Evolution of non-invasive myocardial work variables after transcatheter aortic valve implantation in patients with severe aortic stenosis

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Abbreviated title: Transcatheter aortic valve implantation and myocardial function

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HIGHLIGHTS

- Study of the effects of TAVI on myocardial function using myocardial work variables
- Myocardial work indices can predict symptoms and postoperative LV systolic function
- A prognostic study will have to confirm these promising results

ABSTRACT

Introduction: Guidelines recommend aortic valve replacement in patients with severe aortic stenosis who present with symptoms or left ventricular ejection fraction < 50%, both conditions representing a late stage of the disease. Whereas global longitudinal strain is load dependent, but interesting for assessing prognosis, myocardial work has emerged.

Aim: To evaluate acute changes in myocardial work occurring in patients undergoing transcatheter aortic valve implantation (TAVI).

Methods: Patients who underwent TAVI were evaluated before and after by echocardiography. Complete echocardiographies were considered. Myocardial work indices (global work index, global constructive work, global work efficiency, global wasted work) were calculated integrating mean transaortic pressure gradient and brachial cuff systolic pressure.

Results: One hundred and twenty-five patients underwent successful TAVI, with a significant decrease in mean transaortic gradient (from 52.5 ± 16.1 to 12.2 ± 5.0; $P < 0.0001$). There was no significant change in left ventricular ejection fraction after TAVI. Myocardial work data after TAVI showed a significant reduction in global work index (1389 ± 537 vs 2014 ± 714; $P < 0.0001$), global constructive work (1693 ± 543 vs 2379 ± 761; $P < 0.0001$) and global work efficiency (85.0 ± 7.06 vs 87.1 ± 5.98; $P = 0.0034$). The decrease in global work index and global constructive work after TAVI was homogeneous among different subgroups, based on global longitudinal strain, left ventricular ejection fraction and New York Heart Association status before TAVI. We observed a significant association between global work index and global constructive work before TAVI, and global longitudinal strain degradation after TAVI.

Conclusions: Myocardial work variables show promising potential in best understanding the left ventricular myocardial consequences of aortic stenosis and its correction. Given their ability to discriminate between New York Heart Association status and global longitudinal strain evolution, we can hypothesize about their clinical value.

Keywords:

Aortic stenosis

Transcatheter aortic valve implantation

Myocardial work

Speckle tracking analysis

Abbreviations

AS	Aortic stenosis
GCW	Global constructive work
GLS	Global longitudinal strain
GWE	Global work efficiency
GWI	Global work index
GWW	Global wasted work
LV	Left ventricular
LVEF	Left ventricular ejection fraction
NT-proBNP	N-terminal prohormone of B-type natriuretic peptide
NYHA	New York Heart Association
TAVI	Transcatheter aortic valve implantation

1. Introduction

Aortic stenosis (AS) is the most common valvular heart disease [1], and is characterized by progressive fibrosis and calcification of the aortic valve, resulting in leaflet restriction and obstruction. The consequent increase in left ventricular (LV) afterload is initially compensated by hypertrophy of the left ventricle, in order to normalize wall tension and therefore maintain stroke volume [2]. Over time, the chronic pressure overload and compensatory LV remodelling lead to progressive LV dysfunction [3].

Current guidelines recommend surgical or transcatheter aortic valve replacement in patients with severe AS who present with symptoms or in asymptomatic patients with reduced (< 50%) LV ejection fraction (LVEF) [4]. Both the presence of symptoms and impaired LV function related to severe AS represent a late stage of the disease [5], and permanent damage may have already occurred [6]. LVEF is well validated and utilized to evaluate global LV systolic function. However, it has a number of limitations, including the assessment of subclinical dysfunction. Early impairment in one of the three myocardial wall layers can be compensated by the others, so the LVEF remains preserved [7].

Global longitudinal strain (GLS) has been shown to have better prognostic value for predicting cardiovascular outcomes than LVEF [8]. GLS has emerged as a subclinical marker of LV dysfunction in AS, while LVEF remains within normal limits [9]. However, neither of these variables takes into account the cardiac afterload [10], which can compromise the accuracy of the severity assessment [11].

Relationship between ventricular pressure and volume allows the evaluation of LV function and the effect of afterload. This relationship can be visualized as a close left ventricle pressure-volume loop throughout the entire cardiac cycle, allowing a comprehensive overview of the stroke work. Such a tool was initially obtained using invasive conductance transducers [12], making it impractical in daily clinical practice. In 2012, Russell et al. showed excellent correlation of a non-invasive approach, and further established an association with regional oxygen consumption and myocardial metabolism using fluorodeoxyglucose positron emission tomography (FDG-PET), then proposing the basic concepts of non-invasive myocardial work [13]. Excellent intraobserver and interobserver repeatabilities in myocardial work indices have been confirmed [14, 15]. Although initially not evaluated in a population presenting with AS, feasibility has been demonstrated in this population, and

uses the addition of the mean transaortic gradient to non-invasive systolic blood pressure [16, 17]. Our team has also proposed a computational model that has shown promising results for the assessment of LV function and myocardial work indices in patients with AS [18, 19]. The acute impact of transcatheter aortic valve implantation (TAVI) on variables of LV function might help, in a second step, our understanding of cardiac remodelling and its reversibility.

Thus, we sought to evaluate changes in myocardial work occurring in patients presenting with severe AS and undergoing transcatheter aortic valve implantation (TAVI), to compare them with more standard variables evaluating LV systolic function, such as LVEF and GLS.

2. Methods

2.1. Study population

In this single-centre study, patients with severe AS scheduled for TAVI at CHU Rennes (France), from January 2020 to September 2021, were screened retrospectively.

Patients were evaluated by our Heart Team before being accepted as appropriate candidates for TAVI, according to current guidelines. Severe AS was defined by a high gradient (V_{max} > 4 m/s and mean gradient > 40 mmHg) or by AS with a low gradient, but an area < 1 cm^2 or < 0.6 cm^2/m^2 associated with low flow (stroke volume < 35 mL/m^2). Patients were deemed eligible for TAVI if they presented with severe AS associated with or without symptoms, but had left ventricular dysfunction (LVEF < 50%) without another cause. During this time period, 749 patients underwent TAVI in our centre: 417 procedures were performed on patients who came from other institutions, and it was not possible to get all the images for these patients; of the remaining 332 patients who were fully explored in our centre, 207 were included in competing protocols or were not imaged with the views needed to measure myocardial work variables (165 patients did not have complete pre- and postoperative echocardiography).

Echocardiographic images before and after TAVI had to be available and of sufficiently good quality to perform speckle tracking echocardiography. Patients were excluded if they had poor image quality that meant that speckle tracking could not be performed, if all three apical chamber views were not obtained or if blood pressure was not measured.

3.2. Study timeline

Clinical examination and history, electrocardiography and laboratory tests were collected at baseline during the final evaluation before the Heart Team decision. Transthoracic echocardiography was performed before and in the week after TAVI. Non-invasive blood pressure was recorded on the same day as the echocardiographic evaluation, with patients lying in a calm and comfortable position for at least 15 minutes. Ideally, blood pressure was measured at the end of the echocardiographic examination. If the patient was too stressed by the results, blood pressure was measured later in the waiting room.

3.3. Echocardiographic analysis

Transthoracic echocardiography was performed using a Vivid E95 ultrasound system (GE Healthcare, Horten, Norway) on patients at rest in the left lateral decubitus position. Electrocardiographically triggered echocardiographic data were acquired with a 3S or M5S 3.5 mHz transducer for two-dimensional, colour, pulsed-wave and continuous-wave Doppler, and were digitally stored in cine-loop format for offline analysis on a dedicated workstation (EchoPAC version 112.99; GE Healthcare, Horten, Norway).

Parasternal, apical and subcostal views were used to acquire two-dimensional, colour, pulsed-wave and continuous-wave Doppler data, based on current European Association of Echocardiography and American Society of Echocardiography guidelines.

AS severity was assessed quantitatively by measuring the maximum velocity through the aortic valve using continuous-wave Doppler. The mean pressure gradient was estimated using the modified Bernoulli equation deriving the peak transaortic pressure gradient from the maximum velocity, and then by averaging the instantaneous gradients over the ejection period. The LV outflow tract diameter was measured from a zoomed parasternal long-axis view, proximal to the aortic valve, at the level of the leaflet's insertion on the aortic wall. 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 aortic valve, and was used to calculate the stroke volume. Aortic valve area was derived using the continuity equation, and was indexed to body surface area. LV end-diastolic and end-systolic volumes were calculated from the apical four- and two-chamber views, and then indexed to body surface area.

