JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY VOL. 81, NO. 8, 2023

PUBLISHED BY ELSEVIER

Cardiac Damage and Quality of Life After Aortic Valve Replacement in the PARTNER Trials

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ABSTRACT

BACKGROUND The extent of extravalvular cardiac damage is associated with increased risk of adverse events among patients with severe aortic stenosis undergoing aortic valve replacement (AVR).

OBJECTIVES The goal was to describe the association of cardiac damage on health status before and after AVR.

METHODS Patients from the PARTNER (Placement of Aortic Transcatheter Valves) 2 and 3 trials were pooled and classified by echocardiographic cardiac damage stage at baseline and 1 year as previously described (stage 0-4). We examined the association between baseline cardiac damage and 1-year health status (assessed by the Kansas City Cardiomyopathy Questionnaire Overall Score [KCCQ-OS]).

RESULTS Among 1,974 patients (794 surgical AVR, 1,180 transcatheter AVR), the extent of cardiac damage at baseline was associated with lower KCCQ scores both at baseline and at 1 year after AVR ($P < 0.0001$) and with increased rates of a poor outcome (death, KCCQ-OS <60, or a decrease in KCCQ-OS of ≥10 points) at 1 year (stages 0-4: 10.6% vs 19.6% vs 29.0% vs 44.7% vs 39.8%; $P < 0.0001$). In a multivariable model, each 1-stage increase in baseline cardiac damage was associated with a 24% increase in the odds of a poor outcome (95% CI: 9%-41%; $P = 0.001$). Change in stage of cardiac damage at 1 year after AVR was associated with the extent of improvement in KCCQ-OS over the same period (mean change in 1-year KCCQ-OS: improvement of ≥1 stage +26.8 [95% CI: 24.2-29.4] vs no change +21.4 [95% CI: 20.0-22.7] vs deterioration of ≥1 stage +17.5 [95% CI: 15.4-19.5]; $P < 0.0001$).

CONCLUSIONS The extent of cardiac damage before AVR has an important impact on health status outcomes, both cross-sectionally and after AVR. (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; 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 2023;81:743-752) © 2023 by the American College of Cardiology Foundation.

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Megan Coylewright, MD, served as Guest Associate Editor for this paper. Javed Butler, MD, MPH, MBA, served as Guest Editor-in-Chief for this paper.

ISSN 0735-1097/$36.00 https://doi.org/10.1016/j.jacc.2022.11.059

ABBREVIATIONS AND ACRONYMS

AVR = aortic valve replacement

KCCQ-OS = Kansas City Cardiomyopathy Questionnaire Overall Score

TAVR = transcatheter aortic valve replacement

For patients with severe symptomatic aortic stenosis, aortic valve replacement (AVR) improves both survival and patient health status—their symptoms, functional limitations, and quality of life.[1-6] Because patients who are typically candidates for AVR are elderly and often have multiple comorbidities, maximizing health status outcomes is a central goal of AVR—targeting patients most likely to benefit, determining timing and type of interventions, and informing modifications to treatment pathways. Prior studies have demonstrated that most factors associated with health status after AVR are to be only marginally modifiable, such as frailty, oxygen-dependent lung disease, and advanced kidney disease.[1]

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Previously, we described a novel staging classification for aortic stenosis that is based on the extent of cardiac damage beyond the aortic valve, itself: stage 0, no extravalvular damage; stage 1, left ventricular damage; stage 2, left atrial/mitral valve damage; stage 3, pulmonary vasculature/tricuspid valve damage; and stage 4, right ventricular damage (**Figure 1**).[7] We recently demonstrated that the extent of extravalvular cardiac damage before AVR and its change at 1 year after AVR are strongly associated with risk of death or heart failure hospitalization at 2 years after AVR.[8] These findings formed the basis for the hypothesis that earlier detection and treatment of aortic stenosis—before the development of irreversible cardiac damage—may improve long-term outcomes after valve replacement. Because aortic stenosis is a potentially modifiable risk factor for poor outcomes, more fully exploring the impact of extravascular cardiac damage on health status after AVR is critically important. We, therefore, used data from the PARTNER (Placement of Aortic Transcatheter Valves) trials and registries to better understand the potential impact that avoiding extravalvular cardiac damage may have on health status outcomes after AVR.

