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ORIGINAL PAPER

Prognostic value of left ventricular myocardial work indices in patients with severe aortic stenosis undergoing transcatheter aortic valve replacement

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Aims Left ventricular myocardial work (LVMW) is a novel echocardiographic-based method to assess left ventricular (LV) function using pressure–strain loops taking into account LV afterload. The aim of this study was to evaluate the prognostic value of LVMW indices in patients with severe aortic stenosis (AS) undergoing transcatheter aortic valve replacement (TAVR).

Methods and results LV global work index (LV GWI), LV global constructive work (LV GCW), LV global wasted work (LV GWW), and LV global work efficiency (LV GWE) were calculated in 281 patients with severe AS [age 82, interquartile range (IQR) 78–85 years, 52% male] before the TAVR procedure. LV systolic pressure was derived non-invasively by adding the mean aortic gradient to the brachial systolic pressure to adjust for afterload and calculate LVMW indices. Overall, the average LV GWI was 1872 ± 753 mmHg%, GCW 2240 ± 797 mmHg%, GWW 200 (IQR 127–306) mmHg%, and GWE 89 (IQR 84–93)%. During a median follow-up of 52 (IQR 41–67) months, 64 patients died. While LV GWI was independently associated with all-cause mortality (Hazard ratio per-tertile-increase 0.639; 95%CI 0.463–0.883; $P = 0.007$), LV GCW, GWW, and GWE were not. When added to a basal model, LV GWI yielded a higher increase in predictivity compared to the left ventricular ejection fraction as well as LV global longitudinal strain and LV GCW, and also across the different haemodynamic categories (including low-flow low-gradient) of AS.

Conclusion LV GWI is independently associated with all-cause mortality in patients undergoing TAVR and has a higher prognostic value compared to both conventional and advanced parameters of LV systolic function.

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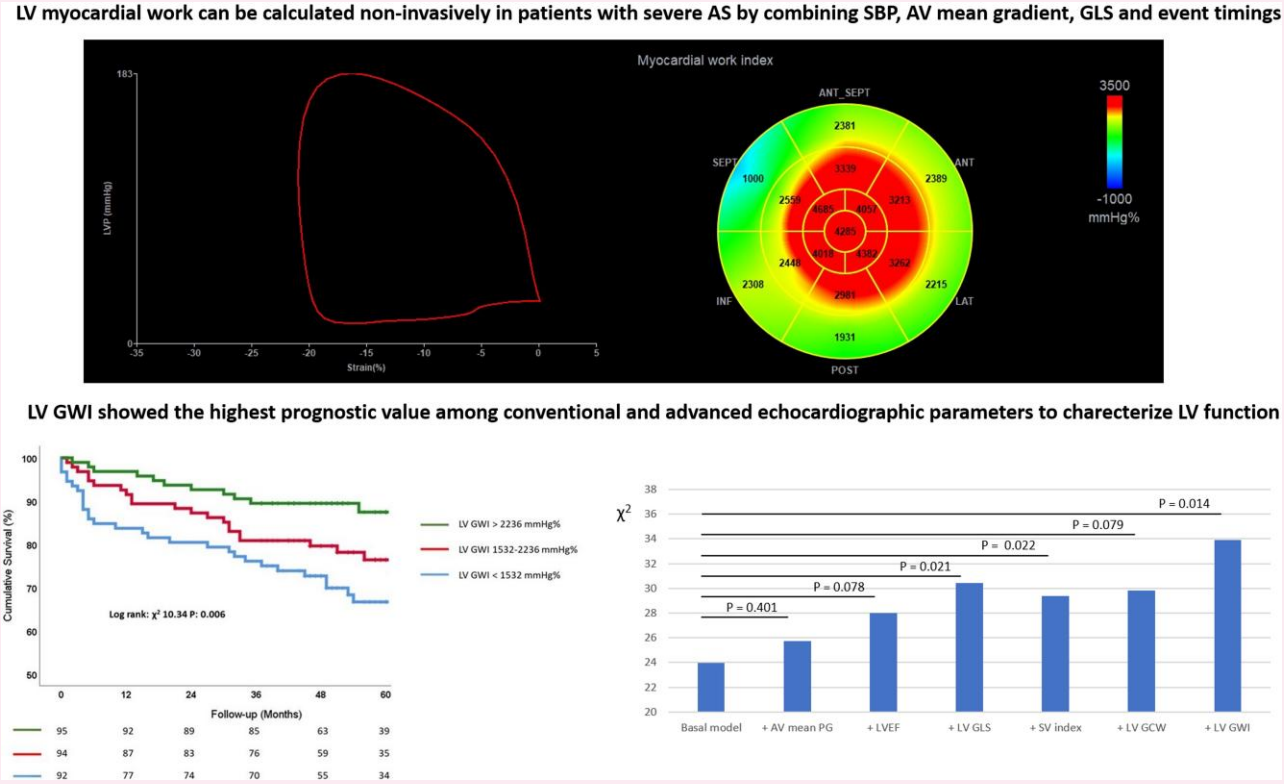
Graphical Abstract



