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ORIGINAL ARTICLE

Evolution and Prognostic Impact of Left Ventricular Myocardial Work Indices After Transcatheter Aortic Valve Replacement in Patients With Severe Aortic Stenosis

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ABSTRACT

Purpose: Left ventricular myocardial work (LVMW) has been shown to better characterize LV function in patients with severe aortic stenosis by correcting LV afterload. The aim of this study was to evaluate the evolution in LVMW indices after transcatheter aortic valve replacement (TAVR) and their prognostic value.

Methods: The following LVMW indices were calculated before and immediately after TAVR in 255 patients (median age 82 years, 51% male): global work index (GWI), global constructive work (GCW), global wasted work (GWW) and global work efficiency (GWE). The study endpoint was all-cause mortality.

Results: After TAVR, LV ejection fraction and LV global longitudinal strain (GLS) did not change significantly (from 56% to 55%, $p = 0.470$ and from 13.6% to 13.2%, $p = 0.068$). Concerning LVMW indices, while LV GWW remained unchanged after TAVR (from 247 to 258 mmHg%, $p = 0.080$), LV GWI, LV GCW, and LV GWE significantly decreased (from 1882 to 1291 mmHg%, $p < 0.001$, from 2248 to 1671 mmHg%, $p < 0.001$, and from 89% to 85%, $p < 0.001$, respectively). During a median follow-up of 59 [40–72] months, 129 patients died. After correcting for potential confounders (sex, diabetes, renal function, atrial fibrillation, Charlson comorbidity index, and pacemaker implantation post-TAVR), post-TAVR LV GLS, GWI, and GCW remained independently associated with all-cause mortality. However, post-TAVR LV GWI demonstrated the highest increase in model predictivity.

Conclusion: In patients undergoing TAVR, LVMW parameters significantly change after intervention. LV GWI after TAVR showed the strongest association with all-cause mortality among both conventional and advanced parameters of LV systolic function both pre- and post-TAVR and might enable better risk stratification of these patients after intervention.

1 | Introduction

Aortic stenosis (AS) imposes a significant pressure overload on the left ventricle (LV), which typically responds with compensatory hypertrophic remodeling. Over time, this compensatory mechanism could lead to LV dysfunction, resulting in heart failure symptoms and adverse outcomes [1]. Aortic valve replacement is therefore currently indicated in

patients with severe AS in the presence of symptoms or reduced LV ejection fraction (EF) [2]. However, it is well-known that LVEF has significant limitations in timely depicting LV dysfunction, and more sophisticated imaging parameters, such as LV global longitudinal strain (LV GLS) have already been proposed to better risk-stratify patients with severe AS [3, 4]. Importantly, the values of LV GLS might be significantly influenced by AS severity since the increased afterload is not taken into consideration in the measurement. Left ventricular myocardial work (LVMW) is a noninvasive echocardiographic-based technique to evaluate LV systolic function using pressure strain loops correcting for LV afterload. It has been demonstrated that calculations of these indices are reliable in patients with severe AS by adding the mean aortic valve gradient to the aortic systolic pressure to estimate the LV systolic pressure [5, 6]. Moreover, recent data showed that LVMW indices could have a significant additional value to conventional echocardiographic assessment and LV GLS when risk-stratifying patients before transcatheter aortic valve replacement (TAVR) [6–8]. However, data on the changes of these parameters after TAVR are limited [7, 9, 10] and their prognostic value after TAVR has not been explored. Subsequently, the aim of this study was to investigate the evolution and the prognostic significance of LVMW indices after TAVR.

2 | Patients and Methods

2.1 | Patient Population

Patients with severe AS undergoing TAVR between 2015 and 2018 at the Leiden University Medical Center, the Netherlands, were retrospectively identified and included in the present study. Transthoracic echocardiography was performed before and in-hospital after TAVR. Patients were excluded when blood pressure measurement was not available within 24 h of the echocardiographic examination or when image quality was poor.