LVEF was derived using the biplane Simpson method. LV mass was derived using the standard linear two-dimensional approach [20]. LV diastolic function was assessed by measuring the peak early (E) and late (A) diastolic velocities on transmitral flow pulsed-wave recordings; septal and lateral e' were measured in the apical four-chamber view on tissue Doppler imaging, and the average E/e' ratio was calculated.

Concomitant valvular heart diseases were identified and graded as recommended [4]. Pulmonary artery systolic pressure was calculated from the tricuspid regurgitation jet peak velocity, applying the modified Bernoulli equation and adding mean right atrial pressure, estimated on the basis of the diameter and collapsibility of the inferior vena cava.

The apical two-, three- and four-chamber views were used to derive LV GLS. Tri-plan acquisition was recorded in arrhythmic patients. The endocardial border was traced at an end-systolic frame, and a region of interest was automatically defined by the software, and manually adapted to include the entire myocardial thickness.

3.4. Calculation of myocardial work

Global LV myocardial work indices were derived using proprietary software (EchoPAC version 112.99; GE Healthcare, Horten, Norway), which integrates LV strain measurements with blood pressure recordings. LV systolic pressure was estimated by adding the mean transaortic gradient to the brachial cuff systolic pressure. Timings of aortic and mitral valve openings and closures were obtained manually from the two-dimensional three-chamber view and Doppler recordings. Measurements of LV strain and the previously defined pressures were then synchronized by cardiac cycle timings (determined by aortic and mitral valve events) to produce pressure-strain loops of the left ventricle [21].

Four myocardial work indices were derived by the software (Fig. 1). Global work index (GWI; mmHg%) gives a comprehensive estimation of LV work contributing to ejection in systole. Global constructive work (GCW; mmHg%) represents the work that is functional to LV contraction during systole and relaxation during diastole. Global wasted work (GWW; mmHg%) provides an estimation of the amount of LV dyssynchrony or paradoxical myocardial lengthening or shortening that does not contribute to LV filling during diastole and LV ejection during systole. Global work efficiency (GWE; %) is LV GCW divided by the sum of GCW and GWW, i.e. GCW/(GCW+GWW); this index indicates the

percentage of total LV work that is useful to LV contraction and relaxation during systole and diastole, respectively, providing a comprehensive estimation of LV performance.

3.5. Data analysis and statistics

Descriptive statistics are presented as means ± standard deviations or medians (interquartile ranges) for quantitative variables, and as percentages for categorical variables.

Firstly, for eleven prespecified echo variables, we calculated relative change, defined as post-TAVI measure minus pre-TAVI measure) divided by pre-TAVI measure. A signed-rank test tested the null hypothesis that relative change equals zero. We present nominal *P* values, as well as multiplicity-adjusted *P* values, using the Holm method (also known as the step-down Bonferroni method), which controls for the familywise error rate without assuming independence. We then evaluated homogeneity for those relative changes across three prespecified strata: GLS < –14 or ≥ –14; LVEF < 55% or ≥ 55%; New York Heart Association (NYHA) functional class I–II or III–IV. The GLS cut-off at –14% was selected from the meta-analysis by Magne et al. [22], and the LVEF cut-off at 55% was taken from current European guidelines [4].

Secondly, we sought to evaluate the relation between pre-TAVI variables of interest and a post-TAVI GLS ≥ –14, as this has been shown to have prognostic value [22]. We therefore conducted a univariate analysis among a prespecified list of clinical, biological and pre-TAVI echocardiographic variables (with the exclusion of GLS), to determine which ones were associated with post-TAVI GLS ≥ –14. Standardized estimates were calculated to give the direction and strength of each association. For variables associated in the univariate analysis ($P < 0.05$), we fitted a multivariable logistic regression model. Having excluded pre-TAVI GLS from the model because of its obvious significant association with post-TAVI value, we conducted a multivariable analysis among the same list of variables in the subgroup of patients with pre-TAVI GLS < –14.

Thirdly, we sought to evaluate the relationship between pre-TAVI variables and post-TAVI GLS evolution, defined as GLS relative change after TAVI. We therefore conducted a univariate analysis among a prespecified list of clinical, biological and pre-TAVI echocardiographic variables, this time including pre-TAVI GLS, to determine which ones were associated with post-TAVI relative change. Standardized estimates were calculated to give the direction and strength of each association.

Finally, we sought to evaluate the relation between pre-TAVI variables of interest and pre-TAVI NYHA class III & IV symptoms. Pre-TAVI rather than post-TAVI NYHA class was preferred because of the short evaluation time after TAVI and the fact that patients had then remained in hospital since TAVI. We therefore conducted a univariate analysis among a prespecified list of clinical, biological and pre-TAVI echocardiographic variables, to determine which ones were associated with pre-TAVI NYHA class III and IV. Standardized estimates were calculated to give the direction and strength of each association. For variables associated in the univariate analysis ($P < 0.05$), we fitted a multivariable logistic regression model.

4. Results

One hundred and twenty-five patients who underwent successful TAVI from January 2020 to September 2021 were selected for this study. Thirty patients were excluded for missing apical chamber recording. The clinical characteristics of the population at baseline are presented in Table 1. Most patients were elderly males. Coronary artery disease was diagnosed at the time of TAVI for 52.8% ($n = 66$) of patients, 50% ($n = 33$) of whom had been treated by angioplasty ($n = 26$) or coronary artery bypass grafting ($n = 7$). History of atrial fibrillation was present in 30.6% ($n = 38$) of patients.

Echocardiographic characteristics of patients before and after TAVI are listed in Table 2. Unsurprisingly, mean transaortic gradient was significantly improved by TAVI (12.2 ± 5.05 vs 52.5 ± 16.1; $P < 0.0001$). We did not see any significant change in LVEF (59.8 ± 13.3 vs 59.6 ± 12.9; $P = 1.0$) [Altered to match data in Table 2] or GLS (–14.0 ± 4.05 vs –14.0 ± 3.90; $P = 1.0$) after TAVI compared with before TAVI. Myocardial work data after TAVI versus before TAVI showed a significant reduction in GWI (1389 ± 537 vs 2014 ± 714; $P < 0.0001$), GCW (1693 ± 543 vs 2379 ± 761; P < 0.0001) and GWE (85.0 ± 7.06 vs 87.1 ± 5.98; $P = 0.0034$). The reduction in GWW was not significant (271 ± 223 vs 282 ± 175; $P = 0.69$). These results were maintained after adjustment for repeated measures.

A comparison of patients presenting at baseline with GLS ≥ –14 and with GLS < –14 is displayed in full in Table 3. Whereas there was no significant change in LVEF in either group, we observed a significant improvement in GLS and stroke volume index only among patients with baseline GLS ≥ –14. Both groups saw a significant reduction in GWI (Fig. 2A) and GCW (Fig. 2B). A decrease in GWE

was observed in both groups (Fig. A.1), but was only significant in patients with baseline GLS < –14. Although not significant, GWW evolution was opposite in the two groups, increasing for patients with baseline GLS < –14 and reducing for patients with baseline GLS ≥ –14 (Fig. A.2).

A comparison of patients presenting at baseline with LVEF < 55% and ≥ 55% is shown in Table 4. Evolution of LVEF was opposite in the two groups, with a significant increase in patients with baseline LVEF < 55% and a significant decrease in patients with baseline LVEF ≥ 55%. Evolution of GLS followed the same trend, but not in a significant matter. Both groups saw a significant reduction in GWI and GCW alongside insignificant decreases of GWE and GWW.

A comparison of patients presenting at baseline with NYHA class I–II and III–IV symptoms is shown in Table 5; the groups are small, thus the display of these results is exploratory and cannot be interpreted statistically. Whereas there was no significant change in LVEF or GLS in either group, patients with baseline NYHA class III–IV experienced a significant improvement in stroke volume. Both groups saw a significant reduction in GWI (Fig. A.3) and GCW (Fig. A.4), alongside insignificant reductions in GWE (Fig. A.5) and GWW (Fig. A.6).

