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ORIGINAL RESEARCH

# Changes and Prognostic Implications of Myocardial Work in Aortic Stenosis Subtypes Undergoing Transcatheter Valve Implantation

Anders Lehmann Dahl Pedersen, MD,[a,b] Christian Alcaraz Frederiksen, MD, PhD,[a,b] Jonas Agerlund Povlsen, MD, PhD,[a,b] Bertil Thyrsted Ladefoged, MD,[a,b] Ali Hussein Jaber Mejren, MD,[a,b] Christian Juhl Terkelsen, MD, PhD, D.M.Sc.,[a,b] Steen Hvitfeldt Poulsen, MD, PhD, D.M.Sc[a,b]

## ABSTRACT

**BACKGROUND** Evaluation of left ventricle (LV) systolic function in patients with aortic stenosis (AS) undergoing transcatheter aortic valve implantation (TAVI) is challenging, as LV ejection fraction (LVEF) and global longitudinal strain are afterload dependent. LV global work indices (GWIs) estimate the afterload corrected systolic function.

**OBJECTIVES** The purpose of this study was to evaluate changes in and prognostic implications of GWIs in subtypes of AS patients before and 1 month after TAVI.

**METHODS** We included 473 patients undergoing TAVI. GWI was estimated using strain imaging and by adding the aortic valve mean gradient to the systolic blood pressure. The primary endpoint was all-cause mortality, evaluated by Cox proportional hazards and Kaplan-Meier curves.

**RESULTS** High gradient, low flow/low gradient, and normal flow/low gradient AS was found in 48%, 27%, and 25%. In patients with LVEF ≥50% delta GWI decreased from preoperative assessment to 1-month follow-up across all subtypes; high gradient (−353 ± 589 mm Hg%, $P < 0.01$), low flow/low gradient (−151 ± 652 mm Hg%, $P = 0.13$), and normal flow/low gradient (−348 ± 606 mm Hg%, $P < 0.01$). For patients with LVEF <50% delta GWI increased; high gradient 127 ± 491 mm Hg%, $P = 0.05$; low flow/low gradient 106 ± 510 mm Hg%, $P = 0.06$; normal flow/low gradient 107 ± 550 mm Hg%, $P < 0.27$. The median follow-up time was 60 months (IQR: 45-69 months). Each step of 100 mm Hg% higher GWI at pre-TAVI assessment was associated with a reduction in all-cause mortality in multivariable analysis (HR: 0.96 [95% CI: 0.92-1.00], $P = 0.033$).

**CONCLUSIONS** GWI increases in patients with reduced LVEF after TAVI across AS subtypes whereas GWI decreases in patients with preserved LVEF. Assessment of GWI offers additional prognostic implications beyond LVEF and global longitudinal strain. (JACC Adv 2024;3:101124) © 2024 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

From the [a]Department of Cardiology, Aarhus University Hospital, Aarhus, Denmark; and the [b]Aarhus University, Institute of Health, Aarhus, Denmark.

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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**ABBREVIATIONS AND ACRONYMS**

**AS** = aortic stenosis

**GCW** = global constructive work

**GLS** = global longitudinal strain

**GWI** = global work index

**HG** = high gradient

**LBBB** = left bundle branch block

**LFLG** = low flow low gradient

**LV** = left ventricle

**LVEF** = left ventricle ejection fraction

**NFLG** = normal flow low gradient

**TAVI** = transcatheter aortic valve implantation

Left ventricle ejection fraction (LVEF) is often used as a marker for systolic function, in patients with aortic stenosis (AS), and is often preserved until late in the course of the AS despite development of unfavorable left ventricular (LV) adaptions including progressive hypertrophy and fibrosis.[1] An important limitation of LVEF is its dependence on both loading conditions and contractility, which limits the ability to discriminate between these factors, as they often change during the disease course. LV global longitudinal strain (LV GLS) is increasingly being used for assessment of systolic function in patients with AS,[2-4] but LV GLS does not incorporate afterload.

The current guidelines recommend valve replacement in patients with severe AS and symptoms, or in asymptomatic patients with impaired LVEF.[3,5] As more elderly patients with more comorbidities are undergoing transcatheter aortic valve implantation (TAVI), determinants of prognosis and morbidity after TAVI are warranted. Assessment of symptoms in patients with various age-related comorbidities is challenging. The comorbidity heterogeneity among the AS patients is further complicated by the heterogeneity of AS subtypes. Especially when stroke volume is decreased, AS severity may be underestimated.[6] Furthermore, determination of whether the impaired stroke volume is due to increased afterload or decreased contractility is difficult with LVEF and LV GLS measurements alone.

LV global work index (LV GWI) is an echocardiographic measure, which estimates the myocardial work of the LV using two-dimensional strain echocardiography and brachial artery cuff pressure as a noninvasive measure of LV pressure to create LV pressure-strain loops.[7] A method for estimating the LV pressure in severe AS has been validated, which showed strong correlation between invasive LV pressure and aortic valve mean gradient added to brachial artery cuff pressure.[8,9]

Although LV GWI has been validated in AS patients, the changes after TAVI in the different AS subtypes have not been investigated in a large cohort of AS patients, and the evidence for the prognostic value of LV GWI in TAVI patients is based on two studies with a limited number of patients included.[10,11]

We aimed to investigate LV GWI in all subtypes of AS patients pre-TAVI, explore the changes of the LV GWI following TAVI, and to assess the prognostic value of LV GWI pre-TAVI.

## METHODS

**PATIENT POPULATION.** Consecutive patients undergoing TAVI from 2016 to 2018 at Aarhus University Hospital were retrospectively identified through the Western Denmark Heart Registry.[12] The pre-TAVI echocardiography leading to the treatment was analyzed in addition to the routine clinical follow-up echocardiography 1 month after TAVI. Targeted echocardiographic LV systolic data 12 months post-TAVI was also included. All clinical and laboratory data were obtained from the electronic patient record. Patients were excluded if they had undergone previous aortic valve replacement, died before 30 days follow-up, or if the echocardiography was inaccessible or had inadequate image quality for speckle tracking strain analysis.

The patients were followed until death of all causes or censoring on March 17, 2023. The primary endpoint was all-cause mortality, which was identified through the Western Denmark Heart Registry. This study was conducted in accordance with the Declaration of Helsinki. This study was approved by the Institutional Review Board and no patient consent was necessary.

**ECHOCARDIOGRAPHY.** Transthoracic echocardiography was performed using a commercially available system (Vivid E95 or E9, GE Healthcare) according to current guidelines.[13] The images were stored for offline analysis performed using a dedicated software (Echopac 203, GE Healthcare).

LVEF was calculated using Simpson's biplane method of discs. Continuous wave Doppler in the aortic valve in the apical 3- or 5-chamber view was used for calculation of aortic valve mean and peak gradients. The aortic valve area was calculated using the continuity equation, with LV outflow tract measured in the parasternal long axis view. Tricuspid annular plane systolic excursion was measured with M-mode in a modified apical 4-chamber view with focus on the right ventricle.