METHODS

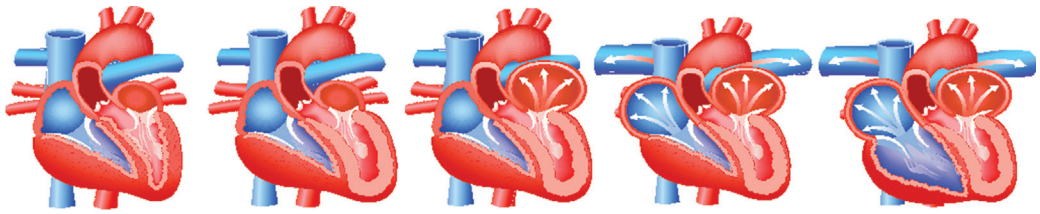
STUDY POPULATION. Our study cohort consisted of patients with severe aortic stenosis across the surgical risk spectrum who underwent either transcatheter AVR (TAVR) or surgical AVR as part of the PARTNER 2A (PARTNER II Trial: Placement of AoRTic TraNscathetER Valves II - XT Intermediate and High Risk; NCT01314313; n = 1,910), PARTNER 2B (The PARTNER II Trial: Placement of AoRTic TraNscathetER Valves - PII B; NCT02184442; n = 543), and PARTNER 3 (PARTNER 3 Trial: Safety and Effectiveness of the SAPIEN 3 Transcatheter Heart Valve in Low Risk Patients With Aortic Stenosis; NCT02675114; n = 948) trials.[9-11] All patients had severe symptomatic aortic stenosis (mean gradient >40 mm Hg or jet velocity >4.0 m/s and aortic valve area ≤0.8 cm^2 or <0.5 cm^2/m^2). Key exclusion criteria included significant renal insufficiency, mixed aortic valve disease with predominant aortic regurgitation, congenital unicuspid or bicuspid aortic valve, and left ventricular ejection fraction of less than 20% to 30%. All patients underwent clinical follow-up at 1 month, 6 months, and 1 year after AVR, and all adverse events were adjudicated by an independent committee blinded to treatment assignment. Each trial was approved by the institutional review board of each participating site, and all patients provided written informed consent.

DEFINITION OF STAGE OF CARDIAC DAMAGE. All patients underwent transthoracic echocardiography at baseline and 1-year follow-up using a uniform image acquisition protocol, which were analyzed by a central core laboratory with quality and measurement methodology previously reported.[12,13] Based on these echocardiograms, patients were categorized into 5 stages of extravalvular cardiac damage, as previously described,[7,8] This classification has been validated in multiple cohorts.[8,14-30] Stages ranged from 0 to 4, where 0 represents no extravalvular cardiac damage and 4 represents the most severe cardiac damage. Details are as follows: stage 0, no other cardiac damage detected; stage 1, left ventricular damage (left ventricular hypertrophy [left ventricular mass index >95 g/m^2 for women, >115 g/m^2 for men], severe left ventricular diastolic dysfunction (E/e′ >14), or left ventricular systolic dysfunction (left ventricular ejection fraction <50%); stage 2, left atrial or mitral valve damage or dysfunction (left atrial enlargement [>34 mL/m^2], atrial fibrillation, or moderate or severe mitral regurgitation); stage 3, pulmonary artery vasculature or tricuspid valve damage or dysfunction (pulmonary hypertension [systolic pulmonary arterial pressure ≥60 mm Hg] or

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.

Manuscript received August 22, 2022; revised manuscript received November 9, 2022, accepted November 22, 2022.

FIGURE 1 Staging of Cardiac Damage Among Patients With Aortic Stenosis



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 left atrial volume >34 mL/m^2	Systolic pulmonary hypertension ≥60 mm Hg	Moderate-severe RV 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 (LV hypertrophy [LV mass index >95 g/m^2 for women, >115 g/m^2 for men], severe LV diastolic dysfunction (E/e' >14), or LV systolic dysfunction (LV ejection fraction <50%). Stage 2: left atrial or mitral valve damage or dysfunction (left atrial enlargement [>34 mL/m^2], atrial fibrillation, or moderate or severe mitral regurgitation). Stage 3: pulmonary artery vasculature or tricuspid valve damage or dysfunction (pulmonary hypertension [systolic pulmonary arterial pressure ≥60 mm Hg] or moderate or severe tricuspid regurgitation). Stage 4: right ventricular (RV) damage (moderate or severe right ventricular dysfunction). Adapted from Généreux et al. *Eur Heart J*. 2017;38:3351-3358.[7]

moderate or severe tricuspid regurgitation); and stage 4, right ventricular damage (moderate or severe right ventricular dysfunction). If patients met the criteria for multiple stages, they were assigned to the highest (worst) stage.

HEALTH STATUS OUTCOMES. Health status was assessed by the Kansas City Cardiomyopathy Questionnaire (KCCQ) at baseline and 1 year.[31] The KCCQ is a 23-item disease-specific patient-reported health status measure that was originally developed to describe and monitor symptoms, functional status, and quality of life in patients with heart failure,[31] but has subsequently been validated in those with severe aortic stenosis.[32,33] The 5 domains of the KCCQ (physical limitations, symptoms, quality of life, social limitations, self-efficacy) are combined into an overall summary score (KCCQ-OS), which ranges from 0 to 100 with higher scores indicating less symptom burden and better quality of life.[34] Changes of 5, 10, and 20 points in the KCCQ-OS correspond with small, moderate, and large clinical improvements, respectively. To integrate health status and survival outcomes, poor outcome at 1 year was defined as death, 1-year KCCQ-OS of less than 60, or a decrease in the KCCQ-OS of 10 or more points.[32,35,36]