LV myocardial work can be calculated non-invasively in patients with severe AS (upper panel). LV GWI can stratify the prognosis of patients with severe AS undergoing transcatheter aortic valve replacement (lower left panel) and showed the highest prognostic value among conventional and advanced echocardiographic parameters of LV function and AS severity (lower right panel). AS = aortic stenosis, AV = aortic valve, GLS = global longitudinal strain, LV = left ventricle, LVEF = left ventricular ejection fraction, LV GCW = left ventricular constructive work, LV GWI = left ventricular global work index, SBP = systolic blood pressure, PG = peak gradient, SV = stroke volume.

Keywords aortic stenosis • myocardial work indices • mortality

Introduction

Aortic stenosis (AS) is a major healthcare burden, being the most common valvular heart disease worldwide with a growing prevalence by the increasing elderly population.[1,2] The narrowed valve orifice exerts a pressure overload on the left ventricle (LV) which leads to a compensatory hypertrophic response to maintain the stroke volume (SV).[3] Consequently, this pressure overload leads to LV remodelling and dysfunction and eventually to heart failure symptoms and adverse outcomes. Current guidelines recommend aortic valve replacement (AVR) in patients with severe AS and the presence of symptoms or LV systolic dysfunction based on reduced left ventricular ejection fraction (LVEF).[4] However, symptoms and LVEF reduction may appear when the LV damage is already irreversible and could impair the beneficial effect of AVR in these patients. Advanced imaging indices of LV damage, such as impaired LV global longitudinal strain (GLS) and presence of LV late gadolinium enhancement evaluated by cardiac magnetic resonance (CMR), have been shown to improve risk stratification in patients with severe AS.[5–7] Still GLS, as well as LVEF, do not take into account the afterload nor they reflect LV myocardial work or oxygen demand.

Left ventricular myocardial work (LVMW) is an emerging non-invasive echocardiographic-based method to assess LV systolic function correcting for LV afterload. Recently, it has been shown that LVMW indices can be reliably calculated also in patients with severe AS taking into account the pressure drop across the aortic valve (AV) which can be estimated with echocardiography.[8] However, data on the prognostic value of the LVMW indices are lacking. Therefore, the aim of this study was to evaluate the prognostic value of LVMW indices in patients with severe AS undergoing transcatheter aortic valve replacement (TAVR).

Methods

Patient population

We retrospectively included patients with severe AS who underwent TAVR between 2015 and 2018 at the Leiden University Medical Center. All patients underwent a transthoracic echocardiogram before TAVR as part of their routine clinical care, which was used for this analysis. Patients were excluded if no blood pressure was measured within 48 h of the echocardiographic exams or in case of inadequate image quality.

The departmental electronic medical record (EPD-vision; Leiden University Medical Center, Leiden, the Netherlands) was used to collect demographic and clinical data. The primary endpoint of this study was all-cause mortality.

Echocardiographic data acquisition and measurements

Echocardiograms were performed using Vivid E9 or E95 ultrasound system (GE Vingmed Ultrasound, Horten, Norway) with patients at rest in the left lateral decubitus position. All echocardiographic measurements were performed according to current recommendations.[4,9,10] The severity of AS was defined by using AS peak jet velocity by continuous-wave Doppler, mean transvalvular pressure gradient (AV mean PG), and aortic valve area (AVA) by the continuity equation.[10] The AVA index was calculated by dividing the AVA by the body surface area. Severe AS was identified by an AVA < 1 cm^2 or an AVA index of <0.6 cm^2/m^2. To classify the haemodynamic categories, stroke volume (SV) index and AV mean PG across the AV were calculated.[4] The velocity-time integral was measured on the pulsed-wave Doppler recordings of the LV outflow tract acquired from the LV apical three- or five-chamber view with the sample volume located below the AV and was used to calculate the SV and SV index.[10] AV mean PG was derived by averaging the instantaneous gradients over the ejection period using the traced velocity curves.[11] Using these parameters, the haemodynamic categories were classified as follows: high-gradient AS was defined by a mean gradient ≥40 mmHg; low-flow, low-gradient AS by a mean gradient <40 mmHg and SV index ≤ 35 mL/m^2; and normal-flow-low-gradient AS by a mean gradient <40 mmHg and SV index > 35 mL/m^2. Pulmonary artery systolic pressure (PASP) was derived as a sum of the tricuspid regurgitation jet peak velocity and the estimated mean right atrial pressure based on the diameter and collapsibility of the inferior vena cava. The tricuspid annular plane systolic excursion (TAPSE) was used to characterize the right ventricular function.[12] Mitral regurgitation and tricuspid regurgitation were defined as significant when graded as moderate or severe according to current recommendations.