**ESTIMATION OF LV STRAIN AND MYOCARDIAL WORK.** LV GLS was estimated with speckle tracking strain imaging using automated function imaging in the apical 2-, 3-, and 4-chamber view focused on the LV. A frame rate >55 frames/s was considered appropriate. Triplane images were used if the patients had atrial fibrillation. If triplane was inaccessible, 2D cine loops with comparable RR intervals were used. A 17-segment model of peak systolic longitudinal contraction of the LV was then created.

The estimation of LV myocardial work requires a measure of the pressure in the LV. A noninvasive

**TABLE 1 Changes in Clinical and Echocardiographic Characteristics in Patients With High Gradient Aortic Stenosis and Normal or Reduced Left Ventricular Ejection Fraction**

| | HG, LVEF >50% | | HG, LVEF <50% | | *P* Value | |
|---|---|---|---|---|---|---|
| | Pre-TAVI (n = 169) | 1 Month Post (n = 169) | Pre-TAVI (n = 60) | 1 Month Post (n = 60) | Pre-TAVI | Post-TAVI |
| Age, y | 80 ± 6 | 81 ± 6 | 80 ± 4 | 81 ± 6 | 0.49 | 0.52 |
| EuroSCORE II | 2.2 (1.6-3.3) | NA | 3.2 (2.1-6.0) | NA | <0.001 | NA |
| eGFR, ml/min/1.73 $m^2$ | 68 (51-82) | 66 (50-82) | 60 (42-75) | 62 (44-80) | 0.01 | 0.26 |
| Sinus rhythm | 76 (129) | 71 (120) | 72 (43) | 67 (40) | 0.47 | 0.53 |
| AF | 14 (24) | 15 (26) | 20 (12) | 15 (9) | 0.29 | 0.94 |
| LBBB | 3 (5) | 19 (32) | 10 (6) | 25 (15) | 0.028 | 0.32 |
| SBP, mm Hg | 143 ± 17 | 151 ± 18 | 131 ± 20 | 148 ± 21 | <0.001 | 0.34 |
| DBP, mm Hg | 75 ± 12 | 76 ± 10 | 74 ± 14 | 75 ± 12 | 0.37 | 0.74 |
| Heart rate, beats/min | 73 ± 13 | 71 ± 11 | 82 ± 16 | 70 ± 13 | <0.001 | 0.53 |
| LV EF, % | 59 ± 6 | 56 ± 6 | 40 ± 8 | 48 ± 8 | <0.001 | <0.001 |
| LV GLS, % | −14.8 ± 3 | −15.8 ± 3 | −10.1 ± 2.8 | −13.5 ± 4 | <0.001 | <0.001 |
| GWI, mm Hg% | 2,396 ± 521 | 2,043 ± 492 | 1,577 ± 494 | 1,703 ± 519 | <0.001 | <0.001 |
| GWE, % | 92 (89-94) | 92 (89-95) | 87 (84-92) | 91 (87-93) | <0.001 | 0.052 |
| GCW mm Hg% | 2,723 ± 550 | 2,331 ± 495 | 1,853 ± 536 | 2,022 ± 545 | <0.001 | <0.001 |
| GWW, mm Hg% | 167 (110-254) | 143 (102-220) | 168 (118-252) | 169 (104-261) | 0.47 | 0.34 |
| AVG mean, mm Hg | 51 (45-61) | 10 (7-12) | 50 (44-64) | 10 (8-11) | 0.80 | 0.66 |
| AVG peak, mm Hg | 90 (77-103) | 21 (16-29) | 83 (73-103) | 20 (16-24) | 0.10 | 0.23 |
| AV VTI, cm | 118 ± 19 | 49 ± 12 | 112 ± 24 | 48 ± 11 | 0.04 | 0.61 |
| AVAi, $cm^2/m^2$ | 0.4 ± 0.1 | 0.9 ± 0.2 | 0.3 ± 0.1 | 0.9 ± 0.58 | <0.001 | 0.58 |
| SVi, $ml/m^2$ | 43 ± 10 | 44 ± 11 | 34 ± 9 | 42 ± 11 | <0.001 | 0.40 |
| TAPSE, cm | 2.3 ± 0.5 | 2.2 ± 0.5 | 2.0 ± 0.4 | 2.1 ± 0.5 | <0.001 | 0.13 |
| E/A | 0.8 (0.6-1.2) | 1.1 (0.7-1.5) | 0.8 (0.7-0.9) | 0.8 (0.6-1.0) | 0.037 | 0.56 |
| E/e' | 13.7 (10.7-18.7) | 13.8 (11.5-22.3) | 13.2 (9.9-16.4) | 12.7 (9.4-18.4) | 0.55 | 0.87 |
| LAVi, $mL/m^2$ | 41 (32-50) | 41 (33-50) | 42 (33-53) | 44 (32-54) | 0.71 | 0.72 |
| Stage (0/1/2/3/4)[a], % | 9/21/63/2/4 | | 0/20/60/7/13 | | 0.008 | NA |

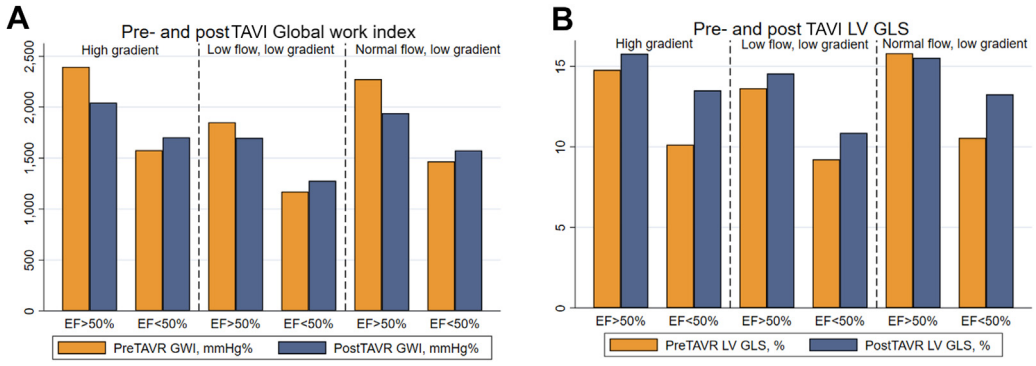
Values are mean ± SD, median (IQR), or % (n). *P* values of comparison of pre-TAVI values in the two groups and the post-TAVI values. [a]Stage according to definition by Généreux et al:[14] Stage 0 defined as no cardiac damage, stage 1 LV damage, stage 2 LA or mitral damage, stage 3 pulmonary vasculature or tricuspid damage and stage 4 RV damage.