Demographic and clinical data were collected using the departmental electronic medical records (EPD-vision; Leiden University Medical Center, Leiden, the Netherlands). The primary endpoint was all-cause mortality. The institutional review board of the Leiden University Medical Center approved the observational design and retrospective analysis of clinically acquired data, and waived the need for patient written informed consent. The study was conducted in accordance with the principles of the Helsinki Declaration.

2.2 | Echocardiographic Data Acquisition and Measurements

All patients underwent transthoracic echocardiography before and after TAVR using a Vivid E9 or E95 ultrasound system (GE Vingmed Ultrasound, Horten, Norway). Echocardiographic measurements were performed according to current recommendations [2, 11, 12]. Quantification of AS was performed by using the AS peak jet velocity, aortic valve mean pressure gradient, and aortic valve area (AVA) estimated with the continuity equation [11]. AS was classified as severe, when AVA was <1 cm^2 or when AVA indexed for BSA was <0.6 cm^2/m^2. Aortic valve mean pressure gradient was assessed by averaging the instantaneous gradients over the ejection period. Right ventricular function was assessed by the tricuspid annular plane systolic excursion (TAPSE) [13].

LVMW indices were derived using proprietary software (EchoPAC version 203) integrating LV GLS with LV systolic pressure measurement to construct pressure-strain loops over the cardiac cycle. LV GLS was measured from the apical 4-, 3-, and 2-chamber views, whereafter the timing of the opening and closure of the aortic and mitral valve, and the LV systolic pressure were entered into the software to correct for afterload. As described previously [8], pre-TAVR LV systolic pressure was estimated by the sum of the mean aortic transvalvular gradient and noninvasively measured brachial systolic pressure [5]. Immediately post-TAVR however, with the resolution of the AS, the uncorrected brachial systolic pressure was used without the incorporation of the mean aortic transvalvular gradient as measure of LV systolic pressure (afterload).

After entering these data, four indices of global myocardial work are provided by the software: (1) LV global work index (GWI) that represents the area within the pressure-strain loop from mitral valve closure to opening. (2) LV global constructive work (GCW) that represents the shortening of the myocardium during systole and lengthening during relaxation. (3) LV global wasted work (GWW) which is the lengthening of the myocardium during systole and shortening during relaxation. (4) LV global work efficiency (GWE) that is obtained by dividing LV GCW by the sum of LV GCW and LV GWW.

2.3 | Statistical Analysis

The statistical analyses were performed using SPSS version 29.0 (IBM, Armonk, New York). Categorical data were expressed as numbers and percentages. Continuous variables were presented as mean ± standard deviation or median and interquartile range (IQR), as appropriate. Differences before and after TAVR were analyzed using the paired *t*-test or the Wilcoxon signed-rank test, as appropriate. Differences between selected groups were analyzed using one-way analyses of variance or Kruskal–Wallis test for continuous variables and the chi-square test for categorical variables. To determine the association between demographic, clinical, and echocardiographic parameters and all-cause mortality, univariable and multivariable Cox regression analyses were performed. Survival analyses were performed using Kaplan–Meier curves. Differences between groups were analyzed using the Mantel–Cox log-rank test. To avoid multicollinearity, one parameter of LV systolic function at a time was added to a basal multivariable Cox regression model and the additional prognostic value of these parameters was calculated as χ^2 change using nested models. Two-sided p values <0.05 were considered statistically significant.

3 | Results

3.1 | Patient Population

A total of 255 patients were included in this study (Figure S1). The clinical characteristics are presented in Table 1. The median age

TABLE 1 | Clinical characteristics of the study population before TAVR.

Variable	Overall ($n = 255$)
Age, years	82 (77–85)
Male sex	131 (51)
Hypertension	177 (69)
Dyslipidemia	133 (52)
Diabetes	70 (28)
Current smoker	33 (13)
COPD	44 (17)
Coronary artery disease	141 (55)
Peripheral vascular disease	52 (20)
Hemoglobin, mmol/L	7.8 ± 1.0
eGFR, mL/min/1.73 m2	61 ± 22
NYHA class III/IV	170 (67)
Atrial fibrillation	43 (17)
Charlson comorbidity index	7 (5–8)
LBBB	27 (11)
Pacemaker	33 (13)

Note: Data are expressed as mean ± SD, median (interquartile range), or number (%).