STATISTICAL ANALYSES. Patients in the analytic cohort were compared with those excluded due to inability to determine echocardiographic cardiac damage stage using standardized differences (>10% indicates clinically important difference). Analysis of variance and chi-square tests were used to compare patient demographics, comorbidities, and baseline KCCQ-OS across pre-AVR stages of cardiac damage. One-year KCCQ-OS was compared across baseline cardiac damage groups using analysis of covariance. We then compared the change in KCCQ-OS from baseline to 1 year across categories of concurrent change in cardiac damage (deterioration vs no change vs improvement) using analysis of covariance, adjusted for baseline KCCQ-OS and baseline cardiac damage stage. Finally, we examined the independent association between baseline cardiac damage stage and poor 1-year outcome using multivariable logistic regression analysis with stratification by study and treatment assignment. Covariates for adjustment were selected a priori and included age, sex, aortic valve area, diabetes mellitus, prior coronary artery bypass grafting, chronic obstructive pulmonary disease, serum creatinine or more than 2.0 mg/dL, and frailty. Frailty was defined as the presence of at least 2 of the following criteria: 1) Katz index of independence in activities of daily living <6; 2) 15-m walk time ≥24 seconds; 3) serum albumin <3.8 g/dL; and 4) grip strength <13 kg (women) or <26 kg (men).

TABLE 1 Baseline Characteristics by Stage of Cardiac Damage

		Baseline Cardiac Damage Stage					
	Total (N = 1,974)	Stage 0 (n = 121)	Stage 1 (n = 287)	Stage 2 (n = 1014)	Stage 3 (n = 412)	Stage 4 (n = 140)	*P* Value
Age, y	80.7 ± 7.76	76.6 ± 7.88	77.9 ± 7.76	80.8 ± 7.47	83.8 ± 6.90	79.3 ± 8.35	<0.0001
Male	1,086/1,974 (55.0)	75/121 (62.0)	138/287 (48.1)	567/1,014 (55.9)	199/412 (48.3)	107/140 (76.4)	<0.0001
STS score	5.8 ± 4.20	3.3 ± 2.73	4.1 ± 3.04	5.6 ± 3.90	7.6 ± 4.77	7.4 ± 4.74	<0.0001
Baseline creatinine, mg/dL	1.1 ± 0.39	1.0 ± 0.26	1.0 ± 0.34	1.1 ± 0.37	1.2 ± 0.42	1.3 ± 0.46	<0.0001
Baseline aortic valve area, cm^2	0.7 ± 0.18	0.8 ± 0.14	0.7 ± 0.16	0.7 ± 0.17	0.6 ± 0.19	0.7 ± 0.22	<0.0001
Baseline mean gradient, mm Hg	46.3 ± 13.12	45.2 ± 10.11	46.5 ± 12.26	47.5 ± 12.96	46.1 ± 14.68	39.1 ± 10.92	<0.0001
Coronary artery disease	1,083/1,973 (54.9)	54/121 (44.6)	117/287 (40.8)	560/1,013 (55.3)	254/412 (61.7)	98/140 (70.0)	<0.0001
Percutaneous coronary intervention	482/1,972 (24.4)	26/121 (21.5)	61/287 (21.3)	248/1,012 (24.5)	105/412 (25.5)	42/140 (30.0)	0.31
Myocardial infarction	284/1,971 (14.4)	8/119 (6.7)	31/286 (10.8)	158/1,014 (15.6)	49/412 (11.9)	38/140 (27.1)	<0.0001
Coronary artery bypass grafting	349/1,970 (17.7)	13/121 (10.7)	33/287 (11.5)	165/1,010 (16.3)	82/412 (19.9)	56/140 (40.0)	<0.0001
Stroke	147/1,974 (7.4)	4/121 (3.3)	14/287 (4.9)	79/1,014 (7.8)	36/412 (8.7)	14/140 (10.0)	0.08
Peripheral vascular disease	465/1,972 (23.6)	21/121 (17.4)	51/286 (17.8)	240/1,013 (23.7)	109/412 (26.5)	44/140 (31.4)	0.006
Diabetes	626/1,973 (31.7)	35/121 (28.9)	102/287 (35.5)	311/1,013 (30.7)	113/412 (27.4)	65/140 (46.4)	0.0004
COPD	434/1,965 (22.1)	16/120 (13.3)	43/285 (15.1)	229/1,011 (22.7)	99/409 (24.2)	47/140 (33.6)	<0.0001
Hypertension	1804/1,972 (91.5)	105/121 (86.8)	263/287 (91.6)	929/1,012 (91.8)	384/412 (93.2)	123/140 (87.9)	0.11
Pacemaker	236/1,974 (12.0)	2/121 (1.7)	10/287 (3.5)	118/1,014 (11.6)	77/412 (18.7)	29/140 (20.7)	<0.0001
Frailty[a]	228/1,972 (11.6)	2/121 (1.7)	12/286 (4.2)	98/1,013 (9.7)	90/412 (21.8)	26/140 (18.6)	<0.0001
Treatment							0.18
TF TAVR	1059/1,974 (53.6)	63/121 (52.1)	155/287 (54.0)	516/1,014 (50.9)	243/412 (59.0)	82/140 (58.6)	
Non-TF TAVR	121/1,974 (6.1)	5/121 (4.1)	15/287 (5.2)	67/1,014 (6.6)	25/412 (6.1)	9/140 (6.4)	
SAVR	794/1,974 (40.2)	53/121 (43.8)	117/287 (40.8)	431/1,014 (42.5)	144/412 (35.0)	49/140 (35.0)	

Values are mean ± SD or n/N (%). [a]Frailty was defined as the presence of ≥2 of the following criteria: 1) Katz index of independence in activities of daily living <6; 2) 15-m walk time ≥24 seconds; 3) serum albumin <3.8 g/dL; and 4) grip strength <13 kg (women) or <26 kg (men).