Myocardial work indices were derived using a proprietary software (EchoPAC version 203) that integrates LV GLS with blood pressure recordings to construct pressure–strain loops over cardiac cycles (graphical abstract, upper panel).[13] LV GLS was measured from the apical four-, two-, and three- or five-chamber views by tracing the endocardial border at an end-systolic frame, whereafter the software automatically defined a region of interest. When needed it was manually corrected to include the entire myocardial thickness. After the GLS measurement, the timing of the opening and closure of the aortic and mitral valve, and LV systolic blood pressure were entered into the software; LV systolic pressure was estimated by the sum of the mean aortic transvalvular gradient and the non-invasively measured systolic pressure to correct for the afterload as previously described and validated.[8]

Subsequently, four indices of global myocardial work were provided by the software. The left ventricular global work index (LV GWI) was calculated as the area within the pressure–strain loop from mitral valve closure to opening. Left ventricular global constructive work (LV GCW) was defined as the shortening during systole and lengthening during relaxation. Left ventricular global wasted work (LV GWW) was determined as the lengthening during systole and shortening during relaxation. Left ventricular global work efficiency (LV GWE) was calculated by dividing LV GCW by the sum of LV GCW and LV GWW.

Statistical analysis

The statistical analyses were performed using SPSS version 25.0 (IBM, Armonk, New York) and R version 4.0.3 (R Foundation for Statistical Computing, Vienna, Austria). Continuous variables were presented as mean ± standard deviation or median and interquartile range (IQR), as appropriate. Categorical data were expressed as numbers and percentages. Differences between groups were analysed using a one-way analysis of variance or the Kruskal–Wallis test for continuous variables and χ^2 test for categorical variables. Univariable and multivariable Cox regression models were used to determine the association between demographic, clinical and echocardiographic parameters, and all-cause mortality. A spline curve analysis was performed to further characterize the association between LV myocardial work indices and mortality. Hazard ratio (HR) and 95% confidence intervals (CIs) were calculated. Survival analyses were performed using Kaplan–Meier curves and differences between groups were analysed using the Mantel–Cox log-rank test. The additional prognostic value of LV systolic function parameters (including LV myocardial work parameters), when added to a Cox regression basal model, was evaluated with the calculation of χ^2 change. Two-sided *P*-values of <0.05 were considered statistically significant.

Results

Patient characteristics

A total of 281 patients were included in the present study (see Supplementary data online, *Figure S1*) and their clinical and echocardiographic characteristics are provided in Supplementary data online, *Table S1* and *S2*. Overall, the median age was 82 years (IQR, 78–85 years), 52% were men, and 67% presented with New York Heart Association (NYHA) III-IV heart failure symptoms. The mean LV GWI was 1872 ± 753 mmHg%, mean LV GCW was 2240 ± 797 mmHg%, while median LV GWW was 200 mmHg% (IQR, 127–306mmHg%), and median LV GWE 89% (IQR, 84–93%).

Association between left ventricular myocardial work indices and all-cause mortality

During a median follow-up of 52 months (IQR, 41–67 months) 64 patients (23%) died. The univariable Cox regression analysis showed an association between all-cause mortality and the following parameters: male sex, diabetes mellitus, haemoglobin, renal function, Charlson comorbidity index, LVEF, LV GLS, LV GWI, and LV GCW (*Table 1*), but neither with LV GWW nor LV GWE. The Spline curve analysis further confirmed the association between LV GWI and all-cause mortality. To avoid overfitting and collinearity issues, several multivariable Cox regression models including one variable of LV systolic function, the AV mean PG, or the SV index at a time were built. While LVEF, LV GCW, and AV mean PG did not show an independent association with all-cause mortality, LV GLS, LV GWI, and SV index were independently associated with death (*Table 2*). Moreover, when added to a basal model including sex, diabetes mellitus, haemoglobin, and renal function, LV GWI yielded a higher increase in predictivity compared to LVEF, but also to the more advanced parameters of LV systolic function (i.e. LV GLS and LV GCW) and the AS classifying parameters (i.e. AV mean PG and SV index) (*Figure 1*). Of note, when also correcting for AS haemodynamic categories or for Charlson comorbidity index, LV GWI retained an independent association with the outcome (see Supplementary data online, *Table S3* and *S4*), confirming its prognostic value also in this clinical setting.

