, or the presence of moderate or severe mitral regurgitation; Stage 3: pulmonary artery vasculature or tricuspid valve damage or dysfunction as defined by the presence of systolic pulmonary hypertension (systolic pulmonary arterial pressure ≥60 mm Hg) or the presence of moderate or severe tricuspid regurgitation; and Stage 4: right ventricular (RV) damage as defined by the presence of moderate or severe RV dysfunction. Adapted with permission from Généreux et al.[3]

judgment and included: age, sex, Society of Thoracic Surgeons (STS) risk score, aortic valve area, coronary artery disease, diabetes mellitus, prior coronary artery bypass grafting, chronic obstructive pulmonary disease (COPD), serum creatinine >2.0 mg/dL, and frailty.

For the analysis of the association between 1-year cardiac damage stage and 2-year outcomes, the analytic approach was similar but the analytic cohort was restricted to patients who were alive with echocardiographic assessment at 1 year, the analytic timeframe was from 1 to 2 years, and we adjusted for baseline cardiac damage stage in addition to the baseline covariates listed previously. Finally, we examined the independent association between change in cardiac damage stage between baseline and 1-year (improved, unchanged, worse) and 2-year outcomes, adjusting for baseline covariates and baseline cardiac damage stage. For this analysis, change in cardiac damage stage was considered as a class variable (resulting in a single *P* value for the change variable) but HRs were calculated separately for improvement and worsening, with no change as the reference group.

RESULTS

STUDY POPULATION. Among 3,401 pooled patients, 1,974 patients (PARTNER 3 low risk, n = 561;

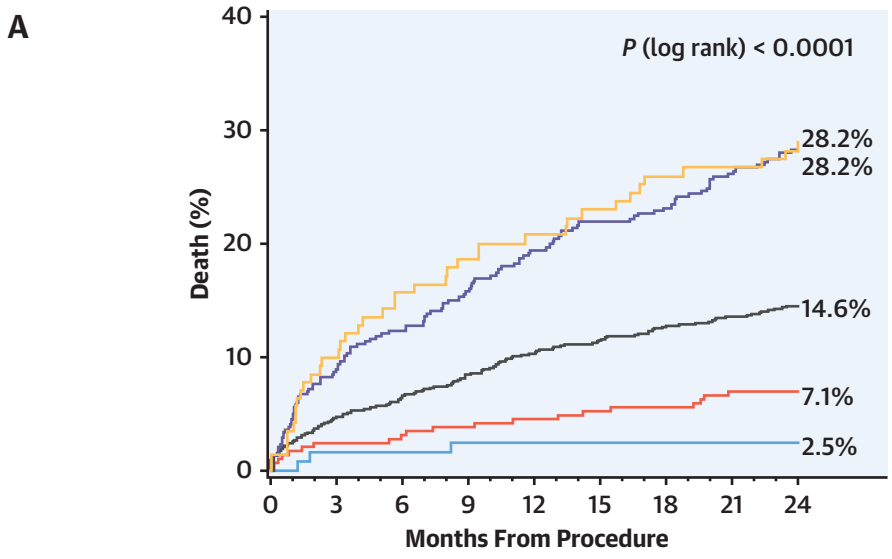
TABLE 1 **Prevalence of Cardiac Damage Stages and Their Individual Components at Baseline (N = 1,974)**[a]

Stage 0	121/1,974 (6.1)
Stage 1	287/1,974 (14.5)
Increased LV mass index[b]	1,124/1,900 (59.2)
E/e' >14	1,069/1,719 (62.2)
LV ejection fraction <50%	443/1,971 (22.5)
Stage 2	1,014/1,974 (51.4)
Left atrial volume index >34 mL/m^2	1,276/1,866 (68.4)
Atrial fibrillation	685/1,974 (34.7)
Moderate/severe mitral regurgitation	379/1,953 (19.4)
Stage 3	412/1,974 (20.9)
PASP ≥60 mm Hg	142/1,904 (7.5)
Moderate/severe tricuspid regurgitation	403/1,963 (20.5)
Stage 4	140/1,974 (7.1)
Moderate/severe RV dysfunction	140/1,974 (7.1)

Values are n/N (%). [a]Components are not mutually exclusive; [b]LV mass index >95 g/m^2 for women, >115 g/m^2 for men.

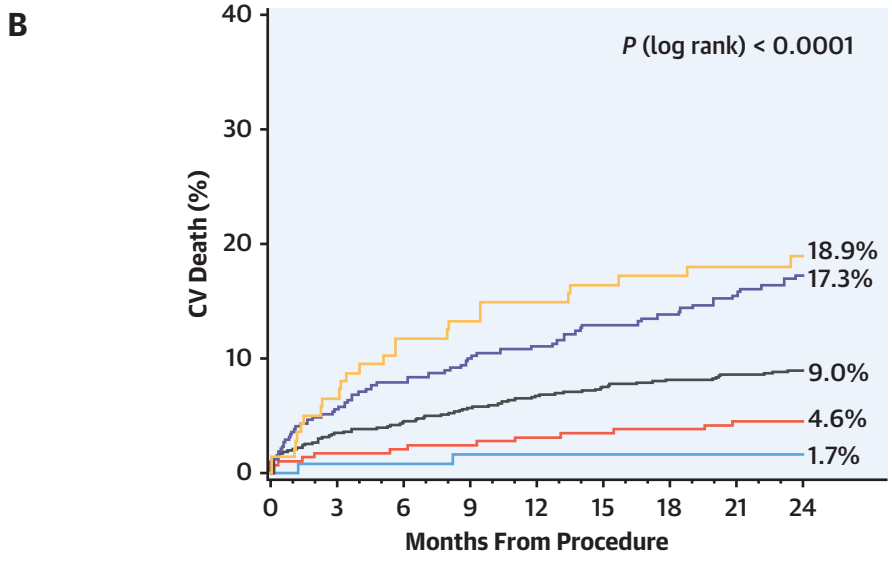
LV = left ventricular; PASP = pulmonary artery systolic pressure; RV = right ventricular.

FIGURE 2 **2-Year Outcomes According to Baseline Stage of Cardiac Damage**



Number at risk:

Baseline Stage 0	121	119	119	118	117	117	116	115	113
Baseline Stage 1	287	279	277	273	271	264	263	259	255
Baseline Stage 2	1,014	957	936	915	891	873	856	844	827
Baseline Stage 3	412	374	359	344	329	313	306	293	284
Baseline Stage 4	140	126	117	112	109	105	100	99	96



Number at risk:

Baseline Stage 0	121	119	119	118	117	117	116	115	113
Baseline Stage 1	287	279	277	273	271	264	263	259	255
Baseline Stage 2	1,014	957	936	915	891	873	856	844	827
Baseline Stage 3	412	374	359	344	329	313	306	293	284
Baseline Stage 4	140	126	117	112	109	105	100	99	96

Kaplan-Meier curves for 2-year outcomes based on the stage of cardiac damage at baseline. **(A)** All-cause death; **(B)** cardiovascular (CV) death; **(C)** composite of all-cause death or heart failure (HF) hospitalization; and **(D)** composite of all-cause death, HF hospitalization, or stroke.

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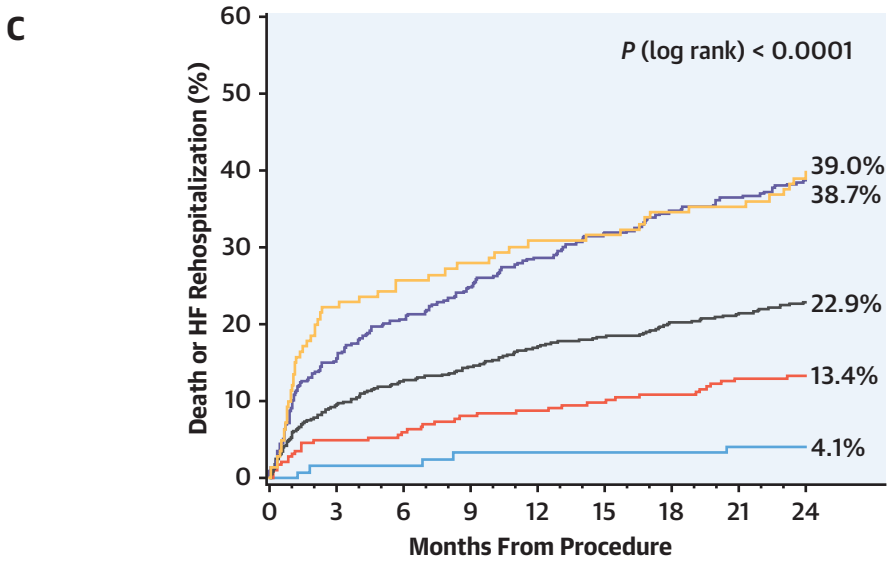
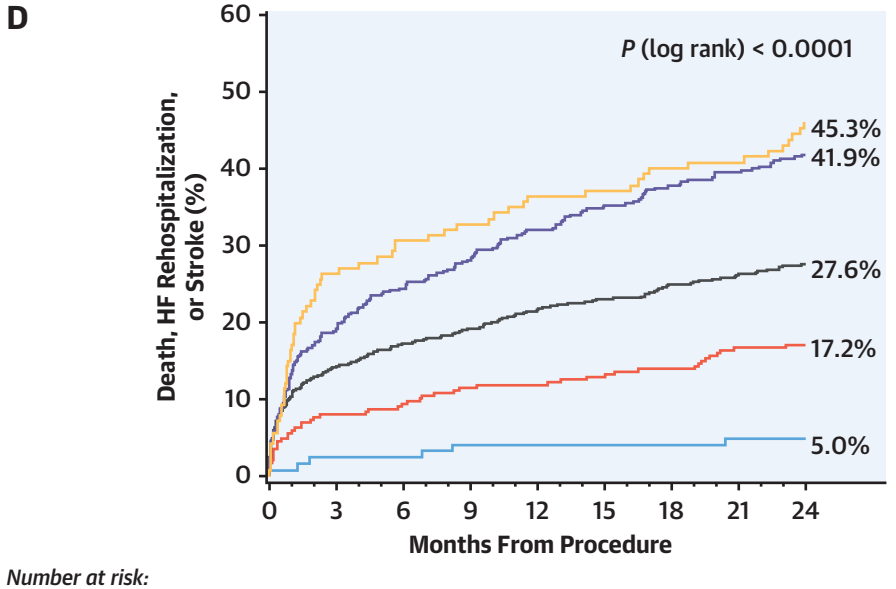
FIGURE 2 Continued