The univariate logistic regression analysis showed a significant association between post-TAVI GLS ≥ –14 and the following pre-TAVI variables (Table A.1): N-terminal prohormone of B-type natriuretic peptide (NT-proBNP), indexed LV mass, LVEF, stroke volume index, tricuspid annular plane systolic excursion, GWE, GWI and GCW. Before TAVI, higher values of NT-proBNP and LV mass on one side and lower values of LVEF, LV output, GWE, GWI and GCW were associated with an increased probability of presenting with GLS ≥ –14 after TAVI. In the multivariable model, after excluding GWI for collinearity reasons, only GWE and GCW kept an independent association. Of course, GLS values before TAVI were excluded from the model. Nonetheless, the multivariable logistic regression analysis (Table A.2) was still showing a significant association between GWE and post-TAVI GLS ≥ –14 in the subpopulation of patients with pre-TAVI GLS < –14.

The univariate logistic regression analysis showed a significant association between post-TAVI GLS evolution and the following pre-TAVI variables (Table A.3): GLS, GWI and GCW. Fig. 3 displays how patients with pre-TAVI GLS ≥ –14, GWI < 1900 and GCW < 2200 are more likely to present an improvement in GLS after TAVI.

The univariate logistic regression analysis showed a significant association between NYHA functional class III or IV and the following pre-TAVI variables (Table A.4): NT-proBNP, E/e', LVEF,

GLS, GWI and GCW. In this population, higher values of NT-proBNP and GLS as well as lower values of LEVF, GWI and GCW were associated with an increased probability of presenting with NYHA class III or IV symptoms. GWI and E/e' were excluded from the multivariable model (GWI for collinearity reasons, and E/e' because of too many missing values), and no variable kept independent association in this model.

5. Discussion

The non-invasive myocardial work variables GWI, GCW and GWE were the only variables exploring LV systolic function that changed significantly with the correction of severe AS through TAVI. Lower values of GWE and GCW measured before TAVI were able to independently predict a GLS ≥ –14 after TAVI, and GWE was further able to predict this in the subpopulation of patients with pre-TAVI GLS < –14. GWI and GCW were able to predict a degradation of GLS after TAVI. Finally, GWI and GCW were associated with symptomatic NYHA class III and IV patients.

The significant decrease in GWI and GCW after TAVI observed in this study is consistent with two other studies [17, 23]. In a population with hypertension (another condition of increased afterload), significant increase in the two variables has been described [24, 25]. Myocardial work is increased to compensate for the increased afterload created by the valve stenosis to maintain stroke volume. Correction of the valve stenosis, and the subsequent drop in afterload, results in lower energy being required and thus lower myocardial work being required to maintain stroke volume. Indeed, the myocardial wall chambers are opposed to a lower LV pressure to deform themselves and push the same amount of blood out.

Compared with healthy subjects [15], in our population we observed GWI and GCW dropping from normal ranges before TAVI to subnormal ranges after TAVI; this demonstrates adverse ventricular remodelling in the population with advanced forms of severe AS. An experimental model of hypertensive rats showed over time a degradation from compensatory hypertrophy to heart failure, with an in parallel increase then decrease in myocardial work variables [26]. In patients with no evidence of early myocardial dysfunction (i.e. pre-TAVI GLS < –14), myocardial work changes from supranormal to normal values with valve replacement (Fig. 2 and Fig. 3). In the GLS ≥ –14 group, presenting with more adverse remodelling, the myocardial work has already dropped to normal or even subnormal values before TAVI.

Compared with healthy subjects who display a myocardial efficiency (GWE) of 96% [15], in our population with severe AS we observed less efficiency, with a pre-TAVI mean GWE of 87%, consistent with previous work [17]. The lack of efficiency can be explained by an increased wasted work (GWW) compared with normal subjects [15]. In our population, the significant decrease in GWE after TAVI can be attributed to the simultaneous drop in GCW, overbalancing the decrease in wasted work after TAVI. Then again, the remaining high amount of wasted work after TAVI could be explained by the residual cardiomyopathy, as a result of adverse remodelling and conduction disturbances related to TAVI. The accuracy of assessment of valve opening and closure in patients in atrial fibrillation could have an impact on the robustness of the measurement [21].

The absence of significant change in LVEF has already been observed [17, 23], but the absence of change in GLS is unprecedented. Degradation of GLS in severe AS has already been found in other studies, ranging from –13.3 to –14.2 [27, 28], with a similar range to the pre-TAVI GLS in our population (–14.0), and can be explained by two main factors: the increased afterload from the AS and the cardiomyopathy from prolonged stenosis leading to adverse cardiac remodelling or other cardiac pre-existing conditions. GLS did not improve in our study, despite the significant drop in afterload. This could be explained by the time between pre-TAVI echocardiography and the TAVI itself (57 days on average), resulting in progressive adverse remodelling that was not recognized before TAVI. The opposite evolution of LVEF and GLS in different subgroups, with improvement trend in “severe patients” (GLS < –14, LVEF < 55%, NYHA III–IV) and deterioration in “less severe patients” should be interpreted with caution; first because these two variables did not evolve significantly in the general population; and second because most of the subgroup results themselves are not significant.

In this study we demonstrated that myocardial work variables GWI, GCW and GWE were the only echocardiographic variables exploring LV systolic function to display a significant change after TAVI. Remaining below normal values despite significant change, GWI and GCW provide insight into the adverse LV remodelling that is persistent immediately after TAVI. GWI and GCW were able to predict post-TAVI GLS ≥ –14 [22], and therefore may be of some prognostic use. This is emphasized by the relationship between NYHA symptoms and echocardiographic variables, found in univariate analysis in this study and in a multivariable analysis by Fortuni et al. [16]. The prognostic value of myocardial work indices needs to be confirmed in further research.

The timing of intervention for AS is evolving to eliminate potential consequences that can arise; GLS and myocardial work may help to identify patients requiring intervention early, rather than waiting until evidence of advanced cardiac dysfunction is present, which can result in ongoing cardiac dysfunction and poorer outcomes after the procedure. Ongoing randomized studies are trying to assess the benefit of aortic valve replacement in asymptomatic patients with severe AS and preserved LVEF [29-33]. Other methods for identifying patients who may benefit from early intervention include late gadolinium enhancement [34], extracellular volume and T1 mapping [35]. Echocardiography will remain indispensable, and myocardial work and strain will be additive measures to identify early cardiac dysfunction. Artificial intelligence may improve the accuracy and speed of obtaining this information.

6. Conclusions

Non-invasive myocardial work variables show great potential in better assessing myocardial consequences of AS and its correction; their ability to discriminate NYHA status from evolution of GLS after TAVI indicates promise for providing prognostic information, and calls for further study.

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None.

Disclosure of interest

The authors declare that they have no competing interest.

Appendix A. Supplementary data

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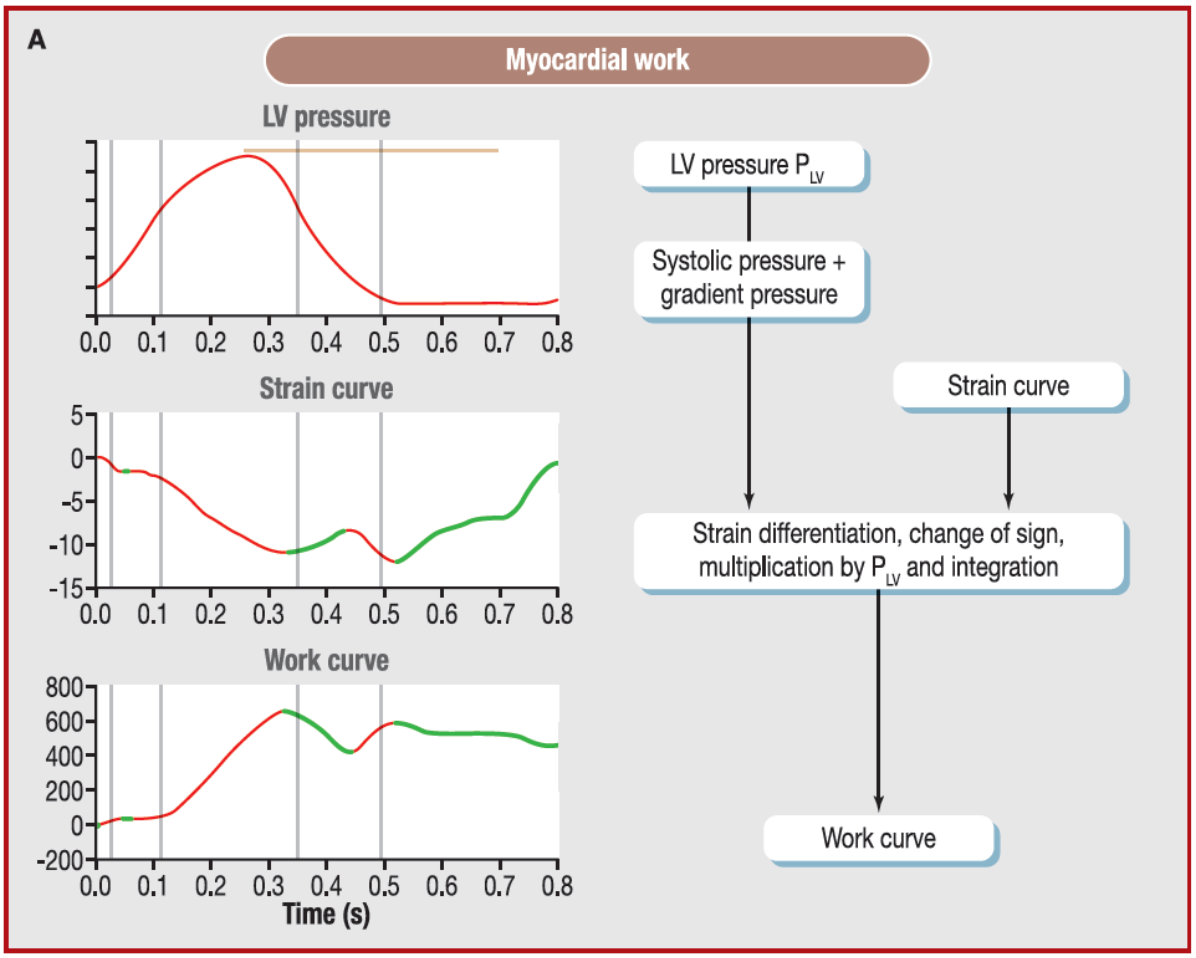
Figure legends