Abbreviations: COPD = chronic obstructive pulmonary disease, eGFR = estimated glomerular filtration rate, LBBB = left bundle branch block, NYHA = New York Heart Association, TAVR = transcatheter aortic valve replacement.

of the study population was 82 years (IQR 77–85), 51% were men, 67% presented with NYHA class III/IV heart failure symptoms and the median Charlson comorbidity index was 7 (IQR 5–8). Table 2 shows the echocardiographic characteristics of the study population. Pre-TAVR, median LVEF, LV GWI, GCW, and GWW were preserved, while median LV GLS and GWE were impaired as referred to previously reported normal values [14].

3.2 | Changes of Echocardiographic Parameters After TAVR and Association With Outcome

As displayed in Table 2, both LVEF and LV GLS remained unchanged immediately after TAVR. As for the LVMW indices, while LV GWI, GCW, and GWE significantly decreased, LV GWW remained stable after TAVR [8, 14, 15].

During a median follow-up of 59 months (IQR 40–72), 129 patients died (51%). Univariable Cox regression analysis identified an association between all-cause mortality and male sex, diabetes, chronic obstructive pulmonary disease (COPD), renal function, atrial fibrillation, Charlson comorbidity index, pacemaker implantation post-TAVR, and the following post-TAVR LV function parameters: LV GLS, LV GWI (per tertile increase), and LV GCW (per tertile increase) (Table 3). To avoid collinearity, three multivariable Cox regression models were built including either post-TAVR LV GLS, LV GWI, or LV GCW together with the other clinical variables (Table 4). While each of these parameters showed an independent association with all-cause mortality, post-TAVR LV GWI demonstrated the highest increase in the predictivity of the model compared to the addition of either post-TAVR LV GLS or LV GCW (Figure 1). Moreover, when corrected for pre-TAVR LV GWI, which has been previously demonstrated to be independently associated with prognosis [8, 15], post-TAVR LV GWI retained an independent association with all-cause mortality (HR 0.771, 95% CI 0.602–0.987, $p = 0.039$).

Given the prognostic relevance of post-TAVR LV GWI, the population was divided into tertiles based on this parameter (first tertile < 1095 mmHg%, second tertile 1095–1468 mmHg%, third tertile > 1468 mmHg%). Kaplan–Meier survival analysis confirmed the worse survival in the group with the lowest LV

TABLE 2 | Echocardiographic characteristics of the study population pre- and post-TAVR.

Variable	Pre-TAVR	Post-TAVR	*p* value
LVEF, %	56 (45–63)	55 (47–62)	0.470
LV GLS, %	−13.6 (−11.0 to −16.1)	−13.2 (−10.7 to −15.4)	0.068
LV GWI, mmHg%	1882 ± 767	1291 ± 438	**<0.001**
LV GCW, mmHg%	2248 ± 809	1671 ± 468	**<0.001**
LV GWW, mmHg%	247 (128–300)	258 (228–339)	0.080
LV GWE, %	89 (84–93)	85 (81–90)	**<0.001**
AV mean pressure gradient, mmHg	43 (33–53)	9 (7–12)	**<0.001**
AV max pressure gradient, mmHg	68 (52–83)	17 (13–22)	**<0.001**
AVA, cm^2	0.7 (0.6–0.8)	1.7 (1.3–2.1)	**<0.001**
TAPSE, mm	20 (17–23)	20 (18–22)	0.145

Note: Data are expressed as mean ± SD, median (interquartile range), or number (%). Bold values denote statistical significance at the p<0.05 level.