Number at risk:

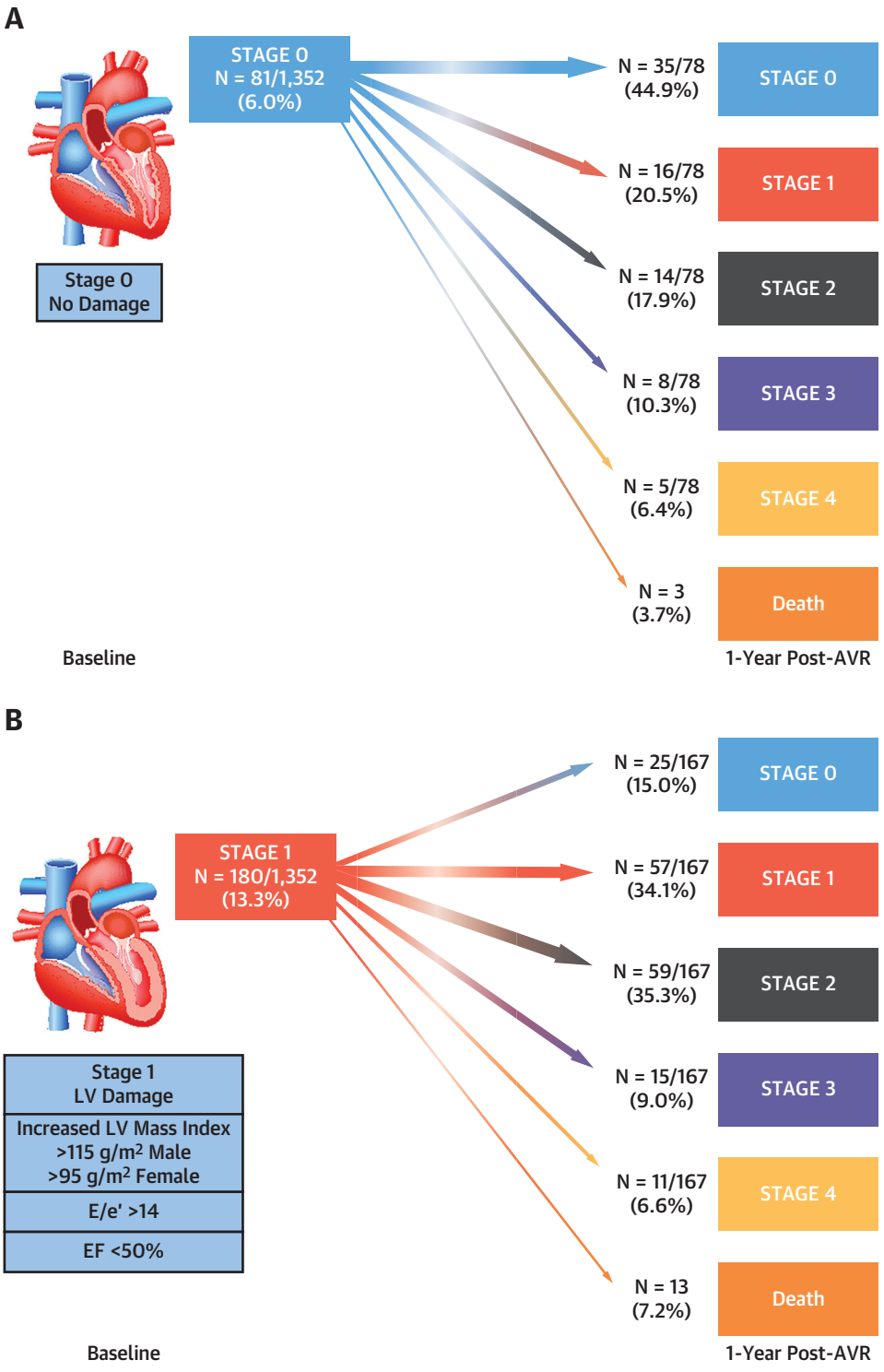
Baseline Stage 0	121	119	119	117	116	116	115	114	112
Baseline Stage 1	287	279	269	261	259	252	249	243	238
Baseline Stage 2	1,014	908	874	854	825	806	783	769	748
Baseline Stage 3	412	347	325	307	291	273	261	253	243
Baseline Stage 4	140	109	103	99	95	93	88	87	82



Number at risk:

Baseline Stage 0	121	118	118	116	115	115	114	113	111
Baseline Stage 1	287	263	259	251	250	243	240	232	227
Baseline Stage 2	1,014	863	830	809	781	762	739	724	705
Baseline Stage 3	412	332	309	293	277	259	248	240	230
Baseline Stage 4	140	103	97	93	88	86	81	80	74

FIGURE 3 Evolution of Cardiac Damage Stage From Baseline to 1-Year Post-AVR



(A) Evolution of patients in stage 0 from baseline to 1 year post-aortic valve replacement (AVR); **(B)** evolution of patients in stage 1 from baseline to 1-year post-AVR; **(C)** evolution of patients in stage 2 from baseline to 1-year post-AVR; **(D)** evolution of patients in stage 3 from baseline to 1-year post-AVR; **(E)** evolution of patients in stage 4 from baseline to 1-year post-AVR. EF = ejection fraction; LA = left atrium; LV = left ventricle; MR = mitral regurgitation; PA = pulmonary artery; RV = right ventricle; TR = tricuspid regurgitation.