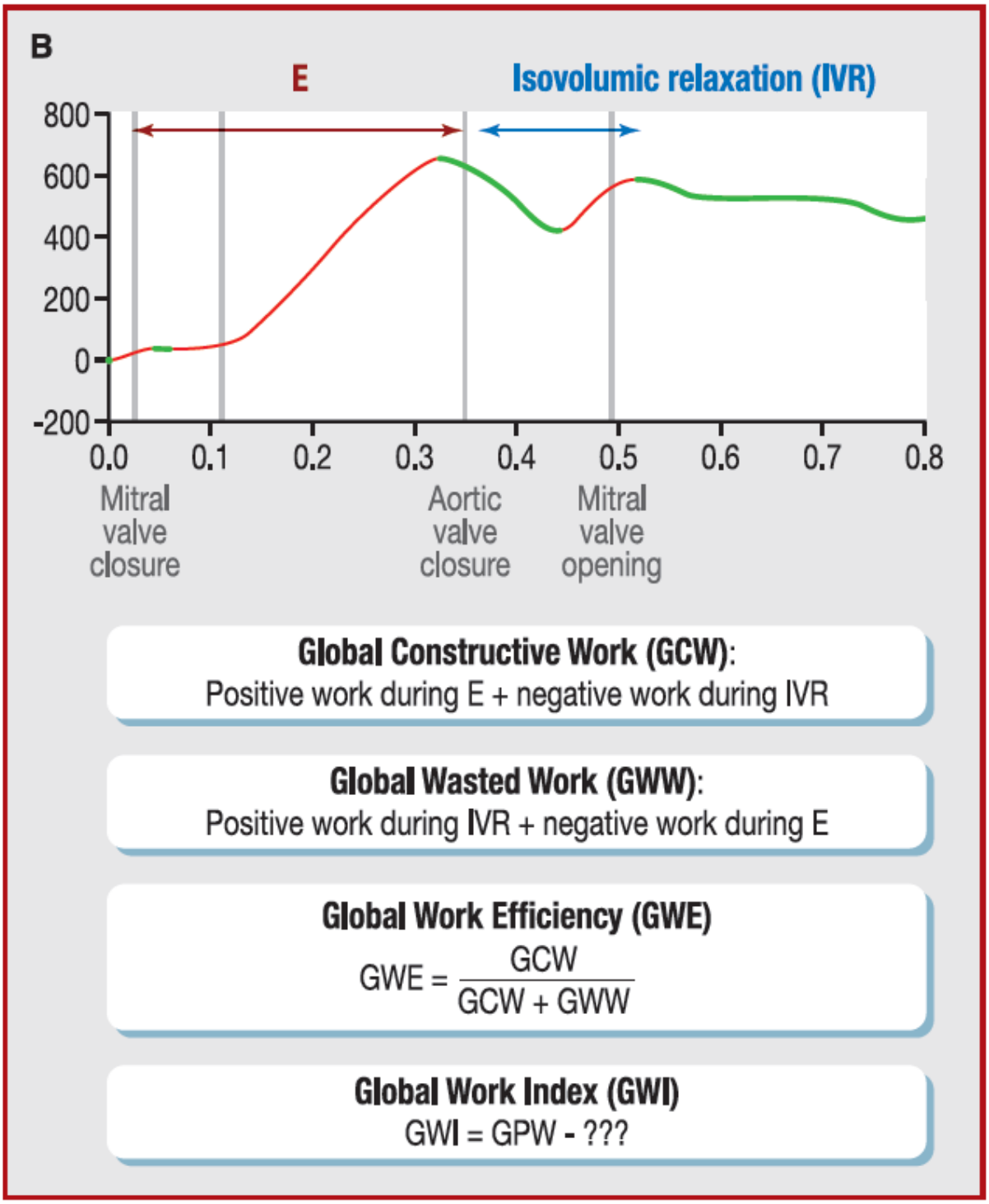


Fig. 1. Principle of non-invasive myocardial work. GCW: global constructive work; GLS: global longitudinal strain; GWE: global work efficiency; GWI: global work index; GWW: global wasted work; IVR: isovolumic relaxation; LV: left ventricular.