Given the highest prognostic relevance of LV GWI (*Figure 1*), the population was divided according to LV GWI tertiles (first tertile <1532 mmHg%, second tertile 1532–2236 mmHg%, third tertile >2236 mmHg%) and the characteristics were compared across these groups. The Kaplan–Meier curves confirmed the significantly lower survival rates in patients with the lowest LV GWI compared with patients with the highest LV GWI (log-rank χ^2: 10.249, *P* 0.001; *Figure 2*). When looking at the clinical characteristics, patients in the lowest LV GWI tertile were more likely to be male, had a worse renal function and a higher prevalence of atrial fibrillation as compared to the other groups (*Table 3*). Concerning the echocardiographic variables, patients presenting with lower LV GWI values had larger LV dimensions, worse LV indexes of systolic function, a higher prevalence of low-flow low-gradient AS, a higher prevalence of significant TR, and worse right ventricular systolic function (*Table 4*).

Table 1 Univariable Cox regression analysis to identify the associates of all-cause mortality

Variable	HR	95% CI	*P*-value
Age, years	0.983	0.951–1.015	0.282
Sex, male	1.685	1.015–2.798	**0.043**
Hypertension	1.361	0.781–2.370	0.277
Dyslipidemia	0.720	0.439–1.180	0.192
Diabetes mellitus	2.304	1.402–3.786	**0.001**
Current smoker	1.637	0.873–3.069	0.124
Coronary artery disease	0.965	0.590–1.579	0.888
Peripheral vascular disease	1.135	0.636–2.025	0.669
Haemoglobin, mmol/L	0.777	0.616–0.980	**0.033**
Creatinine, mmol/L	1.003	1.001–1.005	**0.001**
eGFR, mL/min/1.73 m^2	0.978	0.967–0.990	**<0.001**
NYHA class III or IV	1.064	0.627–1.806	0.818
Atrial fibrillation	1.720	0.977–3.030	0.060
Charlson comorbidity index	1.288	1.146–1.448	**<0.001**
LVEDD, mm	1.024	0.996–1.053	0.098
LVEF, %	0.980	0.962–0.997	**0.023**
LV GLS, %	1.089	1.025–1.158	**0.006**
LV GWI, per tertile increase	0.603	0.440–0.827	**0.002**
LV GCW, per tertile increase	0.708	0.521–0.961	**0.027**
LV GWW, per tertile increase	0.832	0.615–1.126	0.233
LV GWE, %	0.983	0.955–1.012	0.244
Haemodynamic classification AS			
High gradient vs. low-flow low-gradient	0.891	0.441–1.799	0.747
High gradient vs. normal-flow low-gradient	1.279	0.594–2.750	0.529
AV mean PG, mmHg	0.987	0.970–1.004	0.134
Vmax, m/s	0.661	0.451–0.969	**0.034**
SV index, mL/m^2	0.974	0.950–0.998	**0.031**
Significant MR	0.981	0.484–1.998	0.958
Significant TR	1.782	0.949–3.348	0.072
TAPSE, mm	0.958	0.909–1.010	0.111
PASP, mmHg	1.002	0.980–1.025	0.861

Bold values denote statistical significance at the $p < 0.05$ level. eGFR = estimated glomerular filtration rate, NYHA = New York Heart Association, LVEDD = left ventricular end-diastolic diameter, LVEF = left ventricular ejection fraction, LV GLS = left ventricular global longitudinal strain, LV GWI = left ventricular global work index, LV GCW = left ventricular global constructive work, LV GWW = left ventricular wasted work, LV GWE = left ventricular global work efficiency, AS = aortic stenosis, AV = aortic valve, PG = pressure gradient, Vmax = peak aortic valve velocity, SV = stroke volume, MR = mitral regurgitation, TR = tricuspid regurgitation, TAPSE = tricuspid annular plane systolic excursion, PASP = pulmonary artery systolic pressure.