COPD = chronic obstructive pulmonary disease; SAVR = surgical aortic valve replacement; STS = Society of Thoracic Surgeons; TF = transfemoral; TAVR = transcatheter aortic valve replacement.

All analyses were performed with SAS version 9.4 (SAS Institute), and a 2-sided $P < 0.05$ was considered statistically significant without adjustment for multiple comparisons.

RESULTS

STUDY POPULATION. Among 3,401 pooled patients, 1,974 patients (PARTNER 3 low risk, n = 561; PARTNER 2A intermediate risk, n = 1,071, and PARTNER 2B, inoperable, n = 342) had evaluable cardiac damage staging by echocardiographic assessment at baseline. Of these patients, 794 (40.2%) underwent surgical AVR and 1,180 (59.8%) underwent TAVR. Patients without sufficient echocardiographic data to allow staging of cardiac damage (1,427 patients) differed from those included in the analytic cohort by the fact that they were younger, more often male, had a lower Society of Thoracic Surgeons score, had more coronary artery disease and previous coronary artery bypass graft, were more often diabetic, and had chronic obstructive pulmonary disease more often, but were less often frail, had less previous stroke, and less peripheral vascular disease (Supplemental Table 1, Supplemental Figure 1).

At baseline, 121 patients (6.1%) were categorized as stage 0 (no cardiac damage), 287 (14.5%) stage 1 (left ventricular damage), 1,014 (51.4%) stage 2 (left atrial or mitral valve damage), 412 (20.9%) stage 3 (pulmonary vasculature or tricuspid valve damage), and 140 (7.1%) stage 4 (right ventricular damage). Patients with more advanced stages were more likely to be older, male, have higher surgical risk scores, have diabetes, have chronic lung disease, have a prior myocardial infarction, have a prior coronary artery bypass grafting, and were more likely to be frail (Table 1).

ASSOCIATION OF BASELINE CARDIAC DAMAGE STAGE WITH HEALTH STATUS. At baseline, 1,878 of the 1,974 patients (95%) had KCCQ-OS data, and 1,558 of the 1,742 (89%) surviving patients had KCCQ-OS data at 1 year. The extent of cardiac damage at baseline was associated with lower KCCQ-OS both at baseline (mean baseline KCCQ-OS for stages 0-4: 65.6 ± 21.5 vs 60.6 ± 23.9 vs 58.4 ± 22.7 vs 49.6 ± 23.3 vs

TABLE 2 Baseline and 1-Year Outcomes According to the Extent of Cardiac Damage at Baseline

	Baseline Stage of Cardiac Damage					
	Stage 0 (n = 121)	Stage 1 (n = 287)	Stage 2 (n = 1014)	Stage 3 (n = 412)	Stage 4 (n = 140)	*P* Value
KCCQ-OS						
Baseline	65.6 ± 21.51	60.6 ± 23.90	58.4 ± 22.67	49.6 ± 23.33	47.0 ± 24.91	<0.0001
1 y	87.8 ± 13.08	82.0 ± 19.19	80.5 ± 19.07	74.1 ± 21.24	79.1 ± 19.72	<0.0001
Change at 1 y	21.8 ± 21.65	20.0 ± 21.85	20.6 ± 21.41	22.7 ± 21.66	28.4 ± 28.40	0.011
Poor outcome at 1 y						
Composite	10.6 (12/113)	19.6 (51/260)	29.0 (262/902)	44.7 (153/342)	39.8 (51/128)	<0.0001
Death	2.5 (3/121)	4.5 (13/287)	10.5 (106/1,014)	19.4 (80/412)	21.4 (30/140)	<0.0001
KCCQ-OS <60	3.5 (4/114)	13.9 (35/252)	16.4 (134/818)	25.8 (71/275)	16.2 (16/99)	<0.0001
Decrease in KCCQ-OS ≥10 points	5.5 (6/110)	4.9 (12/243)	6.1 (48/784)	5.0 (13/259)	8.2 (8/97)	0.76

Values are mean ± SD or % (n/N).
KCCQ-OS = Kansas City Cardiomyopathy Questionnaire Overall Score.

47.0 ± 24.9; $P < 0.0001$) and 1 year after AVR among surviving patients (mean 1-year KCCQ-OS for stage 0-4: 87.8 ± 13.1 vs 82.0 ± 19.2 vs 80.5 ± 19.1 vs 74.1 ± 21.2 vs 79.1 ± 19.7; $P < 0.0001$) (Table 2). Higher stages of cardiac damage pre-AVR were also associated with increased rates of the composite poor outcome at 1 year (stage 0-4: 10.6% vs 19.6% vs 29.0% vs 44.7% vs 39.8%; $P < 0.0001$) (Table 2). In a multivariable model adjusting for baseline demographic and clinical factors, the extent of cardiac damage at baseline was independently associated with odds of a poor outcome at 1 year (OR: 1.24 per each increment in stage; 95% CI: 1.09-1.41; $P = 0.001$). In addition, there was no significant interaction between the type of AVR (TAVR vs surgical AVR) and the odds of a poor 1-year outcome ($P_{interaction} = 0.51$).