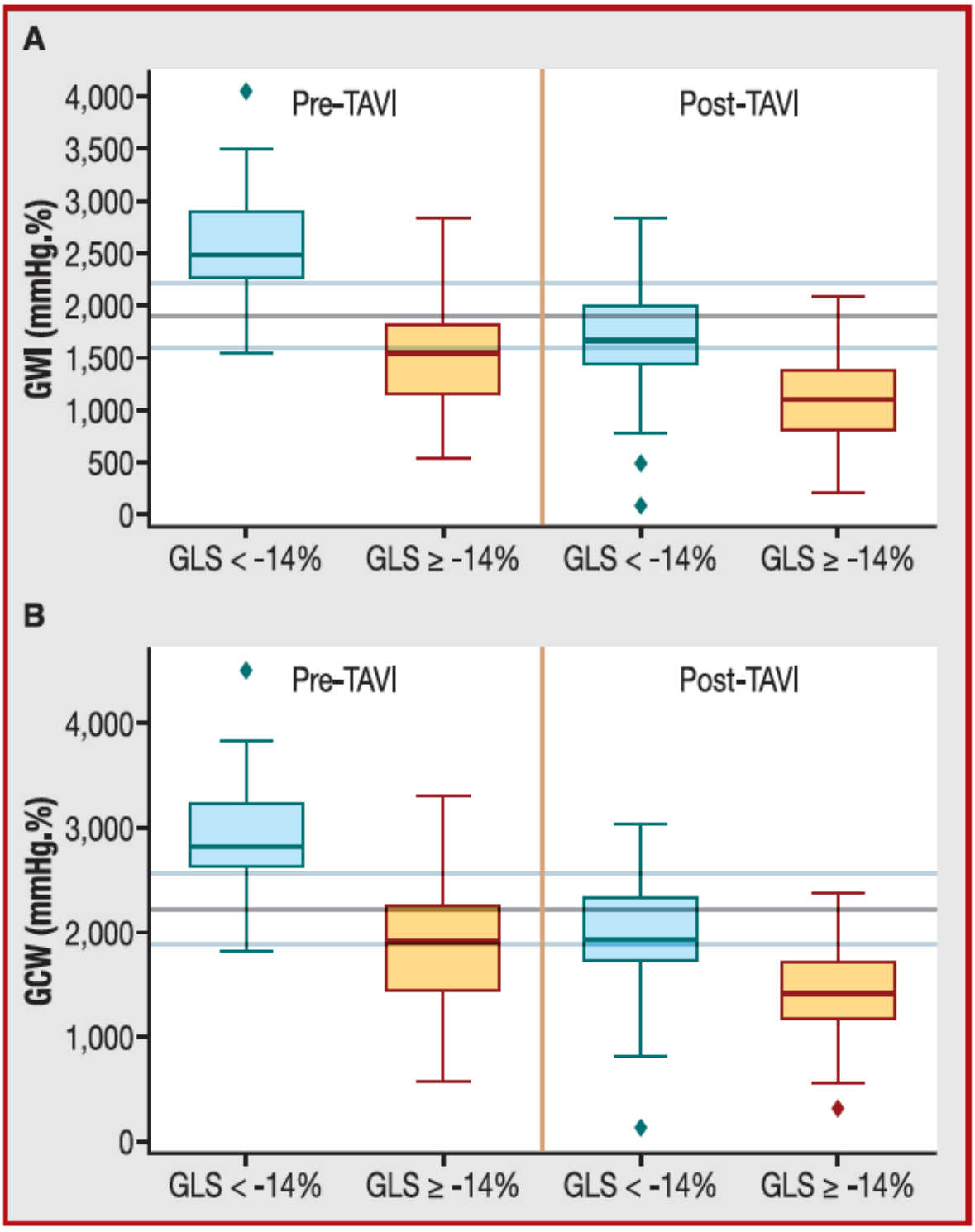


Fig. 2. A. Evolution of global work index (GWI) after transcatheter aortic valve implantation (TAVI), based on pre-TAVI global longitudinal strain (GLS) stratification; relative change was statistically significant in both subgroups (GLS < –14% or GLS ≥ –14%) (*P* < 0.0001), with significant heterogeneity across subgroups (*P* value for interaction = 0.038). B. Evolution of global constructive work (GCW) after TAVI based on pre-TAVI GLS stratification; relative change was statistically significant in both subgroups (GLS < –14% or GLS ≥ –14%) (*P* < 0.0001), with significant

heterogeneity across subgroups (*P* value for interaction = 0.028). Relative change was defined as: (post-TAVI measure minus pre-TAVI measure) divided by pre-TAVI measure. Horizontal grey lines correspond to mean values and standard derivation in the healthy population [15].

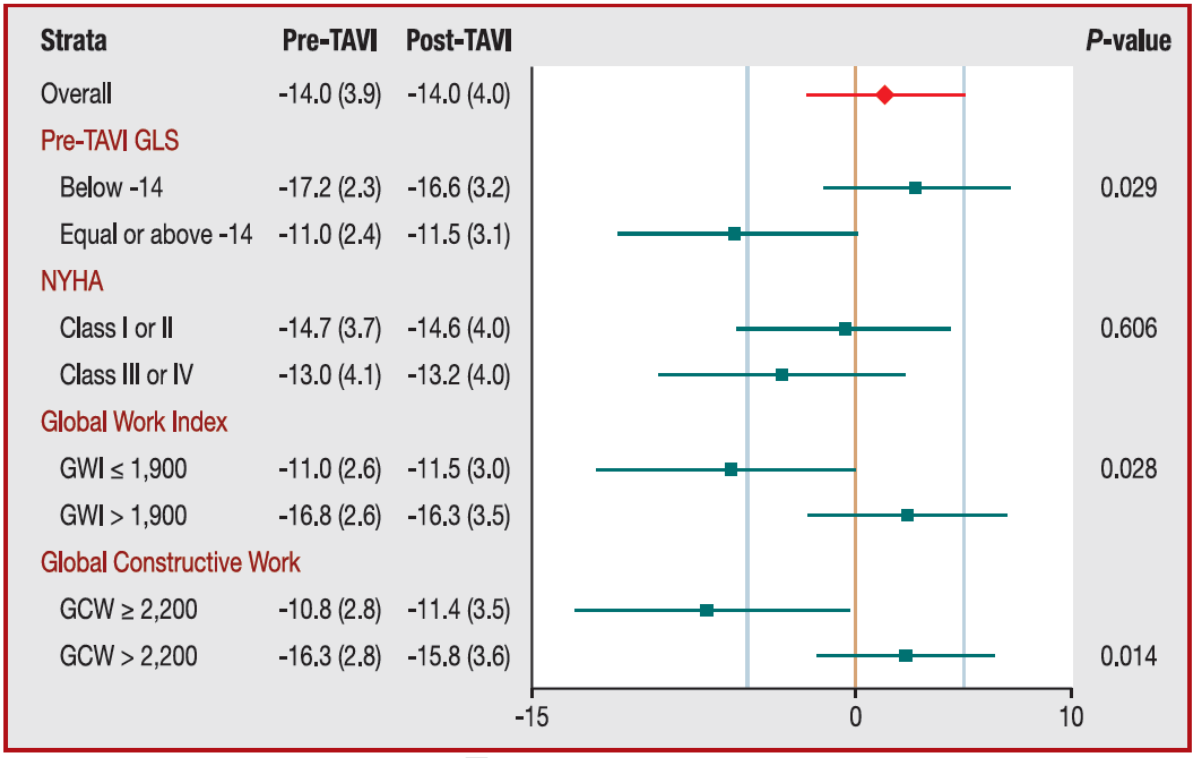


Fig. 3. Evolution of GLS after TAVI according to subpopulations. GWI> 1900 and GCM > 2000 were defined according to median values.

Central Illustration. GCW: global constructive work; GLS: global longitudinal strain; GWE: global work efficiency; GWI: global work index; GWW: global wasted work; IVR: isovolumic relaxation; LV: left ventricular; LVOT: left ventricular outflow tract; NYHA: New York Heart Association; TAVI: transcatheter aortic valve implantation.

Table 1

Baseline characteristics of the global population.

	Number	Number missing	Value
Transaortic mean gradient (mmHg)	125	0	52.5 ± 16.1
LVEF (%)	125	0	59.8 ± 13.3
GLS (%)	125	0	–14.0 ± 3.90
E/e’	100	25	15.8 ± 6.36
Mean e’ (m/s)	102	23	0.07 (IQR 0.03)
LAVi (mL/m^2)	119	6	46.0 (IQR 19.9)
SVi (mL/m^2)	124	1	44.0 (IQR 18.5)
IVS diameter (mm)	125	0	12.8 ± 2.88
V_{max} TR (m/s)	95	30	3.01 ± 0.50
GWE (mmHg%)	125	0	87.1 ± 5.98
GWI (mmHg%)	125	0	2014 ± 714
GCW (mmHg%)	125	0	2379 ± 761
GWW (mmHg%)	125	0	231 (IQR 195)
LV mass index (g/m^2)	119	6	111 (IQR 46.0)
TAPSE (mm)	68	57	21.9 ± 4.95
Age (years)	125	0	84.0 (IQR 6.00)
Male sex	125	0	73 (58.4)
CAD	125	0	66 (52.8)
CABG	125	0	7 (5.6)
Angioplasty	125	0	26 (20.8)
Atrial fibrillation	124	1	38 (30.6)
Diabetes	125	0	20 (16.0)
NT-proBNP (pg/mL)	113	12	1322 (IQR 2527)
Creatinine (μg/mL)	120	5	81.5 (IQR 33.0)

Data are expressed as mean ± standard deviation, median (IQR) or number (%). CABG: coronary artery bypass graft; CAD: coronary artery disease; GCW: global constructive work; GLS: global

longitudinal strain; GWE: global work efficiency; GWI: global work index; GWW: global wasted work; IQR: interquartile range; IVS: interventricular septum; LAVi: left atrium volume index; LVEF: left ventricular ejection fraction; NT-proBNP: N-terminal prohormone of B-type natriuretic peptide; SVi: stroke volume index; TAPSE: tricuspid annular plane systolic excursion; V_{max} TR: maximal tricuspid regurgitation velocity.

Table 2

Echocardiographic data before and after transcatheter aortic valve implantation in the global population.

Variable	Before TAVI	After TAVI	Mean relative change (%)	Nominal *P* value	Multiplicity-adjusted *P* value
LVEF (%)	59.8 ± 13.3	59.6 ± 12.9	–2	0.94	1.00
LAVi (mL/m^2)	50.9 ± 17.4	47.7 ± 20.7	–3	0.15	0.73
GLS (%)	–14.0 ± 3.90	–14.0 ± 4.05	1	0.46	1.00
E/e’	15.8 ± 6.36	15.1 ± 5.92	–4	0.95	1.00
LV output	45.1 ± 14.7	46.1 ± 14.8	11	0.05	0.32
Mean transaortic gradient	52.5 ± 16.1	12.2 ± 5.05	–75	< 0.0001	0.0011
V_{max} TR	3.01 ± 0.50	2.73 ± 0.43	–7	< 0.0001	0.0011
GWE	87.1 ± 5.98	85.0 ± 7.06	–2	0.0034	0.0238
GWI	2014 ± 714	1389 ± 537	–28	< 0.0001	0.0011
GCW	2379 ± 761	1693 ± 543	–25	< 0.0001	0.0011
GWW	282 ± 175	271 ± 223	–18	0.69	1.00

Data are expressed as mean ± standard deviation, unless otherwise indicated. GCW: global constructive work; GLS: global longitudinal strain; GWE: global work efficiency; GWI: global work index; GWW: global wasted work; LAVi: left atrium volume index; LV: left ventricular; LVEF: left ventricular ejection fraction; TAVI: transcatheter aortic valve implantation; V_{max} TR: maximal tricuspid regurgitation velocity.