AF = atrial fibrillation; AV = aortic valve; AVG = aortic valve gradient; AVAi = aortic valve area indexed; BPM = beats per minute; DBP = diastolic blood pressure; eGFR = estimated glomerular filtration rate; GCW = global constructive work; GWE = global work efficiency; GWI = global work index; GWW = global wasted work; HG = high gradient; LA = left atrial; LAVi = left atrial volume index; LBBB = left bundle branch block; LVEF = left ventricle ejection fraction; LVGLS = left ventricle global longitudinal strain; RV = right ventricle; SBP = systolic blood pressure; SVI = stroke volume index; TAPSE = tricuspid annular plane systolic excursion; TAVI = transcatheter aortic valve replacement; VTI = velocity time integral.

method for this in patients with severe AS has previously been described and validated.[8,9] In short, the aortic valve mean gradient is added to the systolic cuff pressure as a measure of peak systolic LV pressure. When combining this sum of pressures with strain analysis of LV GLS, accordingly adjusted to the aortic and mitral valve opening and closing, a noninvasive pressure-strain curve can be generated. This creates a 17-segment model of global strain-pressure values, with the average being GWI equal to the area within the pressure-strain curve. Global constructive work (GCW) can be estimated by adding the negative work performed during isovolumetric relaxation to the segment shortening in systole. The global wasted work is calculated as the lengthening of a segment in systole added to the shortening in the isovolumetric relaxation. Finally, the myocardial work efficiency can be calculated as the sum of the GCW and wasted work divided by the GCW. The systole was defined based on the electrocardiographic tracings and visual inspection of the aortic valve opening and closure. The normal range for LV GWI was considered to be within 2,028 ± 392 mm Hg.[14]

**STRATIFICATION IN AS SUBTYPES.** All patients were divided into AS subtypes based on current guideline recommendations.[3,5] Patients were stratified using the following 3 parameters: LVEF ≥50% or <50%, transaortic flow with a stroke volume index ≥35 or <35 $ml/m^2$, and based on mean Doppler gradient of

**FIGURE 1 Global Work Index and Left Ventricle Global Strain Before and After TAVI Stratified by Ejection Fraction and Subtype of Aortic Stenosis**




(A) Pre- and postTAVI global work index in aortic stenosis subgroups and (B) Pre- and postTAVI global longitudinal strain in aortic stenosis subgroups. GWI = global work index; LV GLS = left ventricle global longitudinal strain; post-TAVI = one-month after TAVI; TAVI = transcatheter aortic valve replacement; EF = ejection fraction.

the aortic valve (high gradient (HG) with mean gradient ≥40 mm Hg and low gradient with a mean gradient <40 mm Hg).

Staging of extent of cardiac damage was conducted according to Généreux et al.[15] Moderate to severe right ventricle damage was defined as tricuspid annular plane systolic excursion <15 mm.

**STATISTICS.** Data were analyzed using STATA (STATA/MP 17.0, Statacorp). Normality of data was visually assessed using QQ-plots and histograms.

Continuous data are reported as mean ± SD if normally distributed and median (IQR: 25th percentile; 75th percentile) if skewed. Categorical variables are reported as percentages (absolute number of patients). Comparisons between AS subtypes were performed with Student's *t*-test, Mann-Whitney U test, and the chi-square test as appropriate. Cox proportional hazards regression analysis was used for univariable and multivariable analysis with event defined as death of any cause and start of follow-up as date of TAVI. As the EuroSCORE contains variables such as age, sex, New York Heart Association (NYHA) functional class, lung diseases, previous coronary artery bypass graft, and LVEF, only EuroSCORE was included in the multivariable analysis. A cutoff of 100 mm Hg for LV GWI was preferred in univariate and multivariate analysis as a 100 mm Hg increase or decrease was considered clinically relevant, whereas hazard ratios for LV GWI on a continuous scale are difficult to assess.[16]

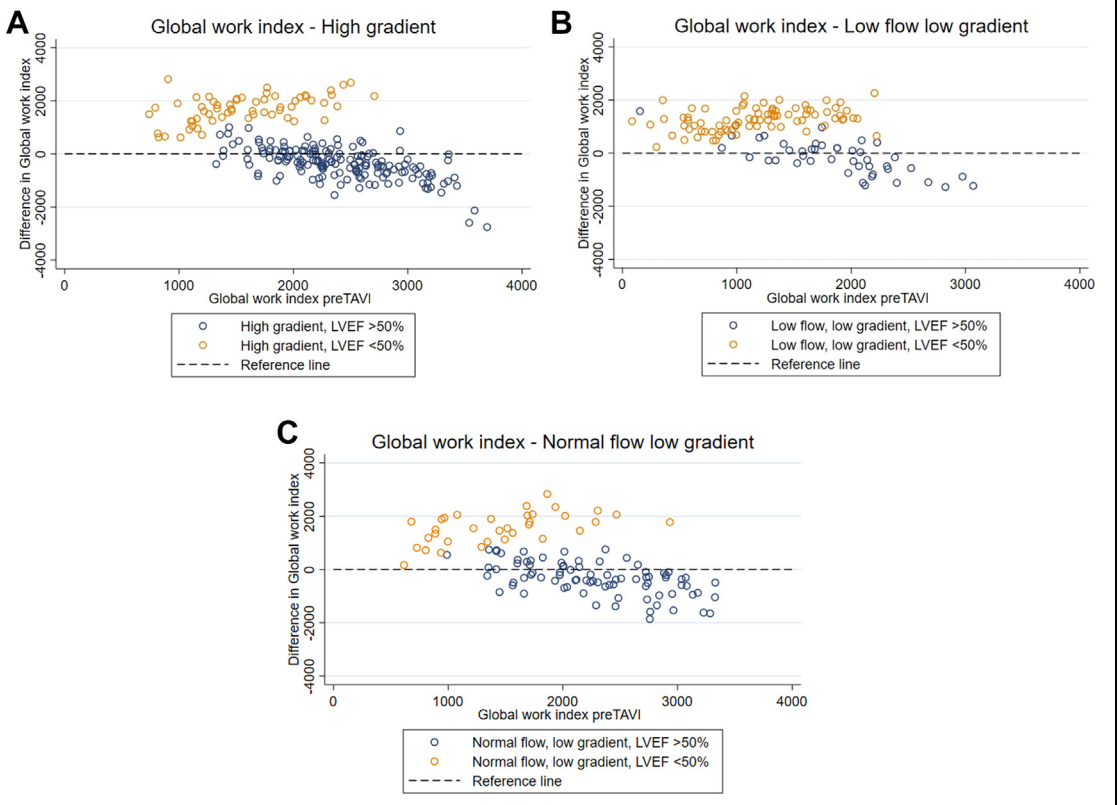
## RESULTS

**STUDY POPULATION.** We included 473 patients of a total cohort of 610 consecutive patients. Twenty-nine patients were excluded due to valve in valve intervention, 6 patients died before 1-month follow-up, and 102 were excluded due to inaccessible or inadequate image quality. The pre-TAVI mean age for all patients was 80 ± 7 years, 52% were female, 74% had hypertension, 21% had diabetes, 34% ischemic heart disease, and the median EuroSCORE II was 2.6 (IQR: 1.7-4.5). A transfemoral TAVI procedure approach was performed in 86% of the patients, 13% were treated transapically. The Edwards Sapien 3 valve was implanted in 79% of the patients. The median pre-TAVI LV GWI was 1,966 mm Hg% (IQR: 1,421-2,414 mm Hg%) with a minimum value of 84 and a maximum of 3694.

Patients with left bundle branch block (LBBB) before TAVI had lower GWI than those without LBBB (1,450 ± 690 mm Hg vs 1,996 ± 698, $P < 0.001$). Patients with LBBB after TAVI had similar GWI compared to those without LBBB (1,796 ± 578 vs 1,732 ± 525, $P = 0.33$).