Discussion

The main findings of this study can be summarized as follows: (1) in patients with severe AS undergoing TAVR, LV GWI was independently associated with all-cause death; (2) LV GWI showed higher prognostic value compared with LVEF and LV GLS, which was maintained also across different haemodynamic categories of AS. (3) Patients in the lower tertile of LV GWI were also characterized by a worse clinical risk profile and had higher prevalence of low-flow low gradient AS.

According to the current guidelines, indications for AVR in severe AS are the presence of symptoms or LV systolic dysfunction (LVEF <50%) without another cause.[4] Nevertheless, symptoms and reduced LVEF may reflect the presence of irreversible LV damage which could limit the beneficial effect of AVR. Accordingly, identifying early markers of myocardial damage is of clinical importance, and parameters such as impaired LV GLS and LV late gadolinium enhancement or increased extracellular volume fraction on CMR, had shown better predictivity for adverse events compared to LVEF and the presence of symptoms in these patients.[5–7] However, these early markers of myocardial damage have limitations. A limitation of LV GLS is that it does not take into account the LV afterload which can have an important impact on LV systolic function, especially in patients with severe AS. CMR has limitations that it is not widely available, requires specific expertise, is time consuming, is challenging in patients with claustrophobia, and requires administration of contrast, which has implications for patients with impaired renal function.

LVMW overcomes these limitations by taking afterload into account, and further considering in the calculations the timings of the cardiac cycle (based on valve opening and closure) and potential dyssynchrony in the contraction. Importantly, LVMW indices are very feasible and repeatable in daily clinical practice: the echocardiographic views performed during standard examinations in fact can be easily combined by the software with the estimation of LV afterload derived from brachial systolic blood pressure and the AV mean PG to measure the LVMW indices without additional recordings.

In this study, LV GWI evaluated before TAVR in patients with severe AS was independently associated with all-cause death. In particular, lower values of LV GWI were associated with higher mortality rates during the follow-up. LV GWI may express the LV adaptation to the increased afterload in patients with severe AS and lower LV GWI values can represent an early marker of adverse LV remodelling and damage. The association between LV GWI and mortality rate could be explained also by the assumption that the LV GWI reflects the global myocardial metabolism and global cardiac function. Russel *et al.* described that the LV pressure–strain area reflects myocardial metabolism showing a strong correlation with the myocardial glucose metabolism measured by positron emission tomography.[13] This suggests that a lower LV GWI reflects lower global myocardial metabolism, and maladaptive LV remodelling to the increased afterload and global cardiac function, resulting in potentially irreversible damage and higher mortality rates even after AVR.

Previous studies have also investigated the role of LVMW indices as compared to other parameters of LV systolic function in patients with different grades of AS. In a small population of patients with severe AS, Jain et al showed that while GLS improves, LVMW indices reduce post-TAVR and both LV GLS and LV GWI remain below normal values after TAVR suggesting the presence of irreversible LV remodelling which seems not to recover after TAVR.[14] Similarly, De Rosa *et al.* showed that while LV GWI and GCW significantly decreased after TAVR, LVEF, and LV GLS did not change. This may suggest that LVMW indices can better characterize LV systolic function in patients with severe AS, whose LV is therefore subjected to a significantly increased afterload, and could play a role in identifying patients with severe AS who may get a greater benefit from AVR.[15] However, the association between LVMW indices and outcomes such as mortality was not investigated. An initial study by Ilardi *et al.* showed an independent association between LV GWI, but also LV GCW, with all-cause mortality but in a mixed population of moderate and severe AS with preserved LV systolic function.[16]

The findings of the current study further demonstrate the incremental value of correcting GLS measure for afterload in the evaluation of LV systolic function in a large population of patients with severe AS undergoing TAVR. In particular, the added prognostic value of LV GWI over

Table 2 Multivariable Cox regression models for all-cause mortality

Variable	Multivariable model 1			Multivariable model 2			Multivariable model 3			Multivariable model 4		
	HR	95% CI	*P*-value	HR	95% CI	*P*-value	HR	95% CI	*P*-value	HR	95% CI	*P*-value
Male sex	1.643	0.969–2.785	1.643	1.539	0.900–2.632	0.115	1.492	0.872–2.553	0.144	1.786	1.046–3.048	0.033
Diabetes mellitus	1.706	1.011–2.877	1.706	1.825	1.085–3.072	0.023	1.835	1.092–3.083	0.022	1.711	1.016–2.884	0.043
Haemoglobin, mmol/L	0.780	0.610–0.997	0.780	0.786	0.616–1.003	0.053	0.768	0.606–0.973	0.028	0.771	0.606–0.982	0.035
eGFR, mL/min/1.73 m^2	0.985	0.973–0.997	0.985	0.985	0.974–0.997	0.018	0.986	0.974–0.998	0.021	0.985	0.973–0.997	0.018
AV mean PG. mmHg	0.992	0.974–1.011	0.405									
LVEF, %				0.983	0.964–1.002	0.074						
LV GLS, %							1.080	1.012–1.152	0.020			
SV index, mL/m^2										0.973	0.949–0.997	0.027