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FIGURE 3 Continued

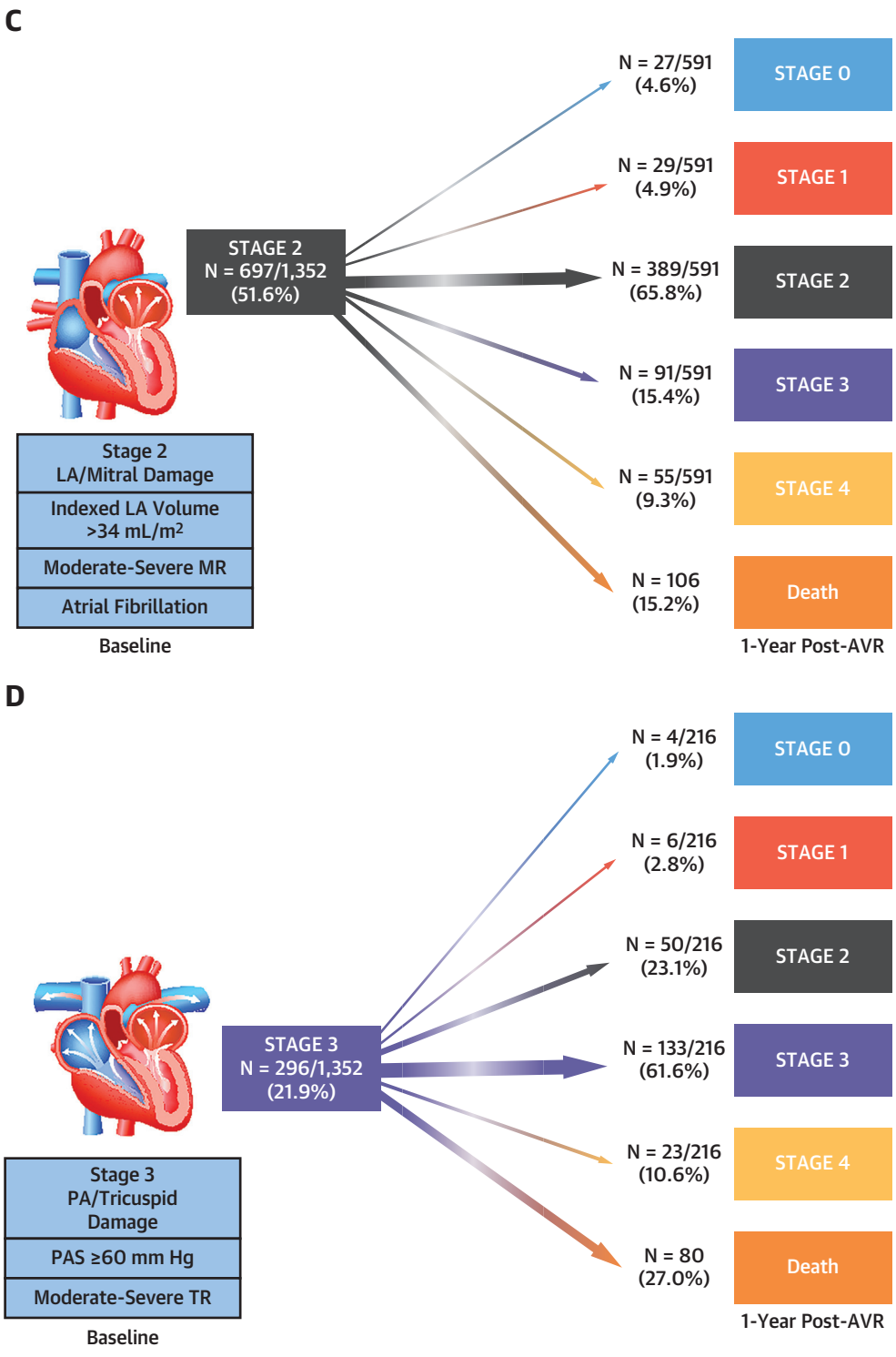

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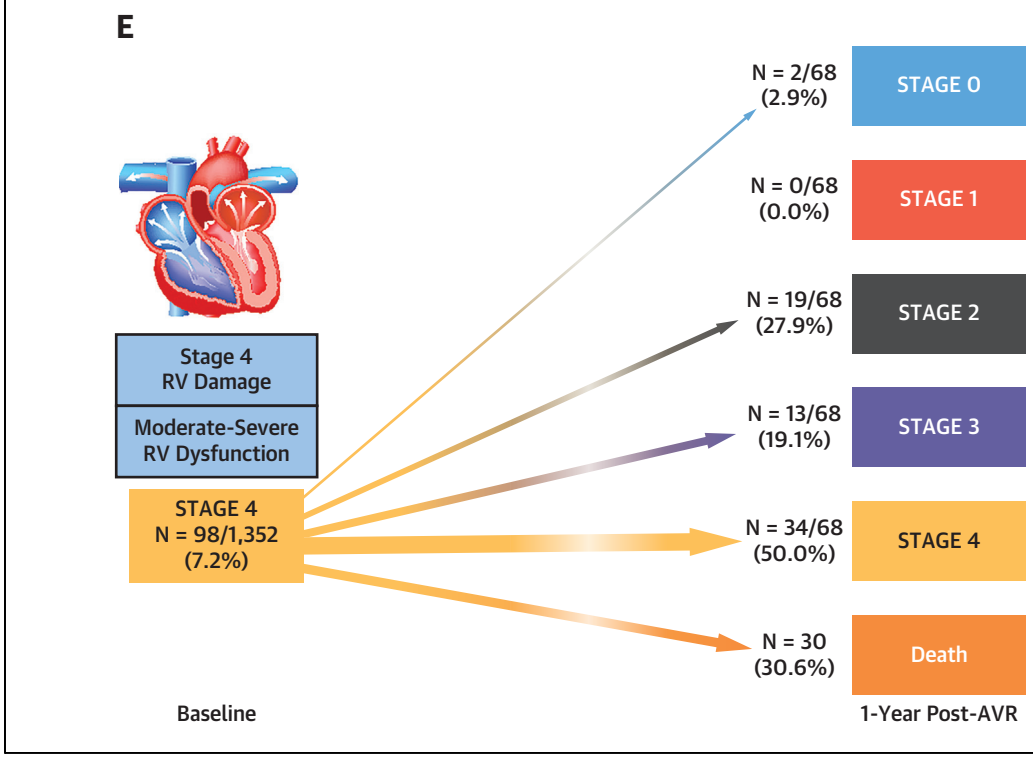
FIGURE 3 Continued



PARTNER 2A intermediate risk, n = 1,071; and PARTNER 2B inoperable, n = 342) had evaluable cardiac damage staging by echocardiographic assessment at baseline (before AVR). Of these, 794 (40.2%) underwent SAVR, and 1,180 (59.8%) underwent TAVR. At baseline, 121 (6.1%) were in stage 0 (no cardiac damage), 287 (14.5%) were in stage 1 (LV damage), 1,014 (51.4%) were in stage 2 (LA or mitral valve damage), 412 (20.9%) were in stage 3 (pulmonary vasculature or tricuspid valve damage), and 140 (7.1%) were in stage 4 (RV damage). The specific components of cardiac damage for patients in each stage are summarized in **Table 1**. Baseline and procedural characteristics according to baseline cardiac damage stage are presented in Supplemental Table 1. In general, patients with more advanced stages were older and more often men; had higher STS scores; were more likely to have diabetes, previous myocardial infarction, prior coronary artery bypass grafting, and COPD; and were more likely to be frail. They also presented more often in New York Heart Association functional class III-IV. Rates of each individual cardiac damage component within each stage are presented in Supplemental Table 2. Median follow-up time was 2 years (IQR: 2, 2 years), with a maximum follow-up of 2 years.

ASSOCIATION OF BASELINE STAGE WITH 2-YEAR OUTCOMES. Among the entire population, estimated 2-year mortality was 2.5% for patients who were in stage 0 at baseline, 7.1% in stage 1, 14.6% in stage 2, 28.2% in stage 3, and 28.2% in stage 4 (overall $P_{\text{log-rank}} < 0.0001$) (**Figure 2A**). In unadjusted analyses, increasing cardiac damage stage was also associated with an increase in rates of cardiovascular death (**Figure 2B**), the composite of death or heart failure hospitalization (**Figure 2C**), and the composite of death, heart failure hospitalization, or stroke (**Figure 2D**). In multivariable analysis, the extent of cardiac damage at baseline was independently associated with increased mortality 2 years after AVR (HR: 1.51 per each increment in stage; 95% CI: 1.32-1.72; $P <$ 0.0001) (Supplemental Table 3).

EVOLUTION OF CARDIAC DAMAGE AND ASSOCIATION WITH 2-YEAR OUTCOMES. At 1 year, 1,120 patients were alive and had paired echocardiographic assessments at baseline and 1 year (Supplemental Figure 1). Compared with pre-AVR, 15.6% of patients improved at least 1 stage at 1-year follow-up, 57.9% remained in the same stage, and 26.5% deteriorated at least 1 stage. Baseline and procedural characteristics according to stage evolution are presented in Supplemental Table 4. **Figure 3** shows the evolution of

cardiac damage stage from baseline to 1-year post-AVR, stratified according to baseline stage. In unadjusted analyses, 1-year stage was associated with a progressive increase in all-cause death (**Figure 4A**), cardiovascular death (**Figure 4B**), the composite of death or rehospitalization for heart failure (**Figure 4C**), and the composite of death, rehospitalization for heart failure, or stroke (**Figure 4D**).

Independent predictors of mortality between 1 and 2 years included 1-year stage of cardiac damage (adjusted HR: 1.76 per stage; 95% CI: 1.29-2.41; $P = 0.0004$), and STS score (HR: 1.07; 95% CI: 1.02-1.12; $P = 0.004$) (Supplemental Table 5). Stage of cardiac damage at 1-year follow-up remained a strong independent predictor of 2-year mortality (HR: 1.67 per stage; 95% CI: 1.18-2.35; $P = 0.004$) and the composite of mortality or rehospitalization for heart failure (HR: 1.93 per stage; 95% CI: 1.54-2.42; $P < 0.0001$), even after adjusting for baseline stage of cardiac damage (Supplemental Table 6).

Table 2 shows the evolution in each stage's components between baseline and 1 year. Among patients with abnormal components at baseline, 18%-64% of individual abnormalities had either improved or resolved at 1 year, with the exception of atrial fibrillation, which did not resolve. Other factors with low rates of improvement 1 year after AVR included LA enlargement (17.9%), increased LV mass (33.9%), and tricuspid regurgitation (29.2%). Among patients with a "normal" component at baseline, 1.7%-31.5% of individual components demonstrated worsening at 1-year follow-up. Those factors most likely to worsen included LA enlargement (31.5%), diastolic dysfunction (30.4%), atrial fibrillation (16.7%), and moderate-to-severe tricuspid regurgitation (15.5%).