ASSOCIATION BETWEEN CHANGE IN CARDIAC DAMAGE AND CHANGE IN HEALTH STATUS. Among 1,742 surviving patients, 1-year cardiac damage stage was evaluable in 1,120 (64%), among whom stage was improved in 175 (15.6%), unchanged in 648 (57.9%), and worsened in 297 (26.5%). Baseline characteristics of those 3 different groups are presented in Supplemental Table 2. Although most patients experienced an improvement in KCCQ-OS after AVR, change in stage of cardiac damage after AVR was associated with the degree of improvement in KCCQ-OS at 1 year. On average, patients who improved their cardiac damage stage demonstrated a greater mean improvement in 1-year KCCQ-OS compared with patients who experienced no change in cardiac stage and those whose cardiac damage stage progressed (26.8 vs 21.4 vs 17.5 points; $P < 0.0001$) (Central Illustration).

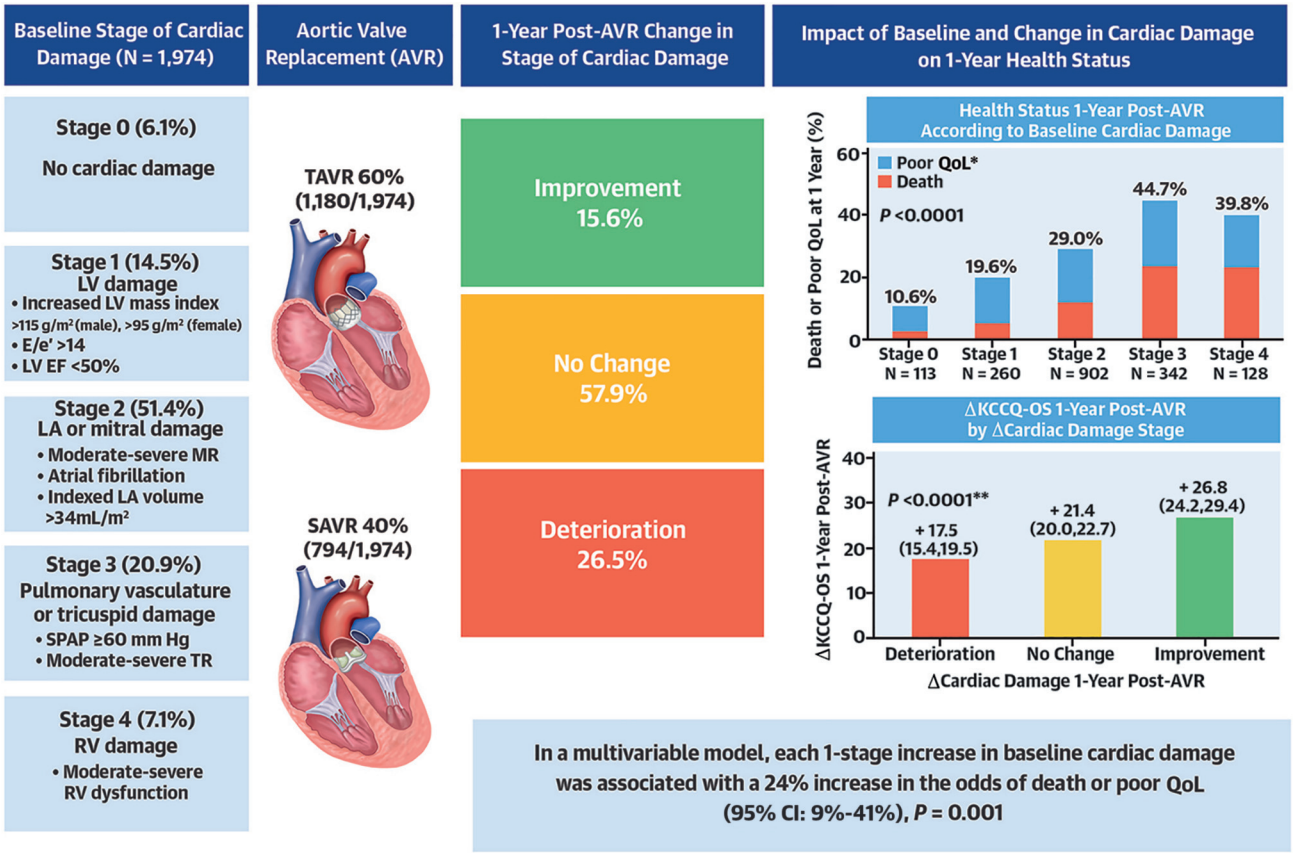
Figure 2 shows the percentage of patients improving their KCCQ-OS by 5 or more points (Figure 2A), 10 or more points (Figure 2B), and 20 or more points (Figure 2C) according to change in cardiac damage at 1 year after AVR. Patients with improvement in their stage of cardiac damage at 1 year were more likely to have greater improvement in their KCCQ-OS compared with patients with no change or deterioration of their cardiac damage.