Abbreviations: AV = aortic valve, AVA = aortic valve area, LVEF = left ventricular ejection fraction, LV GCW = left ventricular global constructive work, LV GLS = left ventricular global longitudinal strain, LV GWI = left ventricular global work index, LV GWE = left ventricular global work efficiency, LV GWW = left ventricular global wasted work, TAPSE = tricuspid annular plane systolic excursion, TAVR = transcatheter aortic valve replacement.

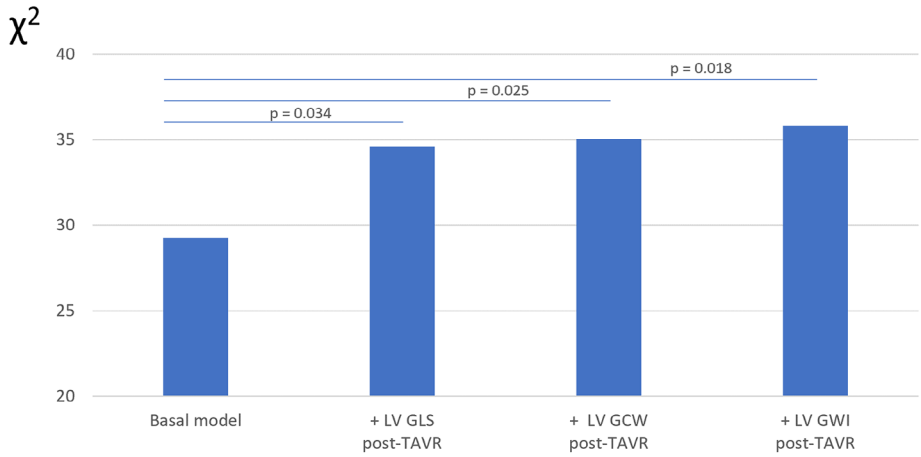

FIGURE 1 | LV GWI post-TAVR demonstrated the highest incremental prognostic value compared to LV GLS and LV GCW post-TAVR when added to the basal model including, male sex, diabetes, renal function, atrial fibrillation, pacemaker implantation post-TAVR, and Charlson comorbidity index. The bars represent the chi-square of the multivariable Cox regression models. LV GLS = left ventricular global longitudinal strain, TAVR = transcatheter aortic valve replacement, LV GCW = left ventricular global constructive work, LV GWI = left ventricular global work index.