Table 3

Echocardiographic data evolution according to global longitudinal strain before transcatheter aortic valve implantation.

GLS value	Variable	Before TAVI	After TAVI	Mean relative change (%)	*P*
< –14	LVEF (%)	66.77 ± 8.37	65.48 ± 8.27	–1	0.61
≥ –14	LVEF (%)	53.20 ± 13.77	53.96 ± 14.07	6	0.77
< –14	LAVi (mL/m^2)	50.04 ± 18.12	42.59 ± 15.03	–11	0.0019
≥ –14	LAVi (mL/m^2)	51.80 ± 16.76	52.49 ± 23.98	5	0.42
< –14	GLS (%)	–17.23 ± 2.29	–16.64 ± 3.20	–3	0.27
≥ –14	GLS (%)	–11.01 ± 2.40	–11.52 ± 3.11	6	0.05
< –14	E/e'	14.63 ± 5.73	14.66 ± 5.40	8	0.50
≥ –14	E/e'	16.93 ± 6.74	15.57 ± 6.51	–1	0.48
< –14	SVi (mL/m^2)	51.47 ± 14.37	47.72 ± 14.57	–3	0.35
≥ –14	SVi (mL/m^2)	39.21 ± 12.36	44.59 ± 14.91	23	0.0005
< –14	AV mean gradient (mmHg)	55.13 ± 16.18	13.21 ± 5.34	–75	< 0.0001
≥ –14	AV mean gradient (mmHg)	50.03 ± 15.82	11.16 ± 4.56	–75	< 0.0001
< –14	V_{max} TR (m/s)	2.98 ± 0.41	2.65 ± 0.37	–9	0.0002
≥ –14	V_{max} TR (m/s)	3.04 ± 0.57	2.80 ± 0.47	–4	0.0427
< –14	GWE (%)	90.43 ± 3.97	87.47 ± 6.58	–3	0.0001
≥ –14	GWE (%)	83.88 ± 5.83	82.71 ± 6.76	–1	0.46
< –14	GWI (mmHg%)	2550.07 ± 511.55	1681.74 ± 513.05	–33	< 0.0001
≥ –14	GWI (mmHg%)	1503.77 ± 460.34	1107.10 ± 391.49	–23	< 0.0001
< –14	GCW (mmHg%)	2913.61 ± 527.44	1984.90 ± 510.30	–31	< 0.0001
≥ –14	GCW (mmHg%)	1870.88 ± 580.21	1411.98 ± 413.02	–20	< 0.0001
< –14	GWW (mmHg%)	244.85 ± 124.40	280.31 ± 269.42	28	0.35
≥ –14	GWW (mmHg%)	317.58 ± 208.22	262.78 ± 168.74	8	0.76

Data are expressed as mean ± standard deviation, unless otherwise indicated. AV: aortic valve; GCW: global constructive work; GLS: global longitudinal strain; GWE: global work efficiency; GWI: global work index; GWW: global wasted work; LAVi: left atrium volume index; LVEF: left ventricular ejection fraction; SVi: stroke volume

index; TAVI: transcatheter aortic valve implantation; V_{max} TR: maximal tricuspid regurgitation velocity.

Table 4

Echocardiographic data evolution according to left ventricular ejection fraction before transcatheter aortic valve implantation.

LVEF value	Variable	Before TAVI	After TAVI	Mean relative change (%)	*P*
< 55%	LVEF (%)	42.12 ± 9.53	48.79 ± 14.16	20	0.0052
≥ 55%	LVEF (%)	66.44 ± 6.88	63.55 ± 9.88	–4	0.0182
< 55%	LAVi (mL/m^2)	57.09 ± 15.12	53.18 ± 18.85	–3	0.73
≥ 55%	LAVi (mL/m^2)	48.68 ± 17.69	45.67 ± 21.06	–3	0.20
< 55%	GLS (%)	–10.45 ± 2.85	–10.74 ± 2.94	–5	0.33
≥ 55%	GLS (%)	–15.39 ± 3.33	–15.24 ± 3.73	0	0.78
< 55%	E/e'	18.74 ± 7.39	15.96 ± 7.18	–10	0.29
≥ 55%	E/e'	14.78 ± 5.62	14.76 ± 5.42	–8	0.33
< 55%	SVi (mL/m^2)	36.89 ± 12.88	45.16 ±16.86	34	0.0009
≥ 55%	SVi (mL/m^2)	48.26 ± 14.14	46.48 ± 14.00	–2	0.952
< 55%	AV mean gradient (mmHg)	48.03 ± 11.88	11.12 ± 4.92	–75	< 0.0001
≥ 55%	AV mean gradient (mmHg)	54.20 ± 17.22	12.55 ± 5.06	–75	< 0.0001
< 55%	V_{max} TR (m/s)	3.07 ± 0.51	2.86 ± 0.45	–3	0.51
≥ 55%	V_{max} TR (m/s)	2.99 ±0.49	2.68 ± 0.41	–8	< 0.0001
< 55%	GWE (%)	84.44 ± 6.35	83.06 ± 5.85	–1	0.36
≥ 55%	GWE (%)	88.05 ± 5.55	85.76 ± 7.36	–2	0.0033
< 55%	GWI (mmHg%)	1367.91 ± 461.31	1068.85 ± 353.51	–17	0.0018
≥ 55%	GWI (mmHg%)	2255.89 ± 638.60	1506.16 ± 546.70	–31	< 0.0001
< 55%	GCW (mmHg%)	1652.12 ± 539.75	1334.24 ± 380.87	–14	0.0110
≥ 55%	GCW (mmHg%)	2651.58 ± 645.67	1824.22 ± 536.63	–29	< 0.0001
< 55%	GWW (mmHg%)	264.56 ± 184.87	239.27 ± 120.09	–22	0.36
≥ 55%	GWW (mmHg%)	288.64 ± 172.65	283.05 ± 249.94	– 17	0.95

Data are expressed as mean ± standard deviation, unless otherwise indicated. AV: aortic valve; GCW: global constructive work; GLS: global longitudinal strain; GWE: global work efficiency; GWI: global work

index; GWW: global wasted work; LAVi: left atrium volume index; LVEF: left ventricular ejection fraction; SVi: stroke volume index; TAVI: transcatheter aortic valve implantation; V_{max} TR: maximal tricuspid regurgitation velocity.

Table 5

Echocardiographic data evolution according to New York Heart Association class before transcatheter aortic valve implantation.

NYHA class	Variable	Before TAVI	After TAVI	Mean relative change (%)	*P*
I–II	LVEF (%)	62.04 ± 10.82	61.74 ± 10.92	–1	0.88
III–IV	LVEF (%)	56.55 ± 15.89	57.18 ± 14.76	5	0.81
I–II	LAVi (mL/m^2)	49.42 ± 16.48	47.04 ± 22.95	–2	0.35
III–IV	LAVi (mL/m^2)	52.73 ± 18.58	48.94 ± 17.55	–3	0.39
I–II	GLS (%)	–14.71 ± 3.66	–14.65 ± 4.02	1	0.68
III–IV	GLS (%)	–13.01 ± 4.06	–13.19 ± 4.04	–3	0.32
I–II	E/e'	13.84 ± 4.97	13.63 ± 4.96	–6	0.65
III–IV	E/e'	18.49 ± 7.22	17.02 ± 6.66	–1	0.64
I–II	SVi (mL/m^2)	46.99 ± 12.58	46.37 ± 14.09	–5	0.53
III–IV	SVi (mL/m^2)	42.63 ± 17.13	46.25 ± 15.90	20	0.0155
I–II	AV mean gradient (mmHg)	54.96 ± 17.49	12.82 ± 5.41	–75	< 0.0001
III–IV	AV mean gradient (mmHg)	49.67 ± 13.62	11.20 ± 4.30	–76	< 0.0001
I–II	V_{max} TR (m/s)	2.94 ± 0.47	2.71 ± 0.41	–5	0.0108
III–IV	V_{max} TR (m/s)	3.13 ± 0.51	2.77 ± 0.46	–9	0.0011
I–II	GWE (%)	87.35 ± 6.12	84.99 ± 7.55	–3	0.0132
III–IV	GWE (%)	86.47 ± 5.80	85.08 ± 6.42	–1	0.17
I–II	GWI (mmHg%)	2137.49 ± 700.55	1430.30 ± 559.05	–31	< 0.0001
III–IV	GWI (mmHg%)	1835.78 ± 713.86	1335.76 ± 514.65	–23	< 0.0001
I–II	GCW (mmHg%)	2534.92 ± 724.12	1756.06 ± 549.44	–28	< 0.0001
III–IV	GCW (mmHg%)	2165.39 ± 779.49	1615.61 ± 537.06	–21	< 0.0001
I–II	GWW (mmHg%)	302.40 ± 192.56	299.65 ± 270.35	–24	0.85
III–IV	GWW (mmHg%)	259.06 ± 147.89	234.53 ± 132.12	–9	0.90