SUBGROUP ANALYSIS. No interaction was detected between the different enrolling studies and the impact of either the baseline stage of cardiac damage ($P_{interaction} = 0.11$) or the change in stage of cardiac damage ($P_{interaction} = 0.11$) on 1-year adjusted KCCQ-OS post-AVR (Supplemental Table 3). Similarly, there was no significant interaction between the AVR (TAVR vs surgical AVR) and the relationship between 1-year change in stage of cardiac damage and the occurrence of either a poor health overall outcome ($P_{interaction} = 0.35$) or 1-year KCCQ-OS score ($P_{interaction} = 0.35$).

DISCUSSION

In a large cohort of patients with severe aortic stenosis across the surgical risk spectrum who underwent AVR, we found that the extent of extravalvular cardiac damage before AVR, as assessed with a simple echocardiographic categorization, was associated with poor concurrent health status as well as worse

CENTRAL ILLUSTRATION **Impact of Cardiac Damage on Health Status After Aortic Valve Replacement**



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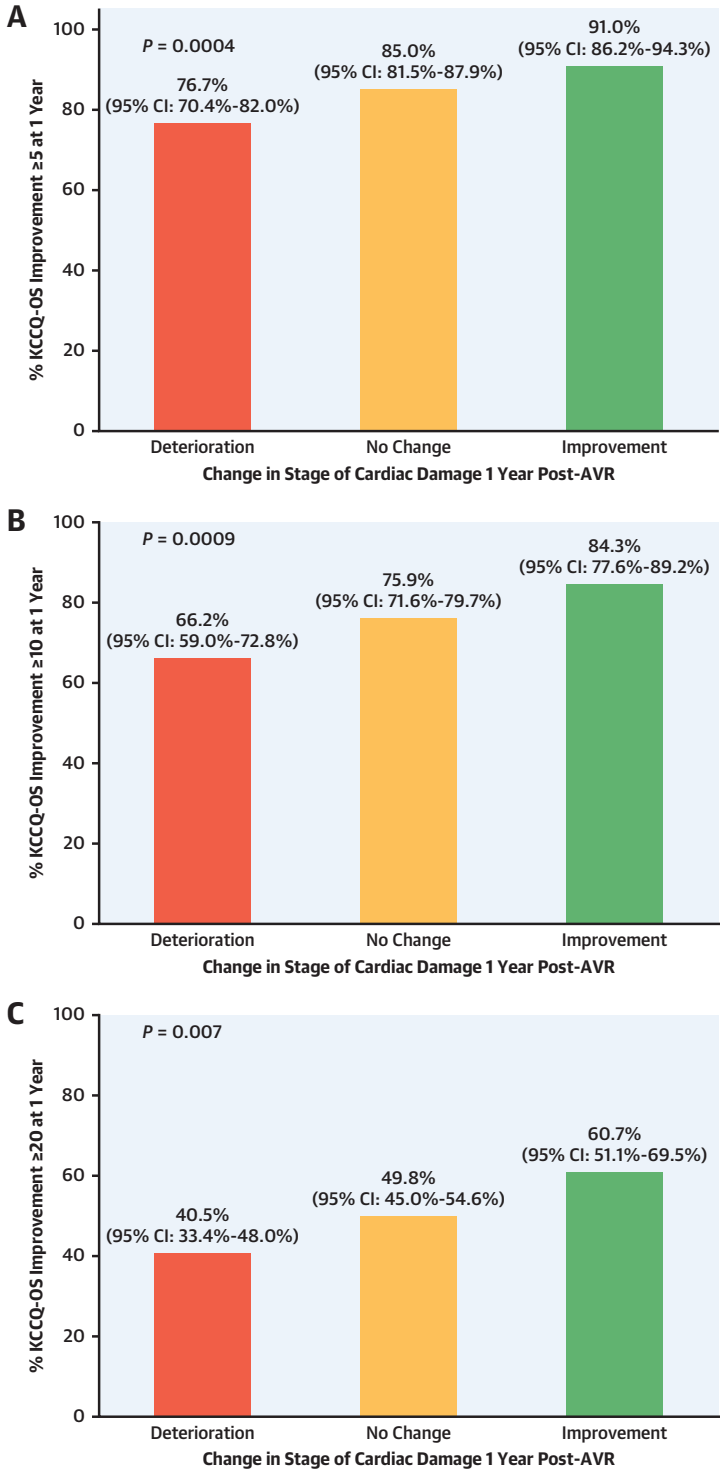
Among 1,974 patients undergoing AVR, 6.1% were in stage 0, 14.5% were in stage 1, 51.4% were in stage 2, 20.9% were in stage 3, and 7.1% in stage 4 of cardiac damage before AVR. At 1 year after AVR, 15.6% improved at least by 1 stage, 57.9% remain unchanged, and 26.5% deteriorated by at least 1 stage. One-year change in stage of cardiac damage was significantly associated with health status outcomes at 1 year after AVR. In a multivariable model, each 1-stage increase in baseline cardiac damage was associated with a 24% increase in the odds of a poor outcome (95% CI: 9%-41%; $P = 0.001$). Change in stage of cardiac damage at 1 year after AVR was associated with the extent of improvement in KCCQ-OS over the same period (mean change in 1-year KCCQ-OS: improvement ≥1 stage +26.8 [95% CI: 24.2-29.4] vs no change +21.4 [95% CI: 20.0-22.7] vs deterioration ≥1 stage +17.5 [95% CI: 15.4-19.5]; $P < 0.0001$). *Poor QoL defined as KCCQ-OS <60 or decline in KCCQ-OS >10. **Adjusted for baseline KCCQ-OS and baseline stage of cardiac damage (ANCOVA); values are ΔKCCQ-OS (95%CI). AVR = aortic valve replacement; EF = ejection fraction; KCCQ-OS = Kansas City Cardiomyopathy Questionnaire Overall Score; LA = left atrial; LV = left ventricular; MR = mitral regurgitation; QoL = quality of life; RA = right atrial; SPAP = systolic pulmonary pressure.