**HG AS WITH LVEF ≥50% OR <50%.** A comparison of pre- and 1-month post-TAVI echocardiography and demography are presented in **Table 1**. Pre- and post-TAVI LV GWI and LV GLS are presented in **Figure 1** and difference in LV GWI before and after TAVI in **Figure 2** and the **Central Illustration**. Prior to TAVI,

**FIGURE 2** Difference in Global Work Index From Pre- to Post-TAVI in AS Subtypes




(A) Difference in global work index from pre- to postTAVI for high gradient aortic stenosis. (B) Difference in global work index from pre- to postTAVI for low flow low gradient aortic stenosis. (C) Difference in global work index from pre- to postTAVI for normal flow low gradient aortic stenosis. The reference line on the y-axis is 0 which indicates no change in LV GWI after TAVI. Patients below the reference line decreased in LW GWI, whereas patients above the line increased in LV GWI after TAVI. AS = aortic stenosis; LVEF = left ventricular ejection fraction; other abbreviations as in Figure 1.

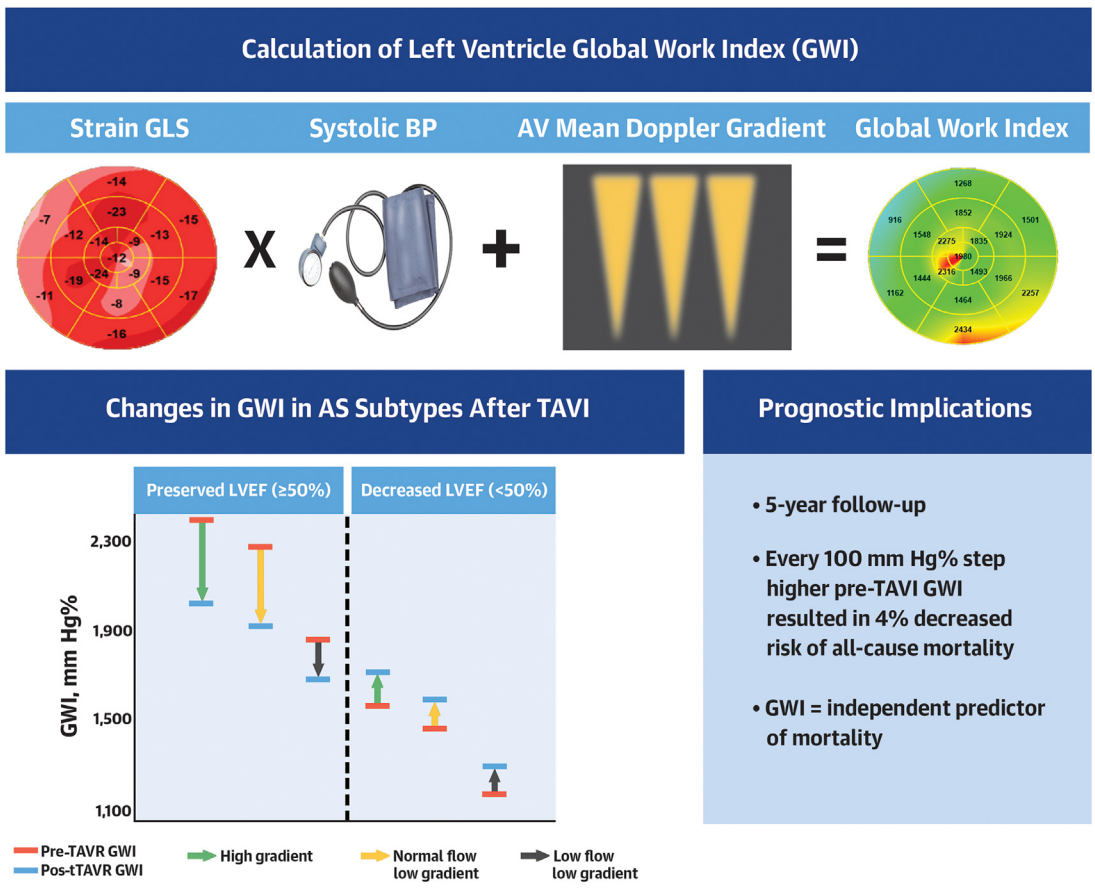
patients with HG and LVEF <50% were more likely to have a higher extent of myocardial damage, EuroSCORE II, atrial fibrillation, lower estimated glomerular filtration rate, lower LV GLS, GWI, GCW, and global work efficiency compared to patients with HG and LVEF ≥50%.

Patients with HG and LVEF <50% demonstrated an increase in LVEF after TAVI (40 ± 7 to 48 ± 8, $P < 0.01$). Conversely, patients with HG and LVEF ≥50% exhibited a decrease in LVEF (59 ± 6 to 56 ± 6, $P < 0.01$). Patients with HG and LVEF <50% improved LV GLS (−10.1 ± 2.8 to −13.5 ± 3.8, $P < 0.01$) surpassing the improvement of HG and LVEF ≥50% (−14.8 ± 2.7-15.8 ± 3.1, $P < 0.01$). HG and LVEF <50% had a borderline improvement in LV GWI (1,577 ± 494 to 1,703 ± 519, $P = 0.05$) whereas HG and LVEF ≥50% decreased in LV GWI (2,396 ± 521 to 2,043 ± 492, $P < 0.01$). The change in LV GWI until 12 months after TAVI for patients with HG is shown in Figure 3 and Supplemental Table 1. No significant changes from 1-month follow-up to 12-month follow-up were noted.

**LOW FLOW, LOW GRADIENT AS WITH LVEF ≥50% OR LVEF <50%.** Patients with low flow (SVI <35 ml/m$^2$) and low gradient (mean AV gradient <40 mm Hg) were divided based on LVEF ≥50% (LFLGEF ≥50) and LVEF <50% (LFLGEF <50). Demographic and echocardiographic variables are presented in Table 2.

LVEF decreased in patients with LFLGEF ≥50 from pre-TAVI to 1-month follow-up (57 ± 6 to 53 ± 9, $P < 0.01$), whereas LVEF increased in patients with LFLGEF <50 (36 ± 9 to 43 ± 10, $P < 0.01$). A nonsignificant increase in LV GLS was noted in patients with LFLGEF ≥50 (−13.6 ± 4 to −14.6 ± 3, $P = 0.08$) compared to patients with LFLGEF <50 who

**CENTRAL ILLUSTRATION** **Changes and Prognostic Implications of Myocardial Work in Aortic Stenosis Subtypes Undergoing Transcatheter Valve Implantation**




Left ventricle global work index in patients with aortic stenosis is calculated using global longitudinal strain and a noninvasive estimate of systolic left ventricle pressure calculated as aortic valve mean gradient added to the systolic blood pressure. The change in global work index is shown in aortic stenosis subtypes stratified by ejection fraction from pre-TAVI to one month after TAVI. Created using Biorender.com. Abbreviations as in Figures 1 and 2.

increased significantly (−9.2 ± 4 to −10.9 ± 3, $P < 0.01$). LV GWI in the patient group of LFLGEF ≥50 decreased slightly (1,850 ± 581 to 1,699 ± 438, $P = 0.13$) which was opposed by an increase for LFLGEF <50 patients (1,171 ± 503 to 1,277 ± 422, $P = 0.06$), although both changes remained statistically insignificant.