Figure 5 shows the relationship between stage evolution at 1-year and 2-year rates of death or heart failure hospitalization, stratified according to baseline stage. Although the relationship was only statistically significant for patients in stage 2 at baseline, for each baseline stage, 2-year outcomes were consistently best among those patients who improved, intermediate in those who remained unchanged, and worst among those who worsened. In the overall population, after adjusting for baseline factors (including cardiac damage stage) and type of AVR, the change in cardiac damage stage between baseline and 1-year after AVR was independently associated with both all-cause mortality ($P = 0.023$) and the composite of death or heart failure hospitalization ($P < 0.001$) (**Central Illustration**). The magnitude of effect was similar for both improvement and worsening of cardiac damage stage. For all-cause mortality, the adjusted HR was 0.49 (95% CI: 0.20-1.16) for improvement and 1.95 (95% CI: 1.02-3.72) for worsening. For the composite of death or heart failure hospitalization, the adjusted HR was 0.60 (95% CI: 0.34-1.06) for improvement and 2.25 (95% CI: 1.46-3.46) for worsening (Supplemental Table 6).

Baseline and procedural characteristics according to stage evolution are presented in Supplemental Table 7. Independent predictors of stage deterioration included the presence of hypertension (OR: 1.73; 95% CI: 1.01-2.96; $P = 0.044$) and index procedure performed with surgical AVR (OR: 2.04; 95% CI: 1.52-2.74; $P < 0.0001$) compared with TAVR.

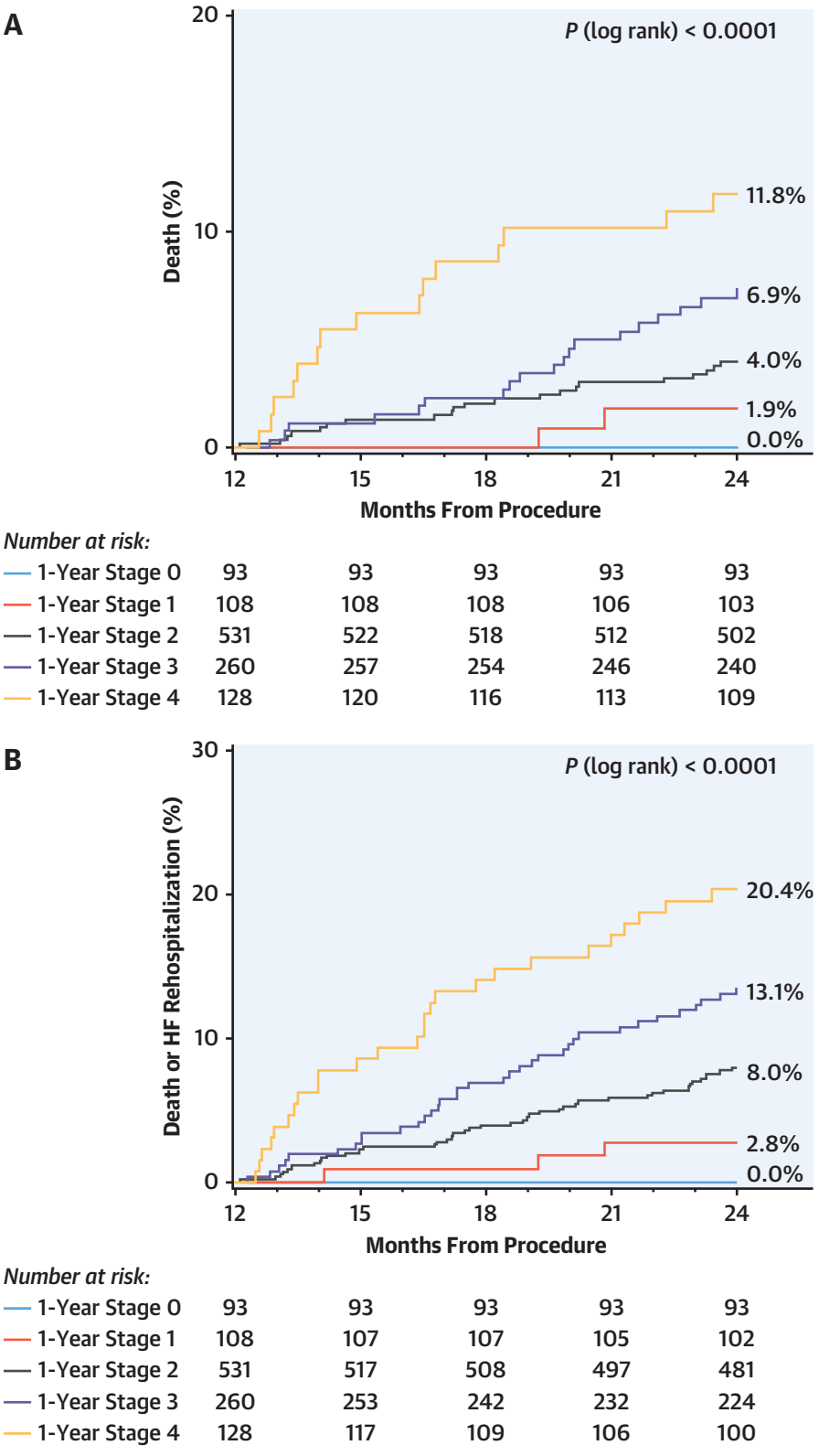
DISCUSSION

The current study, derived from 1,974 patients with severe AS undergoing AVR, demonstrates the following findings: 1) a high proportion of patients have some degree of extravalvular cardiac damage both before and 1 year after AVR; 2) the extent of cardiac damage at baseline and at 1-year post-AVR are strongly associated with an increase in mortality and adverse events at 2 years post-AVR; 3) compared with baseline, most patients demonstrated either no change (~60%) or deterioration (~25%) in cardiac damage stage 1 year after AVR; and 4) change in cardiac damage stage 1 year after AVR was associated with 2-year prognosis, independent of baseline characteristics and baseline cardiac damage stage.

The current study confirms and extends the value of the cardiac damage classification scheme previously published in 2017.[3] In the original validation study, we demonstrated the association between baseline cardiac damage stage and 1-year outcomes among a population of patients undergoing SAVR and TAVR who were at intermediate and high risk for SAVR. The current study extends these findings to an all-comers population, including patients at low risk for surgery, and expands follow-up to 2 years. The extent of cardiac damage was one of the strongest predictors of 2-year mortality, even when we adjusted for well-known prognostic variables such as frailty, COPD, and STS score. More importantly, for the first time, this study has characterized the evolution of global cardiac damage over time and demonstrated that change in cardiac damage stage at 1 year is strongly associated with subsequent prognosis—independent of other factors (including baseline classification).

The approach of classifying patients based on their "global cardiac health" (extent and burden of cardiac damage) rather than focusing on a single variable has several advantages. For example, after successful

FIGURE 4 **2-Year Outcomes According to Stage of Cardiac Damage at 1 Year**



Kaplan-Meier curves for 2-year outcomes based on the stage of cardiac damage at 1-year post-aortic valve replacement. **(A)** death; **(B)** death or HF rehospitalization; **(C)** CV death; **(D)** death, HF rehospitalization, or stroke.

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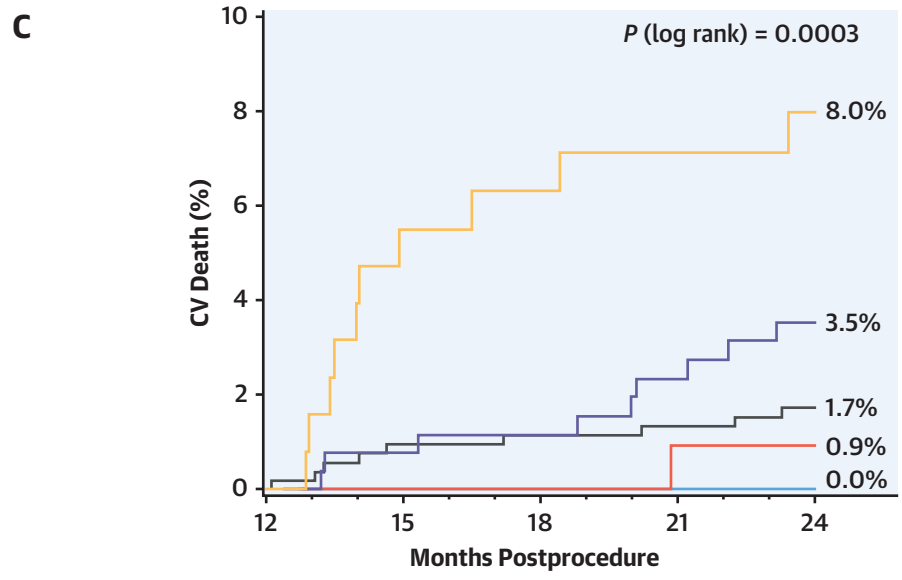
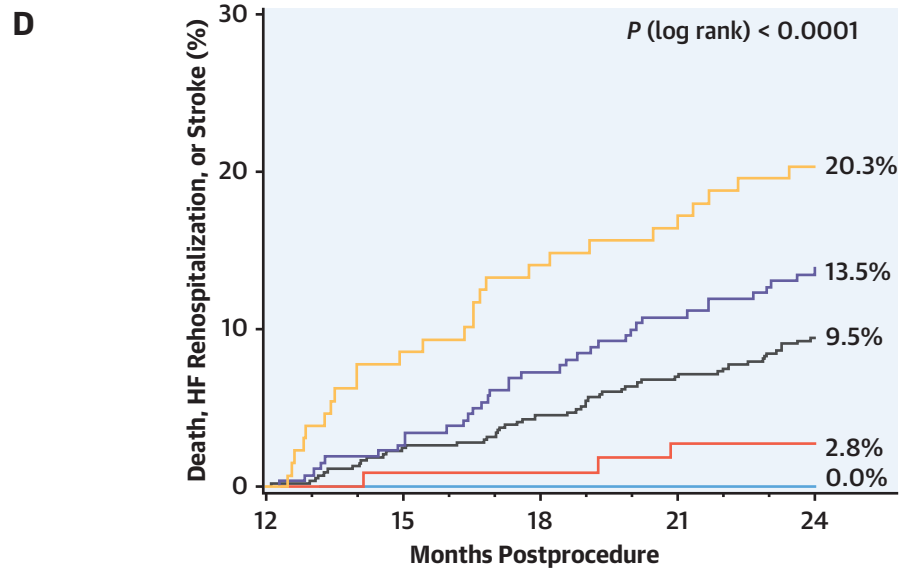
FIGURE 4 Continued