health status at 1 year after AVR. Furthermore, changes in the extent of cardiac damage that occurred after AVR were associated with the degree of health status recovery after AVR; patients whose cardiac damage regressed experienced greater improvements in health status after AVR compared with those whose extravalvular cardiac damage did not change or deteriorated. Our study is thus among the first to demonstrate a strong relationship between anatomic and functional cardiac abnormalities in aortic stenosis and patient's symptoms, functional limitations, and quality of life.

We previously showed that the extent of cardiac damage in patients with severe aortic stenosis is associated with increased risk of death or heart failure hospitalization after AVR, whereas improvements in cardiac damage after AVR attenuated that risk.[7,8] The current study expands on those findings and further supports the hypothesis that earlier detection and treatment of aortic stenosis and aggressive

FIGURE 2 **KCCQ-OS Improvement According to Change in Cardiac Damage 1 Year After AVR**



(A) Percentage of patients improving their Kansas City Cardiomyopathy Questionnaire Overall Score (KCCQ-OS) by 5 points or more according to change in cardiac damage at 1 year. **(B)** Percentage of patients improving their KCCQ-OS by 10 points or more according to change in cardiac damage at 1 year. **(C)** Percentage of patients improving their KCCQ-OS by 20 points or more according to change in cardiac damage at 1 year. Abbreviation as in Figure 2.

"secondary prevention" are needed to optimize both survival and health status outcomes after AVR.

Ongoing randomized trials including EARLY TAVR (Evaluation of TAVR Compared to Surveillance for Patients With Asymptomatic Severe Aortic Stenosis; NCT03042104), EVoLVeD (Early Valve Replacement Guided by Biomarkers of LV Decompensation in Asymptomatic Patients With Severe AS; NCT03094143), PROGRESS (Management of Moderate Aortic Stenosis by Clinical Surveillance or TAVR; NCT04889872), and EXPAND (Evolut EXPAND TAVR II Pivotal Trial II; NCT05149755) will provide important insight into whether or not early intervention among patients with severe asymptomatic aortic stenosis or moderate aortic stenosis will improve prognosis by intervening before development of irreversible cardiac damage.[37] Additionally, undertreatment of patients already affected with severe aortic stenosis with an established class 1 indication for AVR remains frequent (approximately 50%), pointing toward the need for earlier identification and better management of those patients.[38]

Although our study provides a rationale for these trials, it does not suggest a unique threshold for earlier intervention in patients with aortic stenosis. Identifying the optimal time for intervention is challenging across the spectrum of valvular heart disease, particularly when dealing with valve replacement where the lifespan of a bioprosthetic valve is finite. Whether considering left ventricular dilatation as a marker for timing of valve replacement in aortic regurgitation or right ventricular dysfunction in patients with tricuspid regurgitation, identifying the impact of the valve abnormality on extravalvular cardiac function is critical for determining the optimal timing of intervention. However, other than left ventricular systolic dysfunction, current guidelines do not recommend intervening in aortic stenosis on the basis of extravalvular cardiac dysfunction. Our current study provides support for reconsideration of this practice. Given the consistent relationship between extravalvular cardiac damage on outcomes after AVR (both in cross-sectional and dynamic analyses), using this classification scheme to support the decision for AVR timing may benefit patients, not only by leading to improved long-term survival, but also via its impact on health status outcomes. Because many of the factors that impact health status outcomes after AVR are only marginally modifiable,[1] identifying a potentially actionable target to improve patient outcomes needs to be further explored in prospective studies.

STUDY LIMITATIONS. The present study has a number of potential limitations that should be acknowledged. First, a large proportion of patients were excluded from the analysis owing to insufficient echocardiographic or health status data. Although the excluded patients were generally similar to those in the analytic cohort, this factor could have biased our results to some degree. Second, our study population was derived from pooling of data from the recent PARTNER trials; as such, our findings may not generalize to patients outside of those specific inclusion and exclusion criteria. Third, it is clear that the extravalvular cardiac damage observed was not necessarily a consequence of the aortic stenosis (eg, left ventricular systolic dysfunction could be due to ischemic heart disease; mitral regurgitation could represent degenerative mitral valve disease). Regardless of the etiology of the cardiac dysfunction or damage, our results show that these patients are at high risk for poor outcomes. However, the hypothesis that earlier intervention with AVR will lead to improved outcomes assumes that the extent of pre-AVR cardiac damage is at least partially attributable to the aortic stenosis. As such, further prospective studies are needed to explicitly test this hypothesis. Finally, we categorized patients into 1 of 5 categories of cardiac damage, but it is unclear if particular features of one of the categories are more or less prognostically important.