**NORMAL FLOW LOW GRADIENT AS.** Patients with normal flow (SVI ≥35) and low gradient were stratified based on LVEF ≥50% (NFLGEF ≥50) and LVEF <50% (NFLGEF <50). Echocardiographic and demographic variables are presented in Table 3.

NFLGEF ≥50 patients decreased in LVEF from pre-TAVI to 1-month follow-up (59 ± 6 to 55 ± 7, $P < 0.01$) whereas NFLGEF <50 increased in LVEF (40 ± 7 to 47 ± 11, $P < 0.01$). NFLGEF ≥50 patients had stationary LV GLS (−15.8 ± 3.3 to −15.5 ± 4, $P = 0.45$). NFLGEF <50 increased in LV GLS (−10.6 ± 3 to −13.3 ± 4, $P < 0.01$). NFLGEF ≥50 decreased in LV GWI (2,275 ± 576 to 1,940 ± 553, $P < 0.01$), NFLGEF <50 had a nonsignificant decrease (1,468 ± 572 to 1,575 ± 572, $P = 0.27$).

**PROGNOSIS.** The median follow-up from TAVI was 60 months (IQR: 45-69 months). During follow-up,

204 all-cause deaths were registered. One-, 2-, and 3-year mortality rates were 6% (IQR: 4%-8%), 10% (IQR: 8%-13%), and 17% (IQR: 14%-21%). The 5-year mortality was 35% (30-29). Multivariable analysis showed an association between all-cause mortality and increasing age, ischemic heart disease and LV GWI per 100 mm Hg% increase (**Table 4**). Sensitivity analysis without EuroSCORE is presented in Supplemental Tables 2 and 3. Overall, patients with HG AS had the best survival compared to LFLG (**Figure 4**). In a multivariable model adjusted for age and sex, every 100 mm Hg% higher LV GWI at 1-month follow-up was associated with improved prognosis (HR: 0.93 [95% CI: 0.90-0.96], $P < 0.001$). In a multivariate analysis with EuroSCORE, stroke volume index and LV GWI, EuroSCORE (HR: 1.07, $P < 0.001$) and LV GWI (HR: 0.98, $P = 0.033$) remained independent predictors of prognosis, whereas stroke volume index did not (HR: 1.00, $P = 0.563$).

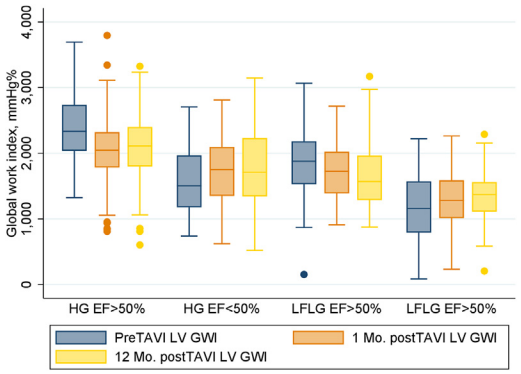
To assess characteristics of which patients increased in LV GWI after TAVI and which decreased, Supplemental Table 4 compares patients who increase in LV GWI to those who decrease. In general, patients who increased in LV GWI had lower blood pressure, decreased systolic function, slightly lower AV gradients, and slightly higher extent of cardiac damage compared to those who increased. To investigate the influence of annulus size on LV GWI, patients were divided into quartiles of aortic annulus area based on cardiac computed tomography. Before TAVI, patients in the quartile with the smallest annuli (<4.13 $cm^2$) had higher LV GWI compared to patients in the quartile with the largest annuli (>5.39 $cm^2$) (2,113 ± 706 mm Hg vs 1,682 ± 756, $P < 0.001$). One month after TAVI, patients with the smallest annuli still had higher LV GWI than patients with the largest annuli (1,895 ± 618 vs 1,618 ± 542, $P = 0.001$).

In Supplemental Figure 1, Kaplan-Meier estimates are shown for patients stratified by stage [14] (stage 0-2 vs 3-4) and pre-TAVI LV GWI above or below the median. The combination of LV GWI > median and stage 0 to 2 had the best prognosis, stage 3 to 4 and LV GWI < median had the worst prognosis. Stage 0 to 2 and LV GWI < median and stage 3 to 4 with LV GWI > median had similar prognosis.

## DISCUSSION

The main findings of this study are the following: [1] For patients with preserved LV systolic function, assessed by LVEF, prior to TAVI, the unloading of the LV resulted in a decrease of LV GWI due to unchanged LV systolic function but decreased afterload across all AS subtypes.[2] In contrast, in patients with decreased LVEF prior to TAVI, the unloading of the LV resulted in increased LV GWI across AS subtypes despite the reduction of the pressure afterload following relief of the AS, due to a substantial improvements of LV systolic function, even for patients with low flow, low gradient AS.[3] Finally, LV GWI exhibited an independent significant association to all-cause mortality as compared to LVEF and LV GLS, likely due to the incorporation of afterload in the assessment of LV systolic function. These findings suggest that LV GWI may be used for risk stratification in AS and with possible implications for timing of aortic valve intervention.

**FIGURE 3** Changes in Global Work Index From Pre-TAVI to 1 Year After Stratified by Ejection Fraction and High Gradient and Low Flow Low Gradient




Abbreviations as in **Figures 1 and 4**.

**LV SYSTOLIC FUNCTION IN AS.** The use of LVEF as a surrogate for stroke volume, cardiac output, and LV systolic function poses several challenges in patients with LV hypertrophy. In AS, the gradually increasing afterload often causes LV remodeling with concentric LV hypertrophy to limit wall stress.[17,18] As the LV hypertrophy increases, the volume of the cavity often decreases.[19] To compensate the decrease in cavity volume and to preserve cardiac output, LVEF often remains normal or may even increase. Thus, LVEF is often preserved even with obvious progression of the AS and even after symptoms appear. Several studies have indicated that a decrease in LVEF in AS is associated with irreversible myocardial damage, which limits the potential of LVEF to detect early systolic myocardial dysfunction.[20-22] LV GLS seems able to detect early impairment of contractile function in AS and impairment is associated with presence of myocardial fibrosis and has prognostic implications in TAVI patients.[4,23,24] However, LV GLS is dependent