Number at risk:

1-Year Stage 0	93	93	93	93	93
1-Year Stage 1	108	108	108	106	103
1-Year Stage 2	531	522	518	512	502
1-Year Stage 3	260	257	254	246	240
1-Year Stage 4	128	120	116	113	109



Number at risk:

1-Year Stage 0	93	93	93	93	93
1-Year Stage 1	108	107	107	105	102
1-Year Stage 2	531	516	505	491	474
1-Year Stage 3	260	253	241	231	223
1-Year Stage 4	128	117	110	107	101

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TABLE 2 Evolution in Each Stage's Components at 1 Year Compared With Baseline

	Baseline	1 Year	Change at 1 Year	
			Abnormal at Baseline and Normalized at 1 Year	Normal at Baseline and Worsened at 1 Year
Stage 1				
Increased LV mass index[a]	632/1,083 (58.4)	452/1,079 (41.9)	206/608 (33.9)	41/445 (9.2)
E/e′ >14	605/996 (60.7)	574/995 (57.7)	141/549 (25.7)	110/362 (30.4)
LV ejection fraction <50%	227/1,119 (20.3)	198/1,118 (17.7)	96/227 (42.3)	66/890 (7.4)
Stage 2				
LA volume index >34 mL/m^2	724/1,069 (67.7)	680/1,036 (65.6)	120/669 (17.9)	106/336 (31.5)
Atrial fibrillation	388/1,120 (34.6)	510/1,120 (45.5)	0/388 (0.0)	122/732 (16.7)
Moderate/severe MR	212/1,111 (19.1)	183/1,097 (16.7)	109/208 (52.4)	81/882 (9.2)
Stage 3				
PASP ≥60 mm Hg	73/1,082 (6.7)	48/1,084 (4.4)	44/69 (63.8)	17/981 (1.7)
Moderate/severe TR	211/1,115 (18.9)	289/1,111 (26)	61/209 (29.2)	139/898 (15.5)
Stage 4				
Moderate/severe RV dysfunction	68/1,120 (6.1)	128/1,120 (11.4)	34/68 (50.0)	94/1,052 (8.9)

Values are n/N (%). [a]LV mass index >95 g/m^2 for women, >115 g/m^2 for men.
LA = left atrium; MR = mitral regurgitation; TR = tricuspid regurgitation; other abbreviations as in Table 1.

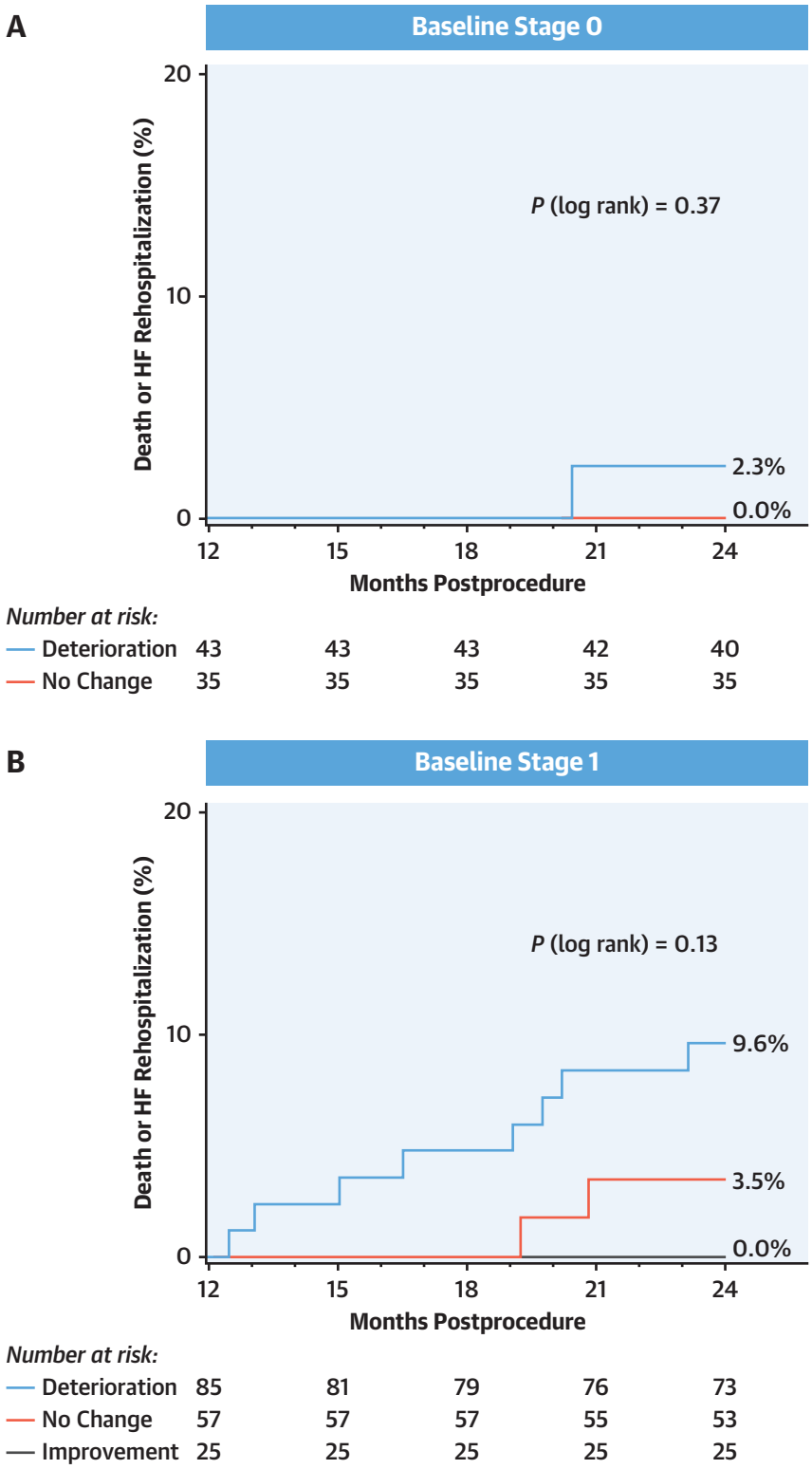
AVR, a patient may experience some regression of LV hypertrophy or improvement in LV ejection fraction, but the patient may continue to have significant mitral regurgitation or tricuspid regurgitation that offset these "downstream" benefits. Similarly, the presence of one cardiac abnormality may prevent the improvement of other cardiac conditions. For example, the presence of atrial fibrillation has been shown to impair LV remodeling and function[23] and can lead to annular dilation with associated secondary mitral regurgitation or tricuspid regurgitation. As such, the multiparametric approach of the staging classification provides a more holistic and patient-centered approach, capturing potential therapeutic benefits of AVR at multiple levels.

Further examination of the evolution of each individual component of cardiac damage provides additional insight into how patients evolve clinically post-AVR (Table 2). Indeed, a surprisingly high number of cardiac damage components remained abnormal or even worsened after AVR. Given the association of residual cardiac damage after AVR with subsequent adverse outcomes, these findings suggest that the extent of cardiac damage present after AVR should continue to be monitored and the intensity of therapy should be adapted accordingly. In addition, patients whose cardiac damage stage fails to improve after AVR should be investigated for other concomitant disease, such as amyloidosis,[24] coronary artery disease,[25] hypertension, other valve diseases, or dysrhythmia,[26] that could be addressed to potentially improve prognosis.