Variable	Multivariable model 5			Multivariable model 6		
	HR	95% CI	*P*-value	HR	95% CI	*P*-value
Male sex	1.472	0.857–2.526	0.161	1.380	0.802–2.374	0.244
Diabetes mellitus	1.817	1.081–3.056	0.024	1.753	1.042–2.951	0.034
Haemoglobin, mmol/L	0.771	0.606–0.980	0.034	0.758	0.596–0.963	0.023
eGFR, mL/min/1.73 m^2	0.985	0.973–0.997	0.014	0.986	0.974–0.998	0.019
LV GCW, per tertile increase	0.734	0.536–1.006	0.054			
LV GWI, per tertile increase				0.639	0.463–0.883	0.007

eGFR = estimated glomerular filtration rate, LVEF = left ventricular ejection fraction, LV GLS = left ventricular global longitudinal strain, LV GWI = left ventricular global work index, LV GCW = left ventricular global constructive work, AV = aortic valve, PG = pressure gradient, SV = stroke volume.

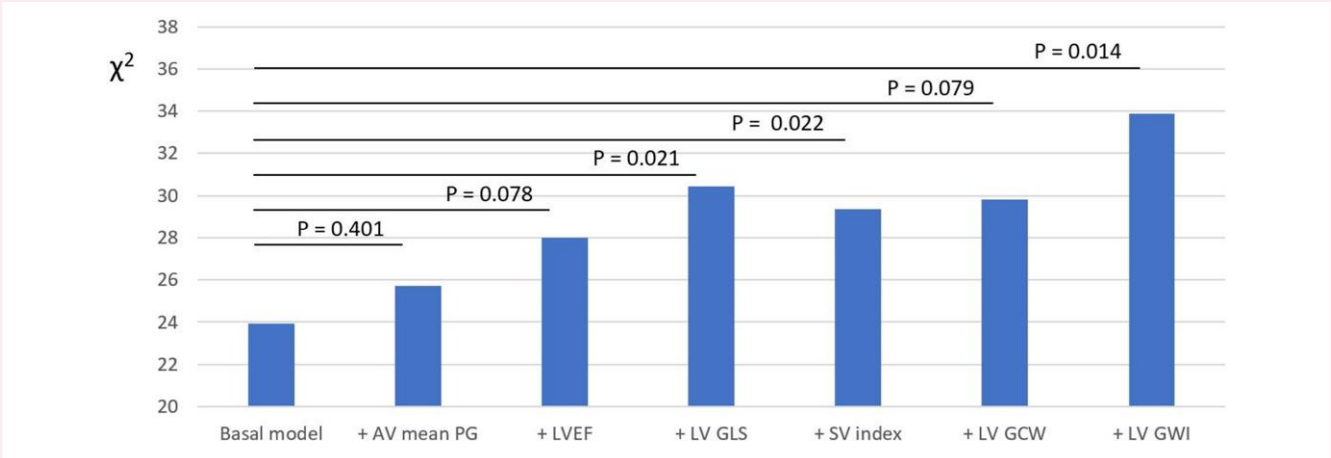


Figure 1 Incremental prognostic value of LV GWI over both conventional and advanced parameters of LV systolic function. The bar charts represent the predictivity (χ^2) of several multivariable Cox regression models. The basal model included sex, diabetes, haemoglobin, and renal function. In this model, one variable of LV systolic function at a time was included. LV GCW and LV GWI were analysed in tertiles. The addition of LV GWI to the basal model yielded a higher increase in predictivity compared to the models including AV mean PG, LVEF, LV GLS, SV index, or LV GCW. AV, aortic valve; PG, pressure gradient; LVEF, left ventricular ejection fraction; LV GLS, left ventricular global longitudinal strain; SV, stroke volume; LV GCW, left ventricular global constructive work; LV GWI, left ventricular global work index.