**TABLE 2 Changes in Clinical and Echocardiographic Characteristics in Patients With Low Flow Low Gradient Aortic Stenosis and Normal or Reduced Left Ventricular Ejection Fraction**

| | LFLG, LVEF >50% | | LFLG, LVEF <50% | | *P* Value | |
|---|---|---|---|---|---|---|
| | Pre-TAVI (n = 45) | 1 Month (n = 45) | Pre-TAVI (n = 82) | 1 Month (n = 82) | Pre-TAVI | Post-TAVI |
| Age, y | 80 ± 7 | 81 ± 7 | 79 ± 8 | 80 ± 8 | 0.37 | 0.33 |
| EuroSCORE II | 2.2 (1.6-3.8) | NA | 4.6 (2.2-8.2) | NA | <0.001 | NA |
| eGFR, ml/min/1.73 $m^2$ | 62 (51-75) | 70 (50-79) | 56 (46-67) | 58 (46-72) | 0.063 | 0.20 |
| Sinus rhythm | 36 (16) | 36 (16) | 49 (40) | 51 (42) | 0.15 | 0.09 |
| AF | 40 (18) | 42 (19) | 35 (29) | 29 (24) | 0.60 | 0.14 |
| LBBB | 16 (7) | 22 (10) | 21 (17) | 33 (27) | 0.48 | 0.20 |
| SBP, mm Hg | 142 ± 19 | 142 ± 17 | 131 ± 20 | 141 ± 21 | 0.004 | 0.86 |
| DBP, mm Hg | 78 ± 12 | 77 ± 10 | 75 ± 14 | 78 ± 11 | 0.15 | 0.72 |
| Heart rate, beats/min | 78 ± 15 | 75 ± 13 | 75 ± 14 | 76 ± 16 | 0.17 | 0.72 |
| LV EF, % | 57 ± 6 | 53 ± 9 | 36 ± 9 | 43 ± 10 | <0.001 | <0.001 |
| LV GLS, % | −13.6 ± 3.9 | −14.6 ± 2.7 | −9.2 ± 3.5 | −10.9 ± 3.2 | <0.001 | <0.001 |
| GWI, mm Hg% | 1,850 ± 581 | 1,699 ± 438 | 1,171 ± 503 | 1,277 ± 422 | <0.001 | <0.001 |
| GWE, % | 90 (87-93) | 90 (86-93) | 87 (81-90) | 88 (79-92) | 0.003 | 0.018 |
| GCW, mm Hg% | 2,190 ± 590 | 2,042 ± 430 | 1,407 ± 533 | 1,560 ± 487 | <0.001 | <0.001 |
| GWW, mm Hg% | 188 (113-263) | 192 (91-260) | 155 (108-207) | 159 (109-250) | 0.23 | 0.81 |
| AVG mean, mm Hg | 30 (25-36) | 8 (6-10) | 28 (21-32) | 8 (7-9) | 0.020 | 0.84 |
| AVG peak, mm Hg | 56 (47-64) | 18 (14-22) | 51 (39-59) | 16 (13-21) | 0.010 | 0.23 |
| AV VTI, cm/$m^2$ | 83 ± 14 | 43 ± 9 | 78 ± 15 | 41 ± 10 | 0.038 | 0.35 |
| AVAi, $cm^2/m^2$ | 0.3 ± 0.1 | 0.9 ± 0.2 | 0.4 ± 0.1 | 0.8 ± 0.2 | 0.24 | 0.17 |
| SVi, ml/$m^2$ | 28 ± 5 | 40 ± 10 | 28 ± 5 | 34 ± 9 | 0.44 | 0.001 |
| TAPSE, cm | 1.9 ± 0.5 | 1.9 ± 0.4 | 1.8 ± 0.5 | 1.9 ± 0.5 | 0.09 | 0.54 |
| E/A | 1.1 (0.8-1.9) | 0.9 (0.6-1.9) | 0.8 (0.6-0.9) | 1.0 (0.7-1.5) | 0.37 | 0.036 |
| E/e' | 13.8 (9.5-18.2) | 11.8 (8.2-16.4) | 12.1 (9.3-18.6) | 12.2 (9.4-15.0) | 0.25 | 0.41 |
| LAVi, mL/$m^2$ | 45 (30-59) | 41 (33-51) | 47 (36-60) | 44 (33-59) | 0.48 | 0.43 |
| Stage (0/1/2/3/4), % | 7/11/56/7/10 | | 0/15/51/4/30 | | 0.11 | NA |

Values are mean ± SD, median (IQR), or % (n). *P* values of comparison of pre-TAVI values in the two groups and the post-TAVI values.
LFLG = low flow low gradient; other abbreviations as in Table 1.

on loading conditions and afterload. Myocardial GWI incorporates a correction for afterload to the strain analysis and an assessment of synchrony in LV contraction using timing of aortic and mitral valvular opening and closing. Therefore, LV GWI has the potential to assess the LV myocardial function in AS patients in a disease-specific perspective with combined analysis of systolic function, LV synchrony, and an afterload correction.[7-9,25] The assessment of LV synchrony is of particular interest in TAVI patients, as these patients often have conduction disorders before TAVI or develop conduction disorders requiring pacemaker implantation with subsequent right ventricular pacing that could induce LV systolic dysfunction. GWI in patients with LBBB was lower before TAVI, but no difference was noted in GWI among those who had or developed LBBB compared to those without. The effect of LBBB on GWI during long-term follow-up remains uncertain. The interobserver and intraobserver variability of the echocardiographic variables are important and often a limitation. The interobserver and intraobserver variability of LV GWI has previously been tested in patients undergoing TAVI and in patients with cardiac amyloidosis, showing great agreement with an interobserver intraclass correlation of 0.92 to 0.97 and intraobserver intraclass correlation of 0.95.[8,26]

**SERIAL CHANGES IN AS SUBTYPES.** LV GLS and LV GWI are based on the same speckle tracking algorithm with an inherent close relationship between the two parameters. However, when incorporating the mean gradient in the calculation in patients with severe AS, the response to TAVI may result in a decrease in LW GWI despite an increase in LV GLS. Jain et al[9] showed that LV GWI decreased after TAVI despite an LV GLS increase when using the calculation with adjustment for the mean gradient prior to TAVI.

**TABLE 3 Changes in Clinical and Echocardiographic Characteristics in Patients With Normal Flow Low Gradient Aortic Stenosis and Normal or Reduced Left Ventricular Ejection Fraction**