Interestingly, hypertension was one of the predictors of worsening in stage of cardiac damage after AVR. In previous studies, hypertension has been associated with cardiac damage, such as LV hypertrophy and fibrosis, that often fails to resolve even after blood pressure is controlled.[27] This finding highlights the importance of optimal blood pressure control among patients with AS because it further increases the afterload imposed by the stenosed aortic valve.[1,2] Another intriguing finding of our study was that compared with TAVR, SAVR was independently associated with worsening stages of cardiac damage. There are several potential explanations for this finding. SAVR is known to be associated with an increased rate of new-onset atrial fibrillation after AVR,[26] increased risk of patient prosthesis mismatch with reduced LV mass regression,[28] and postoperative RV dysfunction related to cardiopulmonary bypass process or suboptimal RV protection during surgery.[29,30] This finding underlines the value of less-invasive approaches to minimize procedural cardiac damage and increase the odds of cardiac recovery post-AVR.

Our findings also have important implications for the timing of valve replacement for patients with aortic stenosis. Current guidelines recommend waiting for the onset of symptoms before consideration of AVR for patients with severe AS.[1,2] However, because few patients demonstrate regression of cardiac damage after AVR, intervention before the AS reaches a severe and symptomatic state could potentially limit the extent of cardiac damage, thus leading to improved long-term outcomes after AVR. Indeed, 2 recent small, randomized trials performed in asymptomatic patients with critical[31] or severe AS[32] have demonstrated reduced rates of mortality

FIGURE 5 2-Year Outcomes by Evolution in Stage of Cardiac Damage



Kaplan-Meier curves for 2-year rates of death or heart failure hospitalization according to the improvement, lack of improvement, or deterioration in stage of cardiac damage at 1-year post-aortic valve replacement for each baseline stage of cardiac damage. **(A)** Baseline stage 0; **(B)** baseline stage 1; **(C)** baseline stage 2; **(D)** baseline stage 3; and **(E)** baseline stage 4.

Continued on the next page

FIGURE 5 Continued

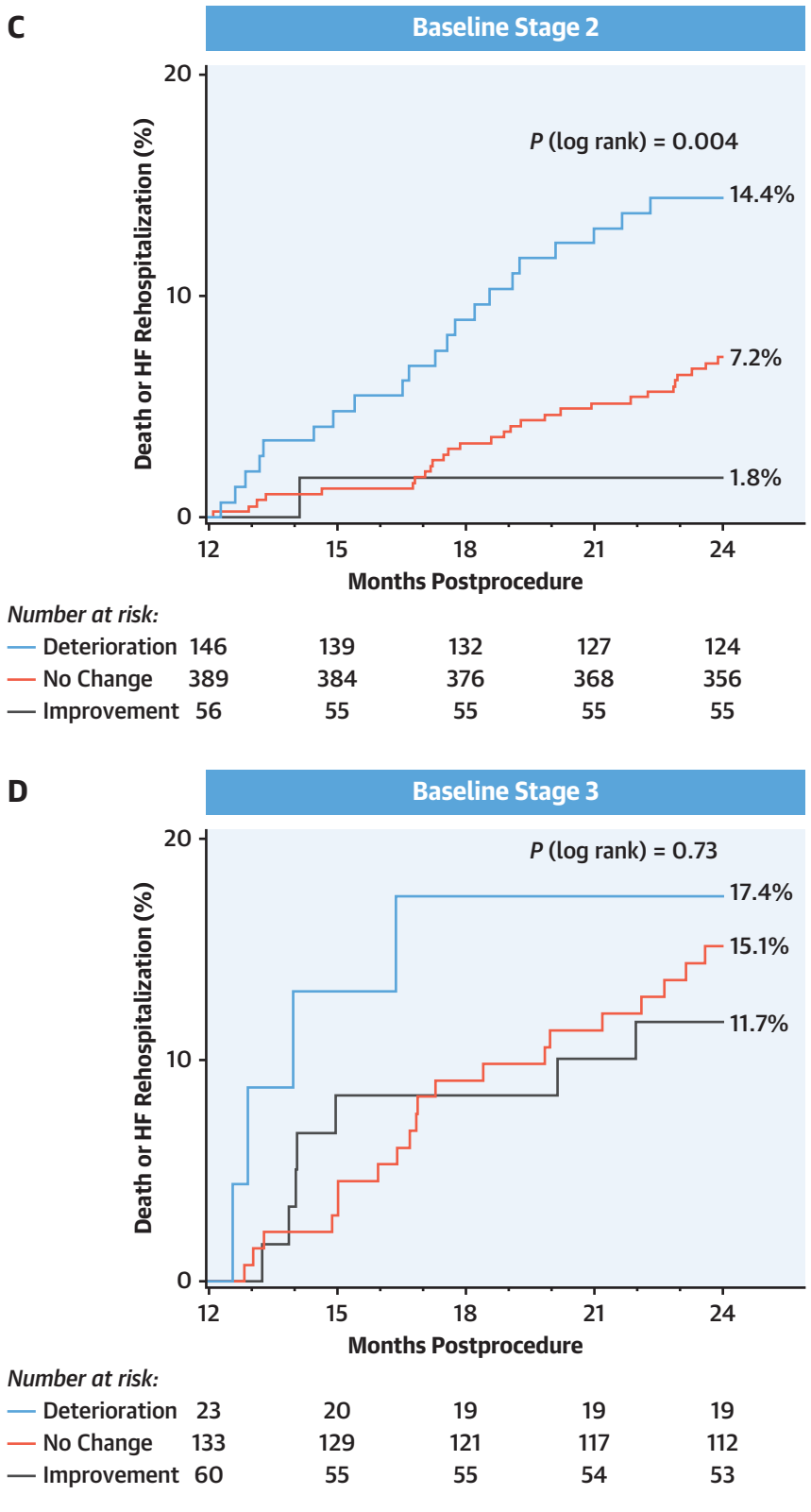


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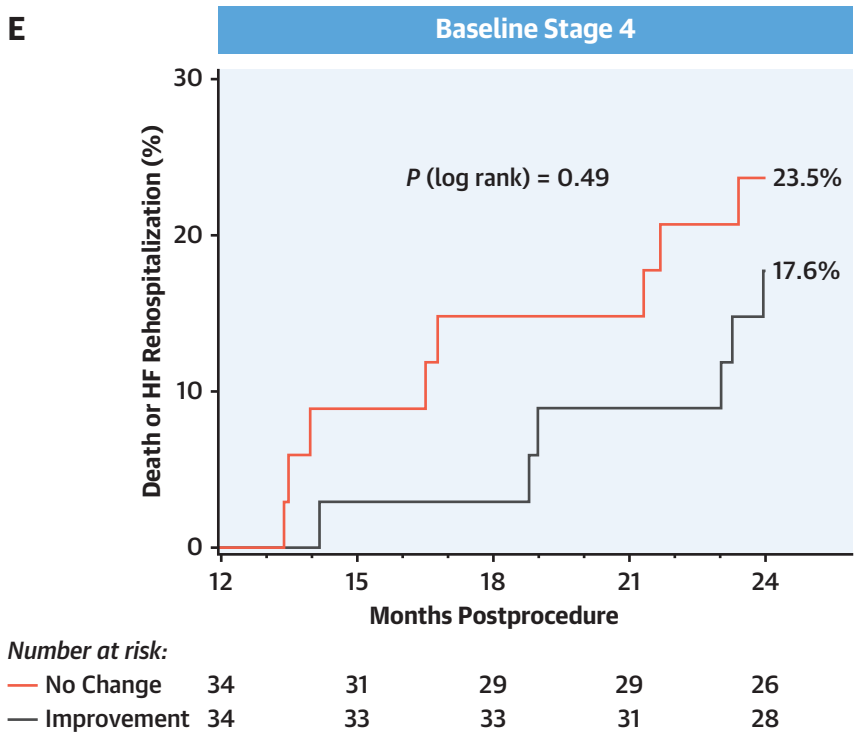
FIGURE 5 Continued