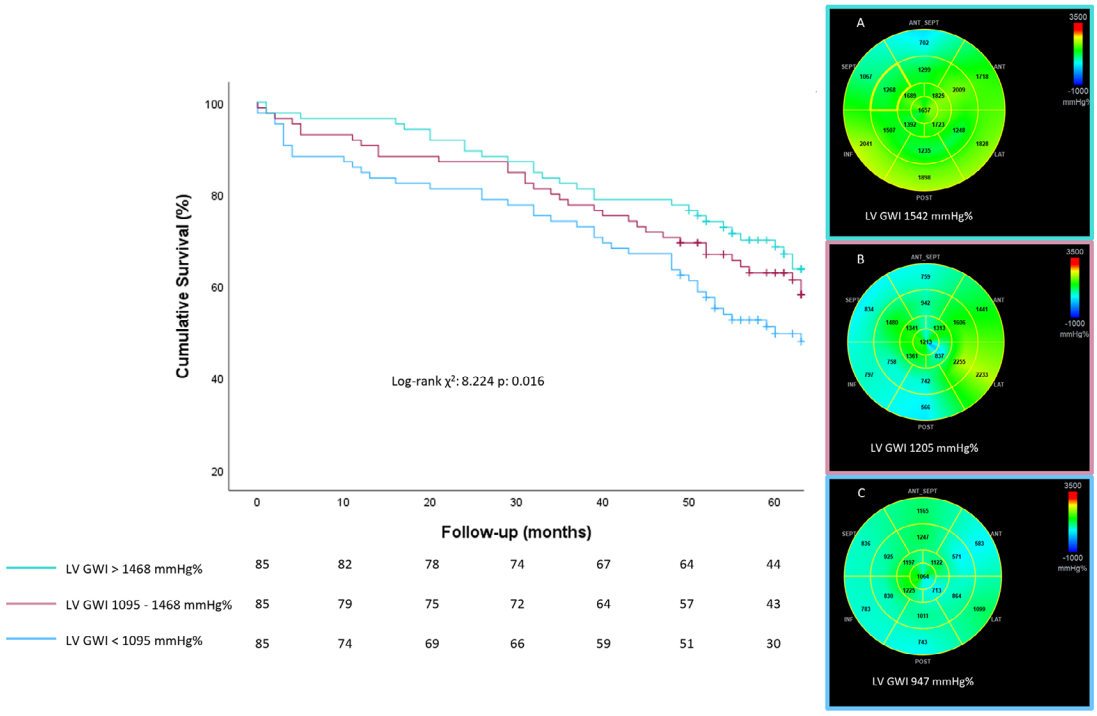

FIGURE 2 | Survival analysis for all-cause mortality according to LV GWI tertiles post-TAVR. Kaplan–Meier curves show that patients with the lowest LV GWI tertile had a significantly lower survival compared to patients with a higher LV GWI. Examples of bull's eyes of LV GWI of the highest (A), middle (B), and lowest (C) tertile. LV GWI = left ventricular global work index, TAVR = transcatheter aortic valve replacement.

GWI compared to the highest tertile (log-rank χ^2: 8.224, $p = 0.016$; Figure 2). A comparison of these groups showed that patients in the lowest LV GWI tertile tended to be more frequently male and had a higher prevalence of atrial fibrillation. Moreover, the lowest tertile demonstrated already worse pre-TAVR LVEF, LV GLS, GWI, GCW, and GWE (Table S1).

In a sub-analysis of patients with preserved LV GLS ($n = 91$) based on the proposed cut-off value in TAVR patients (−14.7% [3]), LV GWI (per tertile increase) maintained its independent association with all-cause mortality (Table S2) and the distinction of LV GWI in tertiles could still further risk stratify these patients (Figure S2).

4 | Discussion

The main findings of the current study can be summarized as follows: after TAVR, (1) LVEF, LV GLS, and LV GWW remained stable, while LV GWI, LV GCW, and LV GWE decreased; (2) LVMW parameters, and specifically LV GWI and LV GCW were indepen-

TABLE 3 | Univariable Cox regression analysis to identify the associates of all-cause mortality.

Variable	HR (95% CI)	*p* value
Age, years	1.013 (0.988–1.038)	0.320
Male sex	1.457 (1.028–2.065)	**0.035**
Hypertension	1.286 (0.872–1.898)	0.204
Dyslipidemia	0.742 (0.525–1.049)	0.092
Diabetes	1.498 (1.030–2.179)	**0.035**
Current smoker	1.097 (0.666–1.807)	0.716
COPD	1.752 (1.163–2.640)	**0.007**
Coronary artery disease	1.167 (0.820–1.660)	0.392
Peripheral vascular disease	1.060 (0.684–1.644)	0.794
Hemoglobin, mmol/L	0.910 (0.771–1.076)	0.270
eGFR, mL/min/1.73 m^2	0.987 (0.980–0.995)	**0.001**
NYHA class III/IV	1.323 (0.902–1.940)	0.152
Atrial fibrillation	1.646 (1.069–2.535)	**0.024**
Charlson comorbidity index	1.198 (1.093–1.313)	**<0.001**
LBBB at baseline	0.627 (03.29–1.196)	0.156
Pacemaker at baseline	1.509 (0.952–2.390)	0.080
New LBBB or pacemaker implantation	1.062 (0.892–1.266)	0.498
New LBBB	0.929 (0.607–1.422)	0.736
Pacemaker implantation post-TAVR	1.822 (1.186–2.798)	**0.006**
Echocardiographic parameters post-TAVR		
LVEF, %	0.993 (0.978–1.008)	0.371
LV GLS, %	1.066 (1.018–1.117)	**0.006**
LV GWI, per tertile increase	0.734 (0.592–0.909)	**0.005**
LV GCW, per tertile increase	0.759 (0.613–0.941)	**0.012**
LV GWW, per tertile increase	1.041 (0.842–1.288)	0.710
LV GWE, per tertile increase	0.871 (0.704–1.077)	0.203
AV mean pressure gradient, mmHg	0.971 (0.930–1.014)	0.188
AV max pressure gradient, mmHg	0.987 (0.963–1.011)	0.291
AVA, cm^2	0.997 (0.972–1.022)	0.809
TAPSE, mm	1.007 (0.952–1.065)	0.810