Data are expressed as mean ± standard deviation, unless otherwise indicated. AV: aortic valve; GCW: global constructive work; GLS: global longitudinal strain; GWE: global work efficiency; GWI: global work index;

GWW: global wasted work; LAVi: left atrium volume index; LVEF: left ventricular ejection fraction; NYHA: New York Heart Association; SVi: stroke volume index; TAVI: transcatheter aortic valve implantation; V_{max} TR: maximal tricuspid regurgitation velocity.

Appendix A

Table A.1

Univariate and multivariable logistic regression to identify the pre-TAVI determinants for post-TAVI global longitudinal strain ≥ –14.

Effect	Unit	Univariate analysis		Multivariable analysis	
		Estimate (95% CI)	*P*	Estimate (95% CI)	*P*
NT-proBNP (pg/mL)	2000	1.89 (1.21–2.96)	0.0055	0.88 (0.58–1.37)	0.58
LV mass index (g/m²)	40	1.67 (1.09–2.55)	0.0173	1.37 (0.75–2.51)	0.31
LVEF (%)	10	0.39 (0.26–0.58)	< 0.0001	0.69 (0.42–1.16)	0.16
SVi (mL/m^2)	12	0.49 (0.33–0.72)	0.0003	0.80 (0.50–1.28)	0.35
GWE (mmHg%)	5	0.38 (0.25–0.58)	< 0.0001	0.55 (0.34–0.91)	0.0209
GWI (mmHg%)	600	0.24 (0.14–0.40)	< 0.0001		
GCW (mmHg%)	600	0.28 (0.18–0.45)	< 0.0001	0.50 (0.27–0.94)	0.0306

CI: confidence interval; GCW: global constructive work; GWE: global work efficiency; GWI: global work index; LV: left ventricular; LVEF: left ventricular ejection fraction; NT-proBNP: N-terminal prohormone of brain natriuretic peptide; SVi: stroke volume index; TAVI: transcatheter aortic valve implantation.

Table A.2

Multivariable logistic regression to identify the pre-TAVI determinants for post-TAVI global longitudinal strain ≥ –14, in the subpopulation with pre-TAVI global longitudinal strain < –14.

Effect	Unit	Estimate (95% CI)	*P*
NT-proBNP (pg/mL)	2000	0.87 (0.16–4.74)	0.88
LV mass index (g/m²)	40	2.03 (0.73–5.60)	0.17
LVEF (%)	10	0.76 (0.32–1.80)	0.53
SVi (mL/m²)	12	0.82 (0.39–1.75)	0.61
GWE (mmHg%)	5	0.22 (0.06–0.81)	0.0225
GWI (mmHg%)	600	4.31 (0.25–72)	0.31
GCW (mmHg%)	600	0.29 (0.02–3.53)	0.33

CI: confidence interval; GCW: global constructive work; GWE: global work efficiency; GWI: global work index; LV: left ventricular; LVEF: left ventricular ejection fraction; NT-proBNP: N-terminal prohormone of brain natriuretic peptide; SVi: stroke volume index; TAVI: transcatheter aortic valve implantation.

Table A.3

Univariate logistic regression to identify the pre-TAVI determinants for post-TAVI global longitudinal strain deterioration.

Effect	Standardized estimate	*P*
GLS	–0.311	0.0004
GWI	–0.212	0.0182
GCW	–0.207	0.0208
LAVi	–0.168	0.07
TAPSE	–0.155	0.21
LVEF	–0.145	0.11
NT-proBNP	0.108	0.26
SVi	–0.107	0.24
Atrial fibrillation	0.099	0.28
Sex	–0.078	0.39
AV mean gradient	–0.074	0.41
CAD	0.040	0.66
GWE	–0.034	0.71
GWW	–0.030	0.74
Diabetes	0.028	0.76
E/E'	–0.024	0.81
LV mass index	–0.024	0.80
V_{max} TR	–0.019	0.86
Age	0.017	0.85
IVS diameter	–0.012	0.90

AV: aortic valve; GCW: global constructive work; GLS: global longitudinal strain; GWE: global work efficiency; GWI: global work index; GWW: global wasted work; IVS: interventricular septum; LAVi: left atrium volume index; LV: left ventricular; LVEF: left ventricular ejection fraction; NT-proBNP: N-terminal prohormone of brain natriuretic peptide; SVi: stroke volume index; TAVI: transcatheter aortic valve implantation; TAPSE: tricuspid annular plane systolic excursion; V_{max} TR: maximal tricuspid regurgitation velocity.

Table A.4

Univariate and multivariable logistic regression to identify the pre-TAVI determinants for New York Heart Association class III and IV symptoms.

Effect	Unit	Univariate analysis		Multivariable analysis	
		Estimate (95% CI)	*P*	Estimate (95% CI)	*P*
NT-proBNP (pg/mL)	2000	1.81 (1.20–2.72)	0.0046	1.53 (0.95–2.46)	0.08
LVEF (%)	10	0.73 (0.55–0.97)	0.0278	1.06 (0.70–1.60)	0.79
GLS (%	3	1.42 (1.06–1.91)	0.0192	1.13 (0.59–2.13)	0.72
GWI (mmHg%)	600	0.69 (0.50–0.95)	0.0238		
GCW (mmHg%)	600	0.67 (0.49–0.91)	0.0100	0.84 (0.45–1.57)	0.59

CI: confidence interval; GCW: global constructive work; GLS: global longitudinal strain; GWI: global work index; LVEF: left ventricular ejection fraction; NT-proBNP: N-terminal prohormone of brain natriuretic peptide; TAVI: transcatheter aortic valve implantation.

Fig. A.1. Evolution of global work efficiency (GWE) after transcatheter aortic valve implantation (TAVI) based on pre-TAVI global longitudinal strain (GLS) stratification. Horizontal grey line corresponds to mean values in healthy population [14]. Relative change, defined as (post-TAVI measure minus pre-TAVI measure) divided by pre-TAVI measure, was statistically significant in patients with GLS < –14%: $P < 0.0001$.

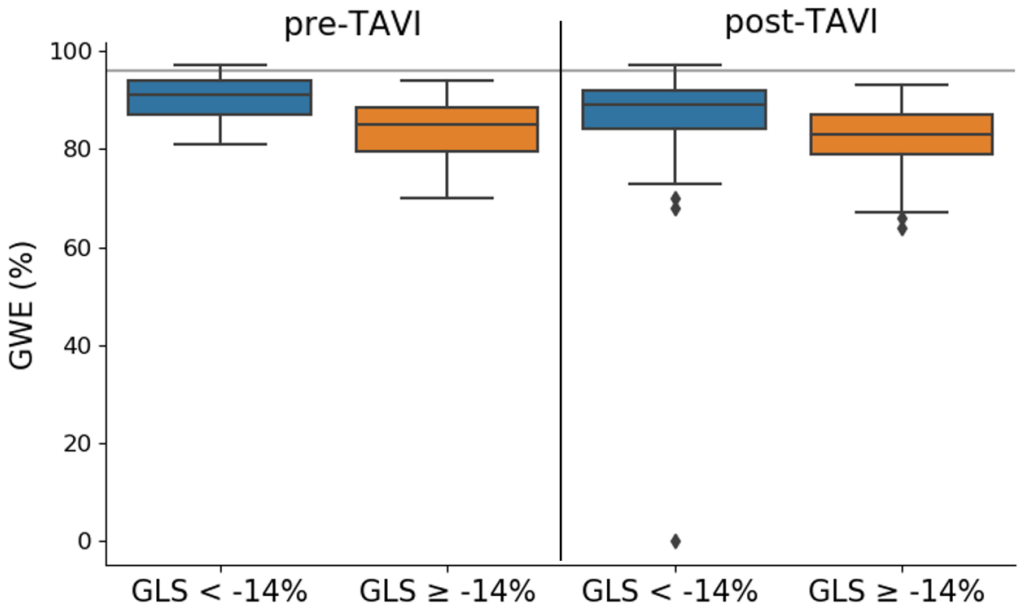


Fig. A.2. Evolution of global wasted work (GWW) after transcatheter aortic valve implantation (TAVI) based on pre-TAVI global longitudinal strain (GLS) stratification. Horizontal grey lines correspond to mean values and standard derivation in healthy population [15]. Relative change, defined as (post-TAVI measure minus pre-TAVI measure) divided by pre-TAVI measure, was statistically not significant in both subgroups (GLS < –14% or GLS ≥ –14%).