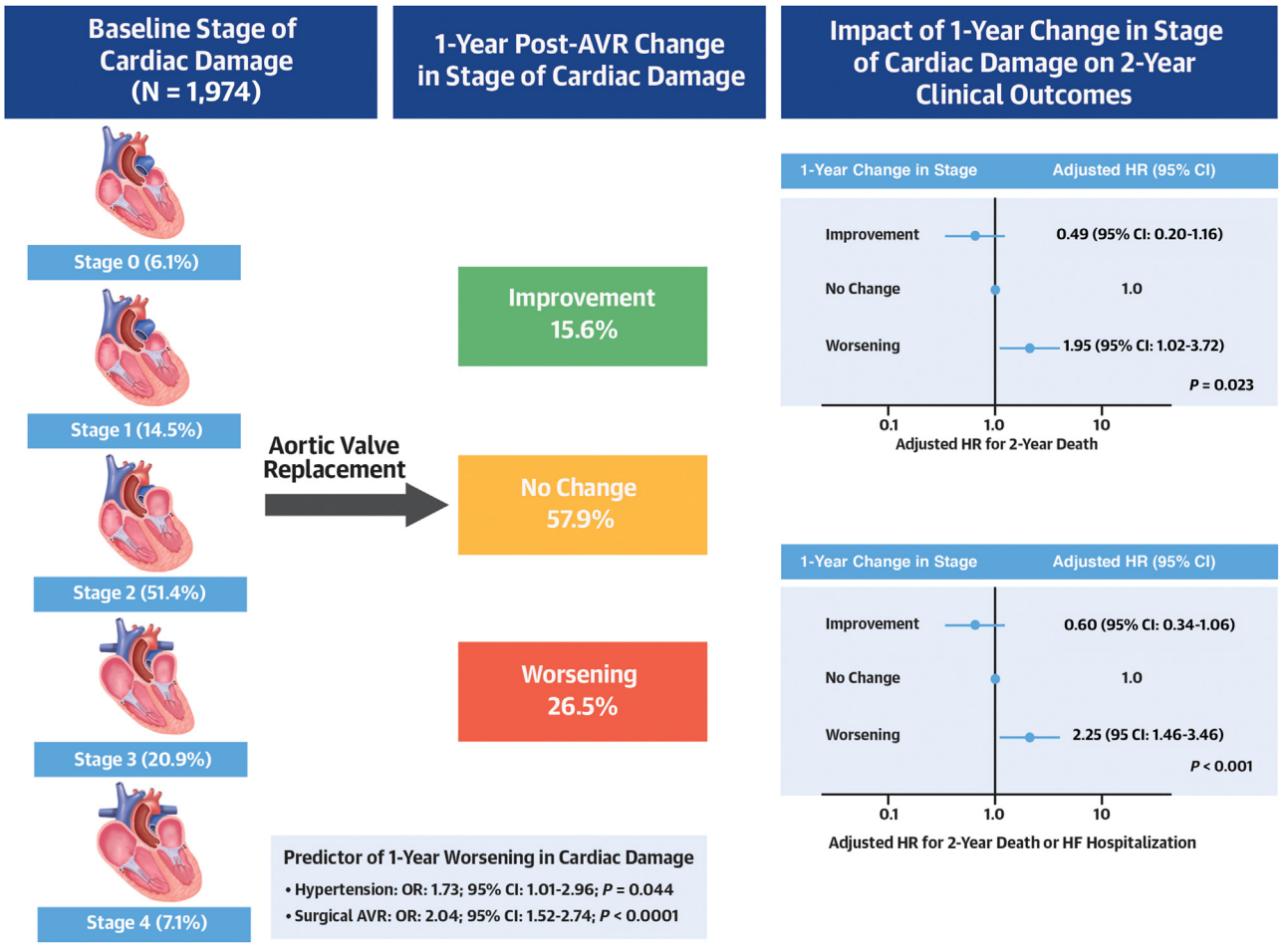
and adverse cardiovascular events when SAVR was performed before symptoms occurred compared with a strategy of clinical surveillance. Larger trials are ongoing that will determine if early TAVR among patients with severe asymptomatic AS (EARLY TAVR [Evaluation of TAVR Compared to Surveillance for Patients With Asymptomatic Severe Aortic Stenosis] [NCT03042104] and EVoLVeD [Early Valve Replacement Guided by Biomarkers of LV Decompensation in Asymptomatic Patients With Severe AS] [NCT03094143]) or moderate AS (PROGRESS [Management of Moderate Aortic Stenosis by Clinical Surveillance or TAVR] [NCT04889872]) will improve prognosis and prevent progression of cardiac damage.[33]

Finally, our findings suggest a role for more aggressive management of extravalvular cardiac damage and its underlying causes after AVR. For example, treatment of hypertension may reduce LV remodeling and improve diastolic dysfunction after AVR.[34,35] Similarly, aggressive treatment of residual cardiac conditions, such as persistent mitral or tricuspid regurgitation, systolic dysfunction, and atrial fibrillation, should be performed if the full benefit of AVR is to be reached.[36-38]

STUDY LIMITATIONS. First, it has been demonstrated that regression of some cardiac abnormalities, such as LV mass, can take up to 5 years after AVR.[39-41] Longer follow-up might have allowed for better characterization of the beneficial impact of AVR on the evolution of cardiac damage. Nonetheless, many components of cardiac damage failed to normalize post-AVR, and some even worsened within a year, highlighting the need to carefully track these components and adjust therapy accordingly during patient follow-up. Second, the current cohort included only patients with severe symptomatic AS. In these patients with very advanced disease, cardiac damage could have been established and essentially permanent, with no potential for reversibility. Whether earlier intervention in patients with severe asymptomatic AS or moderate AS would have resulted in higher rates of normalization is unknown. Third, detailed assessment of medical therapy was not available within the pooled studies, thus limiting any insights regarding the potential protective role of some pharmacological agents.

Fourth, new occurrence or worsening of existing cardiac damage could be caused by other conditions (eg, coronary artery disease, pulmonary embolism, amyloidosis, myocarditis) unrelated to AS. From a pragmatic standpoint, it is often impossible to determine the underlying cause of cardiac damage in such patients. That said, additional imaging such as cardiac magnetic resonance imaging or Technetium

CENTRAL ILLUSTRATION **Evolution and Prognostic Impact of Cardiac Damage Postaortic Valve Replacement**



Généreux P, et al. J Am Coll Cardiol. 2022;80(8):783–800.

Among 1,974 patients undergoing aortic valve replacement, 6.1% were in stage 0, 14.5% were in stage 1, 51.4% were in stage 2, 20.9% were in stage 3, and 7.1% in stage 4 of cardiac damage before aortic valve replacement. At 1-year post-aortic valve replacement, 15.6% improved at least by 1 stage, 57.9% remained unchanged, and 26.5% worsened by at least 1 stage. The 1-year change in stage of cardiac damage was significantly associated with death and with the composite of death or heart failure hospitalization 2 years post-aortic valve replacement.

pyrophosphate scan could help clarify the origin of cardiac anomaly. Notwithstanding this challenge, the prognostic importance of cardiac damage in this population highlights the importance of addressing these nonvalve-related issues as well. Fifth, in line with the original classification published in 2017, we classified patients at baseline and 1-year based on the worst stage, and did not mandate presence of components from prior stages. This method was used in part to account for the nonsequential progression of cardiac damage in some patients, and because patient prognosis is worst with more advanced stage, independent of the presence or absence of cardiac damage from prior stages. Stratification of patients based on a strictly cumulative approach would be challenging, because many patients with advanced stages do not have cardiac damage from prior stages, making classification of those patients impossible. Future work accounting for the cumulative burden of cardiac damage is underway and may provide a different approach to stratify patients. Sixth, a substantial amount of echocardiographic data were missing, both at baseline and 1 year, leading to the exclusion of a high proportion of patients. That being said, our analysis is by far the largest cohort of patients with core laboratory-adjudicated echocardiogram paired with independent events adjudication, making this work unique. Finally, by limiting our classification

system to 2 levels (normal and abnormal), our definitions of "improvement" and "worsening" were relatively insensitive to change. Further studies involving larger numbers of patients will be required to understand if lesser degrees of change are associated with meaningful differences in long-term prognosis after AVR.

CONCLUSIONS

In patients undergoing AVR for severe AS, the extent of extravalvular cardiac damage at baseline and its change at 1 year have important prognostic implications after AVR. Our findings highlight the importance of monitoring global cardiac health, indicate the need for more intensive adjunctive therapy, and suggest that earlier detection of AS and intervention before the development of irreversible cardiac damage may improve cardiac function and prognosis of patients with AS.

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PERSPECTIVES

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS: Among patients with severe aortic stenosis, the extent of cardiac damage at the time of transcatheter or surgical AVR and worsening or failure to improve over the following year are independently associated with mortality by 2 years.

TRANSLATIONAL OUTLOOK: Whether earlier AVR or adjunctive pharmacological therapy targeting hypertension, left ventricular hypertrophy, diastolic dysfunction, or residual cardiac damage improves prognosis after AVR warrants investigation.

REFERENCES

1. Otto CM, Nishimura RA, Bonow RO, et al. 2020 ACC/AHA guideline for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *J Am Coll Cardiol*. 2021;77:e25–e197.

2. Vahanian A, Beyersdorf F, Praz F, et al. 2021 ESC/EACTS guidelines for the management of valvular heart disease. *Eur Heart J*. 2022;43:561–632.

3. Généreux P, Pibarot P, Redfors B, et al. Staging classification of aortic stenosis based on the extent of cardiac damage. *Eur Heart J*. 2017;38:3351–3358.

4. Fukui M, Gupta A, Abdelkarim I, et al. Association of structural and functional cardiac changes with transcatheter aortic valve replacement

outcomes in patients with aortic stenosis. *JAMA Cardiol*. 2019;4:215–222.