| | NFLG, LVEF >50% | | NFLG, LVEF <50% | | *P* Value | |
|---|---|---|---|---|---|---|
| | Pre-TAVI (n = 83) | 1 Month (n = 83) | Pre-TAVI (n = 34) | 1 Month (n = 34) | Pre-TAVI | Post-TAVI |
| Age, y | 78 ± 9 | 79 ± 9 | 80 ± 7 | 81 ± 7 | 0.18 | 0.19 |
| EuroSCORE II | 2.2 (1.7-3.9) | NA | 3.7 (2.4-8.3) | NA | 0.004 | NA |
| eGFR, ml/min/1.73 $m^2$ | 72 (60-85) | 73 (53-84) | 64 (46-74) | 52 (42-73) | 0.015 | <0.001 |
| Sinus rhythm | 83 (69) | 71 (59) | 68 (23) | 59 (20) | 0.06 | 0.20 |
| AF | 7 (6) | 10 (8) | 15 (5) | 6 (2) | 0.21 | 0.51 |
| LBBB | 11 (9) | 11 (9) | 15 (5) | 18 (6) | 0.57 | 0.33 |
| SBP, mm Hg | 143 ± 20 | 149 ± 19 | 138 ± 29 | 145 ± 17 | 0.25 | 0.32 |
| DBP, mm Hg | 75 ± 14 | 76 ± 11 | 69 ± 15 | 73 ± 10 | 0.037 | 0.21 |
| Heart rate, beats/min | 70 ± 12 | 71 ± 12 | 73 ± 13 | 72 ± 13 | 0.17 | 0.99 |
| LV EF, % | 59 ± 6 | 55 ± 7 | 40 ± 7 | 47 ± 11 | <0.001 | <0.001 |
| LV GLS, % | −15.8 ± 3.3 | −15.5 ± 7.1 | −10.6 ± 3.3 | −13.3 ± 4.4 | <0.001 | <0.005 |
| GWI, mm Hg% | 2,275 ± 576 | 1,940 ± 553 | 1,468 ± 572 | 1,575 ± 572 | <0.001 | 0.002 |
| GWE, % | 92 (89-95) | 92 (88-95) | 88 (84-93) | 90 (85-93) | <0.001 | 0.030 |
| GCW, mm Hg% | 2,555 ± 590 | 2,221 ± 602 | 1,707 ± 648 | 1,916 ± 642 | <0.001 | 0.016 |
| GWW, mm Hg% | 143 (98-216) | 143 (84-212) | 155 (114-237) | 171 (119-252) | 0.29 | 0.19 |
| AVG mean, mm Hg | 33 (27-37) | 9 (7-11) | 33 (25-36) | 9 (7-10) | 0.29 | 0.34 |
| AVG peak, mm Hg | 59 (51-66) | 20 (15-26) | 58 (48-64) | 18 (15-24 | 0.26 | 0.37 |
| AV VTI, cm/$m^2$ | 91 ± 14 | 47 ± 11 | 88 ± 13 | 45 ± 9 | 0.27 | 0.36 |
| AVAi, $cm^2/m^2$ | 0.5 ± 0.1 | 0.9 ± 0.2 | 0.4 ± 0.1 | 0.9 ± 0.2 | 0.45 | 0.99 |
| SVi, ml/$m^2$ | 44 ± 9 | 43 ± 9 | 41 ± 7 | 42 ± 10 | 0.09 | 0.08 |
| TAPSE, cm | 2.2 ± 0.4 | 2.2 ± 0.4 | 2.1 ± 0.4 | 2.0 ± 0.4 | 0.12 | 0.07 |
| E/A | 0.8 (0.7-1.1) | 0.8 (0.6-0.9) | 0.7 (0.6-0.9) | 0.7 (0.6-1.0) | 0.33 | 0.71 |
| E/e' | 13.5 (10.0-15.9) | 12.0 (9.7-17.9) | 12.6 (9.0-16.2) | 12.9 (10.4-15.5) | 0.89 | 0.77 |
| LAVi, mL/$m^2$ | 34 (27-48) | 38 (31-51) | 36 (28-47) | 43 (32-52) | 0.20 | 0.17 |
| Stage (0/1/2/3/4), % | 11/33/50/2/4 | | 0/35/53/6/6 | | 0.30 | NA |

Values are mean ± SD, or median (IQR), or % (n). *P* values of comparison of pre-TAVI values in the two groups and the post-TAVI values.
NFLG = normal flow low gradient; other abbreviations as in Table 1.

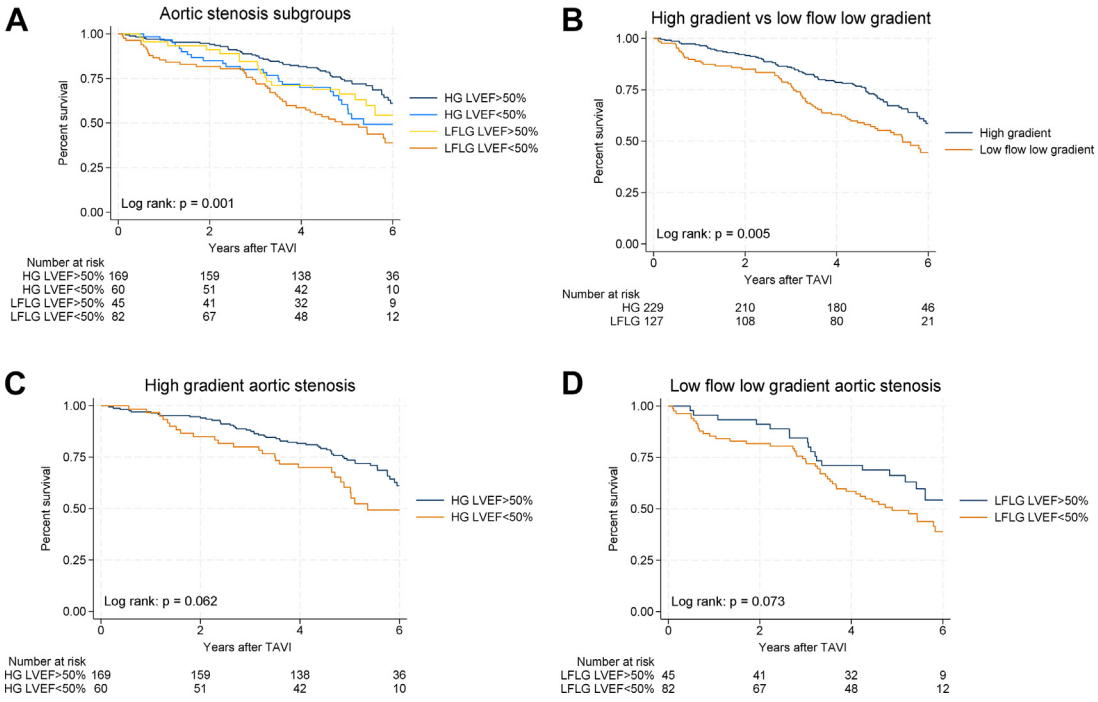
This is the first study to explore the response of LV GWI after TAVI in AS subtypes. LV GWI has been correlated to myocardial oxygen consumption and represents the work performed by the LV.[7,27] As the aortic valve narrows, the work by the LV must increase to preserve stroke volume. Thus, the work and oxygen demand of the LV will subsequently increase. While LVEF is often preserved in severe AS, LV GLS is in contrast often impaired.[28] The decrease in LV GLS has been attributed to the pressure overload and myocardial fibrosis, with the latter to some extent being irreversible. In HG AS, it would seem likely that the decrease in LV GLS is due to the high afterload as the LV is capable of generating a high pressure and gradient, especially if LVEF is preserved. In our study, we confirm this hypothesis, as patients with HG and preserved LVEF increased slightly in LV GLS and decreased in LV GWI due to the afterload reduction. For patients with HG and decreased LVEF, the LV GWI increased despite the afterload reduction and this increase was seen alongside an increase in stroke

**TABLE 4 Univariable and Multivariable Analysis for Associations With All-Cause Mortality After TAVI**

| | Univariable | | Multivariable 1 | |
|---|---|---|---|---|
| | HR (95% CI) | *P* Value | HR (95% CI) | *P* Value |
| Age, y | 1.04 (1.01-1.07) | 0.002 | | |
| Female | 0.94 (0.71-1.23) | 0.641 | | |
| EuroSCORE | 1.09 (1.06-1.11) | <0.001 | 1.07 (1.05-1.10) | <0.001 |
| NYHA functional class | 1.31 (1.13-1.52) | <0.001 | | |
| Hypertension | 1.07 (0.78-1.47) | 0.671 | | |
| Diabetes | 1.03 (0.73-1.43) | 0.882 | | |
| COPD | 1.46 (1.03-2.07) | 0.033 | | |
| IHD | 1.46 (1.10-1.94) | 0.009 | | |
| BMI, kg/$m^2$ | 1.00 (0.97-1.03) | 0.898 | | |
| LVEF, % | 0.98 (0.97-0.99) | <0.001 | | |
| SVi | 0.98 (0.97-0.99) | 0.003 | | |
| LV GLS, % | 1.08 (1.04-1.11) | <0.001 | 0.97 (0.90-1.04) | 0.448 |
| GWI/100[a], mm Hg | 0.95 (0.94-0.97) | <0.001 | 0.96 (0.92-1.00) | 0.033 |

Multivariable analysis included EuroSCORE, LV GLS, and GWI. Further multivariable models are included in Supplemental Tables 2 and 3. [a]Hazard ratio for each 100 mm Hg% step higher at pre-TAVI assessment.
BMI = body mass index; COPD = chronic obstructive pulmonary disease; IHD = ischemic heart disease; other abbreviations as in Table 1.