CONCLUSIONS

The extent of cardiac damage before AVR has an important impact on patient's health status, both cross-sectionally and after AVR. Moreover, regression of cardiac damage within the first year after AVR is associated with greater improvement in health status relative to patients whose cardiac damage stage was unchanged or worsened. These findings emphasize the importance of assessing extravalvular cardiac damage before AVR to provide clinicians and patients with accurate projections of long-term outcomes and should prompt investigation into developing strategies to minimize the development of cardiac damage before AVR and to regress damage after AVR, as both approaches are needed to optimize patient-centered outcomes.

FUNDING SUPPORT AND AUTHOR DISCLOSURES

The PARTNER 2 and PARTNER 3 Trials were sponsored by Edwards Lifesciences (Irvine, California). Dr Généreux has served as a consultant for Abbott Vascular, Abiomed, BioTrace Medical, Boston

Scientific, CARANX Medical, Cardiovascular System Inc (PI Eclipse Trial), Edwards Lifesciences (PI EARLY-TAVR trial, PI PROGRESS trial), GE Healthcare, iRhythm Technologies, Medtronic, Opsens, Pi-Cardia, Puzzle Medical, Saranas, Shockwave, Siemens, Soundbite Medical Inc, Teleflex, and 4C Medical (PI feasibility study); has served as an advisor for Abbott Vascular, Abiomed, BioTrace Medical, Edwards Lifesciences, and Medtronic; has received speaker fees from Abbott Vascular, Abiomed, BioTrace Medical, Edwards Lifesciences, Medtronic, and Shockwave; has served as a proctor for and received an institutional research grant from Edwards Lifesciences; and has equity in Pi-Cardia, Puzzle Medical, Saranas, and Soundbite Medical Inc. Dr Pibarot has received funding from Edwards Lifesciences, Medtronic, Pi-Cardia, and Cardiac Phoenix for echocardiography core laboratory analyses and research studies in the field of transcatheter valve therapies, for which he received no personal compensation; and has received lecture fees from Edwards Lifesciences and Medtronic. The Cardiovascular Research Foundation (Drs Redfors, Cohen, Alu, Hahn, and Lyon) receives research funding from Edwards Lifesciences (no direct compensation). Dr Bax reports that the Department of Cardiology (LUMC, the Netherlands) has received research grants from Medtronic, Biotronik, Edwards Lifesciences, and Boston Scientific; and has received speaker fees from Abbott Vascular. Drs Zhao and Prince are employees of Edwards Lifesciences. Dr Makkar has received grant support/research contracts from Edwards Lifesciences and St Jude Medical; and has received consultant fees/honoraria from and served on the speaker's bureau for Abbott Vascular, Cordis Corporation, and Medtronic. Dr Thourani is on the advisory board of Edwards Lifesciences, Abbott Vascular, Atricure, Cryolife, Jenavalve, Shockwave, and Boston Scientific. Dr Mack served as co-primary investigator for the PARTNER Trial for Edwards Lifesciences; served as co-primary investigator for the COAPT trial for Abbott; and served as study chair for the APOLLO trial for Medtronic (all activities unpaid). Dr Nazif is a consultant for Edwards Lifesciences, Medtronic, and Boston Scientific. Dr Lindman has served on the scientific advisory board for Roche Diagnostics; and has received research grants from Edwards Lifesciences and Roche Diagnostics. Dr Babaliaros has received consulting fees from Edwards Lifesciences and Abbott. Dr Russo has received grants from Edwards Lifesciences; and has served as a consultant for Abbott, Boston Scientific, and Edwards Lifesciences. Dr McCabe has served as a consultant for Edwards, Medtronic, Boston Scientific, and Cardiovascular System Inc; and has equity in ConKay Medical. Dr Gillam has served as a consultant for Edwards Lifesciences; and has core lab contracts with Edwards Lifesciences and Medtronic. Dr Hahn has received speaker fees from Abbott Vascular, Baylis Medical, and Edwards Lifescience; has institutional consulting agreements for which she receives no direct compensation with Abbott Vascular, Boston Scientific, Edwards Lifesciences, Medtronic, and Novartis; has equity with Navigate; and is the Chief Scientific Officer for the Echocardiography Core Laboratory at the Cardiovascular Research Foundation. Dr Webb is a consultant for Edwards Lifesciences. Dr Leon serves on the PARTNER Trial Executive Committee for Edwards Lifesciences (non-paid); and has received institutional research grants from and has served as a nonpaid advisor for Abbott, Boston Scientific, and Medtronic; has served as a nonpaid advisor for Sinomed; and has equity in Medinol. Dr Cohen has received research grant support and consulting income from Edwards Lifesciences, Medtronic, Boston Scientific, and Abbott. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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PERSPECTIVES

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS:

Among patients with severe aortic stenosis undergoing TAVR or surgical AVR, the extent of cardiac damage is associated with health status before and after AVR.

TRANSLATIONAL OUTLOOK:

Further research is needed to determine whether improved detection of cardiac damage and earlier treatment of aortic stenosis will improve health outcomes after AVR.

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KEY WORDS aortic stenosis, aortic valve replacement, cardiac damage, Kansas City Cardiomyopathy Questionnaire, quality of life, transcatheter aortic valve implantation, transcatheter aortic valve replacement

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