5. Vollema EM, Amanullah MR, Ng ACT, et al. Staging cardiac damage in patients with symptomatic aortic valve stenosis. *J Am Coll Cardiol*. 2019;74:538–549.

6. Berkovitch A, Barbash IM, Finkelstein A, et al. Validation of cardiac damage classification and addition of albumin in a large cohort of patients undergoing transcatheter aortic valve replacement. *Int J Cardiol*. 2020;304:23–28.

7. Maeder MT, Weber L, Weilenmann D, et al. Invasive hemodynamic staging classification of cardiac damage in patients with aortic stenosis undergoing valve replacement. *Can J Cardiol*. 2020;36:1667–1674.

8. Baz L, Dannberg G, Grun K, et al. Serum biomarkers of cardiovascular remodelling reflect extra-valvular cardiac damage in patients with severe aortic stenosis. *Int J Mol Sci*. 2020;21(11):4174. https://doi.org/10.3390/ijms21114174

9. Vollema EM, Amanullah MR, Prihadi EA, et al. Incremental value of left ventricular global longitudinal strain in a newly proposed staging classification based on cardiac damage in patients with severe aortic stenosis. *Eur Heart J Cardiovasc Imaging*. 2020;21:1248–1258.

10. Schewel J, Kuck KH, Frerker C, Schmidt T, Schewel D. Outcome of aortic stenosis according to invasive cardiac damage staging after transcatheter aortic valve replacement. *Clin Res Cardiol*. 2021;110:699–710.

11. Okuno T, Heg D, Lanz J, et al. Staging cardiac damage associated with aortic stenosis in patients undergoing transcatheter aortic valve implantation. *Int J Cardiol Heart Vasc*. 2021;33:100768.

12. Snir AD, Ng MK, Strange G, et al. Cardiac damage staging classification predicts prognosis in all the major subtypes of severe aortic stenosis: insights from the National Echo Database Australia. *J Am Soc Echocardiogr*. 2021;34:1137–1147. e13.

13. Avvedimento M, Franzone A, Leone A, et al. Extent of cardiac damage and mortality in patients undergoing transcatheter aortic valve implantation. *J Clin Med*. 2021;10(19):4563. https://doi.org/10.3390/jcm10194563

14. Zhu Q, Yuan Z, Xu Y, et al. Validation of a novel staging classification system based on the extent of cardiac damage among Chinese patients after transcatheter aortic valve replacement: A single-center retrospective study. *Catheter Cardiovasc Interv*. 2022;99(Suppl 1):1482–1489. https://doi.org/10.1002/ccd.30147

15. Amanullah MR, Pio SM, Ng ACT, et al. Prognostic implications of associated cardiac abnormalities detected on echocardiography in patients with moderate aortic stenosis. *J Am Coll Cardiol Img*. 2021;14:1724–1737.

16. Tastet L, Tribouilloy C, Marechaux S, et al. Staging cardiac damage in patients with asymptomatic aortic valve stenosis. *J Am Coll Cardiol*. 2019;74:550–563.

17. Park SJ, Lee S, Lee SA, et al. Impact of early surgery and staging classification on survival in asymptomatic very severe aortic stenosis. *J Am Coll Cardiol*. 2021;77:506–508.

18. Leon MB, Smith CR, Mack MJ, et al. Transcatheter or surgical aortic-valve replacement in intermediate-risk patients. *N Engl J Med*. 2016;374:1609–1620.

19. Webb JG, Doshi D, Mack MJ, et al. A randomized evaluation of the SAPIEN XT transcatheter heart valve system in patients with aortic stenosis who are not candidates for surgery. *J Am Coll Cardiol Intv*. 2015;8:1797–1806.

20. Mack MJ, Leon MB, Thourani VH, et al. Transcatheter aortic-valve replacement with a balloon-expandable valve in low-risk patients. *N Engl J Med*. 2019;380:1695–1705.

21. Douglas PS, Waugh RA, Bloomfield G, et al. Implementation of echocardiography core laboratory best practices: a case study of the PARTNER I trial. *J Am Soc Echocardiogr*. 2013;26:348–358. e3.

22. Hahn RT, Pibarot P, Stewart WJ, 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.

23. Pabel S, Knierim M, Stehle T, et al. Effects of atrial fibrillation on the human ventricle. *Circ Res*. 2022;130:994–1010.

24. Nitsche C, Scully PR, Patel KP, et al. Prevalence and outcomes of concomitant aortic stenosis and cardiac amyloidosis. *J Am Coll Cardiol*. 2021;77:128–139.

25. Patel KP, Michail M, Treibel TA, et al. Coronary revascularization in patients undergoing aortic valve replacement for severe aortic stenosis. *J Am Coll Cardiol Intv*. 2021;14:2083–2096.

26. Shahim B, Malaisrie SC, George I, et al. Postoperative atrial fibrillation or flutter following transcatheter or surgical aortic valve replacement: PARTNER 3 Trial. *J Am Coll Cardiol Intv*. 2021;14:1565–1574.

27. Kwiecinski J, Lennen RJ, Gray GA, et al. Progression and regression of left ventricular hypertrophy and myocardial fibrosis in a mouse model of hypertension and concomitant cardiomyopathy. *J Cardiovasc Magn Reson*. 2020;22:57.

28. Pibarot P, Weissman NJ, Stewart WJ, et al. Incidence and sequelae of prosthesis-patient mismatch in transcatheter versus surgical valve replacement in high-risk patients with severe aortic stenosis: a PARTNER trial cohort A analysis. *J Am Coll Cardiol*. 2014;64:1323–1334.

29. Kempny A, Diller GP, Kaleschke G, et al. Impact of transcatheter aortic valve implantation or surgical aortic valve replacement on right ventricular function. *Heart*. 2012;98:1299–1304.

30. Musa TA, Uddin A, Fairbairn TA, et al. Right ventricular function following surgical aortic valve replacement and transcatheter aortic valve implantation: a cardiovascular MR study. *Int J Cardiol*. 2016;223:639–644.

31. Kang DH, Park SJ, Lee SA, et al. Early surgery or conservative care for asymptomatic aortic stenosis. *N Engl J Med*. 2020;382:111–119.

32. Banovic M, Putnik S, Penicka M, et al. Aortic valve replacement versus conservative treatment in asymptomatic severe aortic stenosis: the AVATAR trial. *Circulation*. 2022;145:648–658.

33. Genereux P, Stone GW, O'Gara PT, et al. Natural history, diagnostic approaches, and therapeutic strategies for patients with asymptomatic severe aortic stenosis. *J Am Coll Cardiol*. 2016;67:2263–2288.

34. Marquis-Gravel G, Redfors B, Leon MB, Genereux P. Medical treatment of aortic stenosis. *Circulation*. 2016;134:1766–1784.

35. Lindman BR, Sukul D, Dweck MR, et al. Evaluating medical therapy for calcific aortic stenosis: JACC state-of-the-art review. *J Am Coll Cardiol*. 2021;78:2354–2376.

36. Witberg G, Codner P, Landes U, et al. Effect of transcatheter aortic valve replacement on concomitant mitral regurgitation and its impact on mortality. *J Am Coll Cardiol Intv*. 2021;14:1181–1192.

37. Tomii D, Okuno T, Praz F, et al. Potential candidates for transcatheter tricuspid valve intervention after transcatheter aortic valve replacement: predictors and prognosis. *J Am Coll Cardiol Intv*. 2021;14:2246–2256.

38. Ryan T, Grindal A, Jinah R, et al. New-onset atrial fibrillation after transcatheter aortic valve replacement: a systematic review and meta-analysis. *J Am Coll Cardiol Intv*. 2022;15:603–613.

39. Lindman BR, Stewart WJ, Pibarot P, et al. Early regression of severe left ventricular hypertrophy after transcatheter aortic valve replacement is associated with decreased hospitalizations. *J Am Coll Cardiol Intv*. 2014;7:662–673.

40. Chau KH, Douglas PS, Pibarot P, et al. Regression of left ventricular mass after transcatheter aortic valve replacement: the PARTNER trials and registries. *J Am Coll Cardiol*. 2020;75:2446–2458.

41. Gonzales H, Douglas PS, Pibarot P, et al. Left ventricular hypertrophy and clinical outcomes over 5 years after TAVR: an analysis of the PARTNER trials and registries. *J Am Coll Cardiol Intv*. 2020;13:1329–1339.

42. Lang RM, Badano LP, Mor-Avi V, 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.

43. Nagueh SF, Smiseth OA, Appleton CP, et al. Recommendations for the evaluation of left ventricular diastolic function by echocardiography: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *J Am Soc Echocardiogr*. 2016;29:277–314.

KEY WORDS aortic stenosis, aortic valve, aortic valve replacement, cardiac damage, staging, transcatheter aortic valve implantation, transcatheter aortic valve replacement, valve disease, prognosis

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