LVEF and other important parameters of LV function, such as LV GLS and SV index, suggests a potential role of this parameter in these patients to improve risk stratification and timing for AVR before LV damage has taken place, and in order to achieve optimal beneficial effects of AVR. Of interest, the prognostic value of LV GWI was maintained across the different haemodynamic categories of AS, including low-flow low-gradient AS in which other echocardiographic parameters of LV function or impedance are less accurate.

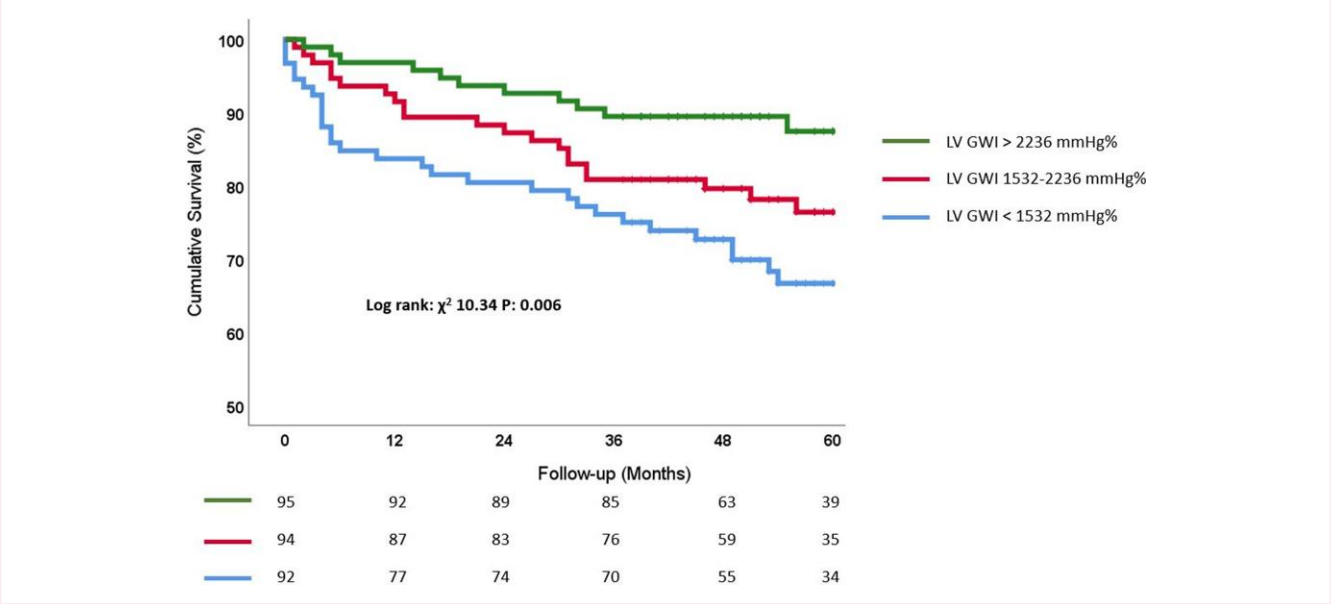


Figure 2 Kaplan–Meier curves estimated for cumulative event rates of all-cause mortality according to LV GWI tertiles. The Kaplan–Meier curves show that patients with the lowest GWI (bottom line) had significantly worse survival during the follow-up compared to patients with higher LV GWI (top line). LV GWI, left ventricular global work index.

Table 3 Clinical characteristics of the study population according to LV GWI tertiles

Variable	LV GWI < 1532 mmHg% (*n* = 92)	LV GWI 1532– 2236 mmHg% (*n* = 94)	LV GWI > 2236 mmHg% (*n* = 95)	*P*-value
Age, years	82 (76–86)	82 (78–85)	82 (77–85)	0.659
Male sex	58 (63)	53 (56)	35 (37)	**0.001**
Hypertension	55 (60)	69 (73)	70 (74)	**0.041**
Dyslipidemia	48 (52)	47 (50)	51 (54)	0.878
Diabetes mellitus	30 (33)	19 (20)	27 (28)	0.531
Current Smoker	11 (12)	16 (17)	11 (12)	0.476
COPD	19 (21)	12 (13)	19 (20)	0.293
Coronary artery disease	53 (58)	56 (60)	46 (48)	0.258
Peripheral vascular disease	21 (23)	21 (22)	20 (21)	0.955
Haemoglobin, mmol/L	7.9 ± 1.0	7.9 ± 0.9	7.6 ± 1.0	**0.047**
eGFR, mL/min/1.73 m^2	53 (41–70)	64 (49–77)	62 (49–73)	**0.038**
NYHA class III/IV	61 (66)	67 (71)	61 (64)	0.569
Atrial fibrillation	24 (26)	18 (19)	8 (8)	**0.006**
LBBB	9 (10)	13 (14)	6 (6)	0.226
RBBB	6 (7)	8 (9)	4 (4)	0.482

Data are expressed as mean ± SD, median (interquartile range), or number (%). Bold values denote statistical significance at the $p < 0.05$ level.
COPD = chronic obstructive pulmonary disease, eGFR = estimated glomerular filtration rate, NYHA = New York Heart Association, LBBB = left bundle branch block, RBBB = right bundle branch block, LV GWI = left ventricular global work index.