Note: Bold values denote statistical significance at the p<0.05 level. Abbreviations: AV = aortic valve, AVA = aortic valve area, COPD = chronic obstructive pulmonary disease, eGFR = estimated glomerular filtration rate, LBBB = left bundle branch block, LVEF = left ventricular ejection fraction, LV GCW = left ventricular global constructive work, LV GLS = left ventricular global longitudinal strain, LV GWE = left ventricular global work efficiency, LV GWI = left ventricular global work index, LV GWW = left ventricular global wasted work, NYHA = New York Heart Association, TAPSE = tricuspid annular plane systolic excursion, TAVR = transcatheter aortic valve replacement.

dently associated with all-cause mortality; (3) among the echocardiographic parameters of LV performance, post-TAVR LV GWI showed the highest prognostic value and was also able to stratify the prognosis in patients with preserved LV GLS after TAVR.

Impaired LV function is a crucial criterion to indicate intervention in patients with severe AS, as it portends a poor prognosis [1]. In principle, structural and functional LV myocardial abnormalities in response to AS may become irreversible over time [16], and therefore the earlier they are identified, the better will be the outcome after a timely intervention. Several approaches have been proposed in these patients to assess LV function more sensitively and accurately than using LVEF, such as echocardiographic-derived LV GLS and LVMW indices [3, 16]. The latter were developed to correct LV GLS for the increase in afterload characteristic of AS, and have recently demonstrated additional prognostic value over LVEF and LV GLS [7, 8, 15]. Particularly, these studies showed that reduced values of pre-TAVR LV GWI were associated with increased mortality and adverse clinical events.

However, after TAVR or surgical intervention, when the afterload is suddenly reduced, little is known about the changes in LVMW indices, or if they still retain an association with long-term outcomes. Initial studies including small cohorts reported a trend of reduction of LVMW indices immediately post-TAVR [6, 7, 9, 10]. These findings were confirmed and expanded by the current study describing the evolution of these indices immediately after TAVR, and the observation that LV GWI, LV GCW, and LV GWE significantly decreased after TAVR, while LVEF, LV GLS, and LV GWW remained unchanged. These findings could be explained by the correction of the AS and subsequent drop in afterload after TAVR, resulting in lower energy requirement [7]. However shortly after TAVR, LV hypertrophy and remodeling remain unchanged, and myocardial energetics studies revealed that myocardial efficiency is significantly reduced in the presence of myocardial hypertrophy [17, 18]. The observed decrease in LVMW indices immediately after TAVR suggests the persistent detrimental effect of LV remodeling and hypertrophy on LV performance. However, a recent study by Myon et al. was the first to assess LVMW indices also at long-term follow-up after TAVR and reported that although LV GWE, LV GWI, and LV GCW decrease immediately after TAVR, long-term follow-up values increased, and in average were comparable to pre-TAVR values [19]. The authors therefore concluded that no significant improvement in LV performance was observed after TAVR, suggesting that in some patients, LV myocardial damage could not be reversed and the intervention might have come too late. However, no data on the impact of LVMW indices on the long-term outcome after TAVR was explored.