**FIGURE 4** Kaplan-Meier Plots for All-Cause Mortality After TAVI Stratified in High Gradient, Low Flow Low Gradient, and by Ejection Fraction




(A) Kaplan-Meier curve for subtypes of aortic stenosis. (B) High gradient aortic stenosis versus low flow low gradient aortic stenosis. (C) High gradient with preserved or decreased left ventricle ejection fraction. (D) Low flow low gradient with preserved or decreased left ventricle ejection fraction. HG = high gradient; LFLG = low flow low gradient; other abbreviations as in Figures 1 and 2.

volume index suggesting a subacute hemodynamic effect of unloading the LV. The LV GWI did not change from one to 12 months after TAVI. This finding implies that systolic function of the LV is stable from 1 month and forward and that systolic function at 1 month after TAVI could be a key target in improving prognosis. Although afterload is incorporated in the calculation of GWI, the annulus size seemed to affect GWI as we found that small aortic annuli were associated with higher LV GWI.

Low gradient severe AS has been associated with a higher degree of myocardial fibrosis.[21] Fibrosis may partly explain the decreased LV GLS in LFLG AS, which would correlate with decreased LV GWI. The LV GWI values for patients with low flow, low gradient, and decreased LVEF were severely decreased before TAVI and although they increased slightly after TAVI the values were still severely impaired, which seems to affect the prognosis. Other explanations for the decreased LV GWI in this group could be a high EuroSCORE II and potential undiagnosed cardiac diseases such as transthyretin cardiac amyloidosis which would affect the myocardial function. The question for future studies to determine is whether patients with LFLG could benefit from early intervention, ie, before LV GWI decreases, or whether concomitant myocardial pathologies limits the potential to intervene before a decrease in LV GWI.

**PROGNOSIS.** In the present study, each step of 100 mm Hg% higher LV GWI pre-TAVI was associated with 4% lower risk of all-cause mortality in multivariable analysis. This is in accordance with findings by Wu et al who demonstrated an improved prognosis with increasing LV GWI before TAVI with a HR of 0.64 (95% CI: 0.46-0.88) in an adjusted model in 281 TAVI patients.[11] Overall, the study cohort investigated by Wu et al was comparable to ours with respect to age, comorbidities, and NYHA functional class. We found slightly higher LV GWI in our cohort (1,939 vs 1,872 mm Hg%), lower LVEF (51% vs 56%), and more impaired LV GLS (−13.0% vs −13.5%) even though we had fewer patients with HG AS (48% vs 60%). These

differences in LW GWI may be due to differences in blood pressure.

De Rosa et al[10] investigated changes and prognostic implications of myocardial work indices after TAVI in 73 patients and found LV GWI measured prior to TAVI as a predictor of all-cause mortality in adjusted analysis. Interestingly, De Rosa et al[10] found LV GWI prior to TAVI correlated with readmission for heart failure after TAVI. Anwer et al[29] found that LV GWI predicted cardiovascular mortality in 147 TAVI patients, although LV GWI was not corrected for the AV mean gradient. Although these studies and our study are retrospective, it seems LV GWI is a strong prognostic marker of mortality in TAVI patients across AS populations and may be related to morbidity as well.

**POTENTIAL CLINICAL IMPLICATIONS.** Assessment of LV GWI seems to be able to detect early myocardial damage and has prognostic implications in AS patients. It is noninvasive and feasible to implement in the daily clinical routine as the calculation is a quick and easy add-on to strain analysis. Early markers of myocardial dysfunction and prognosis are urgently warranted in the monitoring of AS.[30] Furthermore, the prognostic value of LV GWI suggests it may be a parameter with value in guiding the timing of aortic valve replacement, especially in patients with low gradient AS. Several studies of aortic valve replacement in asymptomatic patients are ongoing which mainly focus timing of aortic valve replacement in these patients around biomarkers and standard echocardiography.[30] Whether certain LV GWI cutoffs are suitable timing of aortic valve replacement may be determined in future prospective studies.

**STUDY LIMITATIONS.** Although many patients were included in this study, the observational and retrospective nature of the study carries a risk of residual confounding and bias from patient selection as poor image quality inhibits GWI analysis. Furthermore, measures of E/a ratio and E/e' were only available in 265 and 255 patients prior to TAVI and in 343 and 429 1 month after TAVI, respectively. Continuous wave Doppler was not registered routinely from the right parasternal window which may lead to underestimation of the AV gradients and LV GWI. Myocardial work indices may be influenced by undiagnosed myocardial diseases such as amyloidosis, for which we did not systematically screen patients, although patients were referred based on clinical suspicion. The blood pressure was measured at the outpatient visit, most often just before the echocardiography and not simultaneously with the acquisition of the images for LV GLS. The software for myocardial work analysis is vendor-specific which limits implementation in general. Twenty-five percent of the patients had NFLG AS making truly severe AS unlikely according to guidelines.[3] We do not have data concerning why these patients anyhow underwent TAVI.

## CONCLUSIONS

LV GWI increases in patients with reduced LVEF across subtypes of AS patients due to increased contractility. LV GWI decreases in patients with preserved LVEF due to stationary contractility and decreased afterload after TAVI. Preoperative assessment of LV GWI in AS patients undergoing TAVI offers additional prognostic implications beyond LVEF and GLS.

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**ADDRESS FOR CORRESPONDENCE:** Anders Lehmann Dahl Pedersen, Department of Cardiology, Aarhus University Hospital, Palle Juul-Jensens Boulevard 99, DK-8200 Aarhus N, Denmark. E-mail: ANLEPE@rm.dk.

## PERSPECTIVES

**COMPETENCY IN MEDICAL KNOWLEDGE:** In this study of 473 patients with severe AS undergoing TAVI, we use GWIs as an afterload-corrected measure of systolic function and demonstrate different responses in global work in AS subtypes after TAVI and that GWIs are associated to all-cause death. These findings suggest that GWIs could be used for risk stratification of patients with severe AS.

**TRANSLATIONAL OUTLOOK:** Further studies should determine whether the prognostic capabilities of GWIs could be used for timing of aortic valve replacement.

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**KEY WORDS** aortic stenosis, transcatheter aortic valve implantation, myocardial work index, global work index, echocardiography, prognosis

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