Limitations

This is a retrospective, single-centre study which has limitations inherent to the study design. The specific cause of death was not systematically available and therefore not considered as endpoint. Although we corrected for possible confounders, the analysis was predisposed to bias from other unmeasured confounders. Nevertheless, these limitations are partially overcome by the fact that a large and homogenous cohort with a long-term follow-up was included and hard endpoints were considered for the prognostic analyses. Another limitation could be considered the inclusion criteria of the blood pressure being

Table 4 Echocardiographic characteristics of the study population according to LV GWI tertiles

Variable	LV GWI < 1532 mmHg% (*n* = 92)	LV GWI 1532– 2236 mmHg% (*n* = 94)	LV GWI > 2236 mmHg% (*n* = 95)	*P*-value
LVEDD, mm	52 (44–58)	47 (42–53)	46 (40–50)	**<0.001**
LVEF, %	41 (32–57)	55 (47–61)	60 (55–66)	**<0.001**
LVMi, g/m^2	132 (106–159)	117 (92–140)	111 (91–133)	**<0.000**
LV GLS, %	−9.0 (−11.3 – −7.1)	−13.6 (−15.5 – −12.1)	−16.3 (−18.2 – −14.5)	**<0.001**
LV GWI, mmHg%	1027 ± 359	1866 ± 214	2698 ± 363	**<0.001**
LV GCW, mmHg%	1394 ± 479	2225 ± 331	3072 ± 400	**<0.001**
LV GWW, mmHg%	220 (135–345)	196 (128–309)	195 (119–282)	0.354
LV GWE, %	83 (76–89)	90 (86–93)	92 (89–94)	**<0.001**
AVA, cm^2	0.7 (0.5–0.8)	0.7 (0.6–0.9)	0.8 (0.6–0.9)	**0.011**
Haemodynamic classification AS				**0.004**
High gradient	43 (47)	60 (64)	65 (68)	
Low-flow, low-gradient	34 (37)	21 (22)	13 (14)	
Normal-flow, low-gradient	15 (16)	13 (14)	17 (18)	
Significant MR	18 (19)	10 (11)	12 (13)	0.196
Significant TR	21 (23)	10 (11)	7 (7)	**0.004**
TAPSE, mm	17 ± 4	21 ± 5	22 ± 4	**<0.001**
PASP, mmHg%	33 (28–41)	32 (27–41)	32 (27–41)	0.991

Data are expressed as mean ± SD, median (interquartile range), or number (%). Bold values denote statistical significance at the $p < 0.05$ level.
LVEDD = left ventricular end-diastolic diameter, LVEF = left ventricular ejection fraction, LVMi = left ventricular mass index, LV GLS = left ventricular global longitudinal strain, LV GWI = left ventricular global work index, LV GCW = left ventricular global constructive work, LV GWW = left ventricular global wasted work, LV GWE = left ventricular global work efficiency, AVA = aortic valve area, AS = aortic stenosis, MR = mitral regurgitation, TR = tricuspid regurgitation, TAPSE = tricuspid annular plane systolic excursion, PASP = pulmonary artery systolic pressure, LV GWI = left ventricular global work index.

measured up to 48 h of the echocardiographic exams. However, in the majority of patients (97.5%), the time between blood pressure measurement and echocardiography was within 3 h. Moreover, given that the patients were under optical medical therapy, the blood pressure is expected to be stable during the day. Still, present findings should be confirmed in further prospective and multi-centre investigations.

Conclusions

In severe AS patients undergoing TAVR, LV GWI is independently associated with all-cause mortality and has the highest prognostic value compared to both conventional and advanced parameters of LV systolic function, and AS classifying parameters. LVMW may, therefore, represent a promising method to evaluate myocardial function in patients with severe AS and could be considered for risk stratification and to optimize the referral timing for TAVR.

Supplementary data

Supplementary data is available at *European Heart Journal - Cardiovascular Imaging* online.

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Data availability

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

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