The current study is the first to assess whether an association remains between LVMW indices measured after TAVR and all-cause mortality in a large cohort of patients with AS. In particular, LV GWI showed a strong association with the outcomes on top of relevant clinical and echocardiographic characteristics and also above pre-TAVR evaluation, suggesting an important prognostic role of LV GWI in these patients. Of interest, in a sub-analysis of patients with preserved LV GLS, LV GWI was still able to stratify patients at higher risk for mortality, which otherwise would have been classified having normal LV function. Therefore, LV GWI could be used both before and after TAVR to

TABLE 4 | Multivariable Cox regression models for all-cause mortality.

	Model 1			Model 2			Model 3		
Variable	**HR**	**95% CI**	***p* value**	**HR**	**95% CI**	***p* value**	**HR**	**95% CI**	***p* value**
Male sex	1.108	0.765–1.603	0.589	1.089	0.751–1.580	0.651	1.118	0.775–1.614	0.550
Diabetes	1.273	0.859–1.886	0.229	1.292	0.875–1.908	0.197	1.289	0.875–1.898	0.199
eGFR	0.997	0.988–1.006	0.452	0.996	0.987–1.005	0.436	0.996	0.987–1.005	0.416
Atrial fibrillation	1.411	0.898–2.217	0.136	1.428	0.915–2.230	0.117	1.447	0.928–2.258	0.103
Charlson comorbidity index	1.147	1.034–1.272	**0.010**	1.151	1.036–1.278	**0.009**	1.150	1.037–1.276	**0.008**
Pacemaker implantation post-TAVR	1.625	1.048–2.520	**0.030**	1.601	1.033–2.483	**0.035**	1.653	1.067–2.59	**0.024**
LV GLS post-TAVR	1.056	1.005–1.111	**0.032**						
LV GWI post-TAVR, per tertile increase				0.764	0.610–0.956	**0.019**			
LV GCW post-TAVR, per tertile increase							0.775	0.620–0.969	**0.026**

Note: Bold values denote statistical significance at the p<0.05 level. Abbreviations: eGFR = estimated glomerular filtration rate, LV GCW = left ventricular global constructive work, LV GLS = left ventricular global longitudinal strain, LV GWI = left ventricular global, work index, TAVR = transcatheter aortic valve replacement.

improve patient management and decision making. Before TAVR, as previously demonstrated [8], impaired LV GWI could be used to identify substantial myocardial damage and possibly optimize patient selection for intervention. After TAVR, the need for closer monitoring could be suggested in patients with impaired LV GWI after intervention, even when LV GLS remains within normal range, in order to assess whether it might improve over time or if not, whether intensification of heart medications might be required.

4.1 | Limitations

This retrospective, single-center study, has limitations inherent to the study design. However, the large and homogenous cohort with long-term follow-up partially overcomes these limitations, and a multivariable adjustment in the analysis of prognosis was applied to limit the possible biases and confounding factors. Nevertheless, prospective, multi-center investigations with longer follow-ups are needed to confirm the findings of this study. In addition, as patients were referred from other hospitals to our center, long-term follow-up data after TAVR was limited. Therefore, information on the evolution of LVMW indices beyond the immediate post-TAVR period was not systematically available, limiting the possibility of exploring their prognostic value when measured at long-term follow-up. Finally, information on potential adjustments in medical therapy during follow-up after TAVR was not available, which might have influenced the outcome of these patients. Therefore, potential confounders that have not been accounted for may have influenced the results.

5 | Conclusions

In severe AS patients, LV GWI, GCW, and GWE decreased immediately post-TAVR, while GWW remained stable. Post-TAVR LV GWI showed the strongest association with all-cause mortality, even in patients with preserved LV GLS, and could be proposed to improve the risk-stratification of these patients after intervention.

Ethics Statement

The institutional review board of the Leiden University Medical Center approved the observational design and retrospective analysis of clinically acquired data and waived the need for patient written informed consent. The study was conducted by the principles of the Helsinki Declaration.

Conflicts of Interest

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Data Availability Statement

The data underlying this article will be shared on reasonable request to the corresponding author.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.