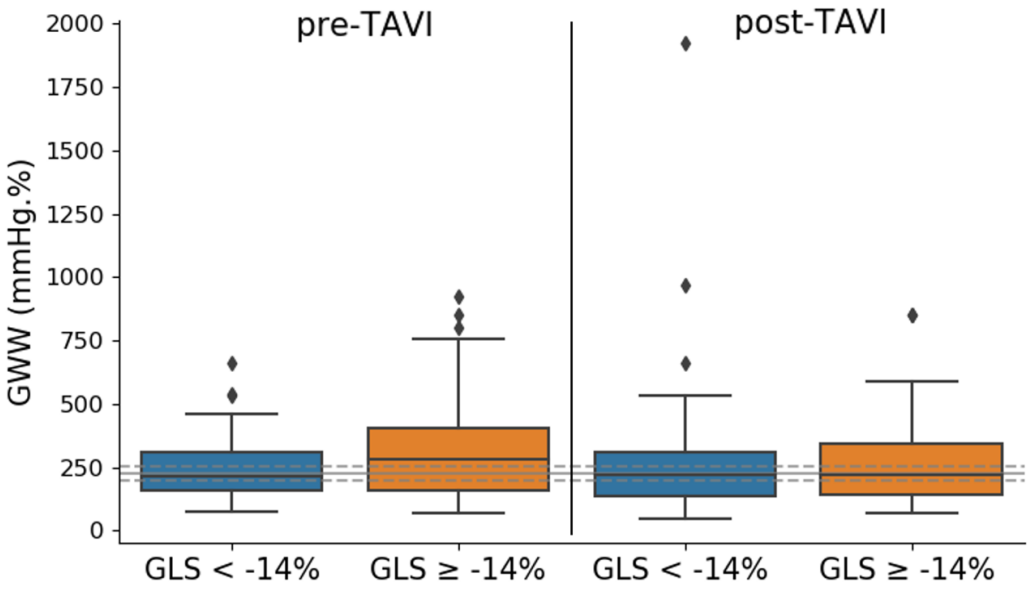


Fig. A.3. Evolution of global work index (GWI) after transcatheter aortic valve implantation (TAVI) based on pre-TAVI New York Heart Association (NYHA) stratification. Horizontal grey lines correspond to mean values and standard derivation in healthy population [15]. Relative change, defined as (post-TAVI measure minus pre-TAVI measure) divided by pre-TAVI measure, was statistically significant in both subgroups (NYHA class I or II versus NYHA class III or IV) ($P < 0.0001$), without significant heterogeneity across subgroups (P value for interaction = 0.162).

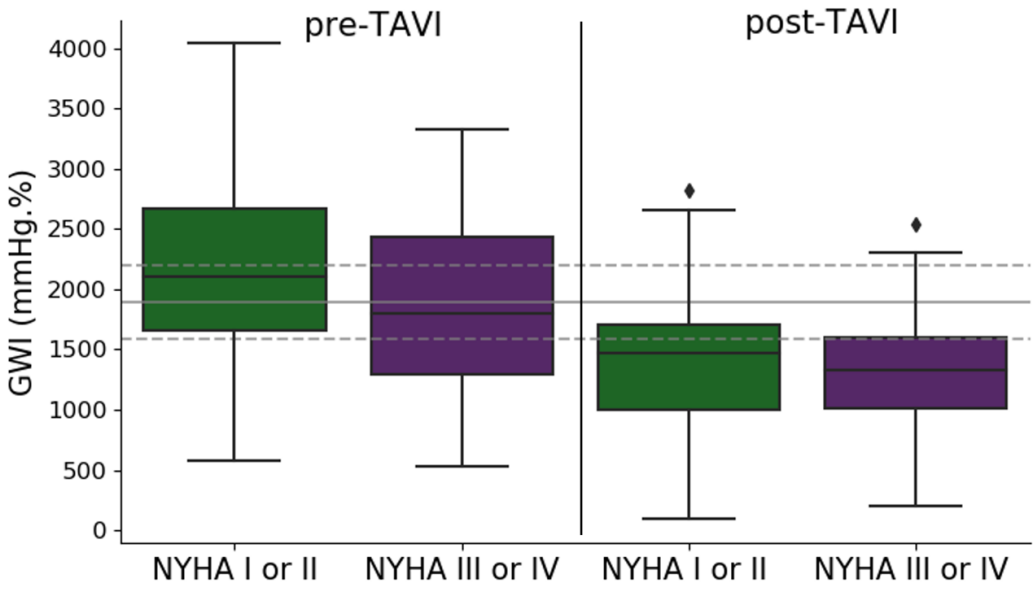


Fig. A.4. Evolution of global constructive work (GCW) after transcatheter aortic valve implantation (TAVI) based on pre-TAVI New York Heart Association (NYHA) stratification. Horizontal grey lines correspond to mean values and standard derivation in healthy population [15]. Relative change, defined as (post-TAVI measure minus pre-TAVI measure) divided by pre-TAVI measure, was statistically significant in both subgroups (NYHA class I or II versus NYHA class III or IV) ($P < 0.0001$), without significant heterogeneity across subgroups (P value for interaction = 0.138).

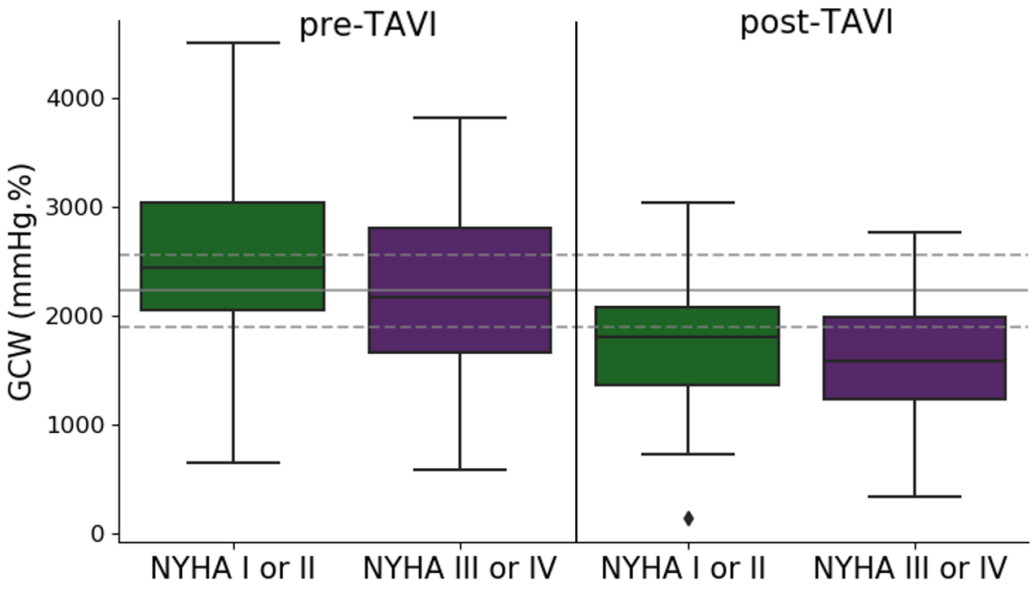


Fig. A.5. Evolution of global work efficiency (GWE) after transcatheter aortic valve implantation (TAVI) based on pre-TAVI New York Heart Association (NYHA) stratification. Horizontal grey line corresponds to mean values in healthy population [15]. Relative change, defined as (post-TAVI measure minus pre-TAVI measure) divided by pre-TAVI measure, was statistically significant only in patients with pre-TAVI NYHA class I or II: $P = 0.0132$.

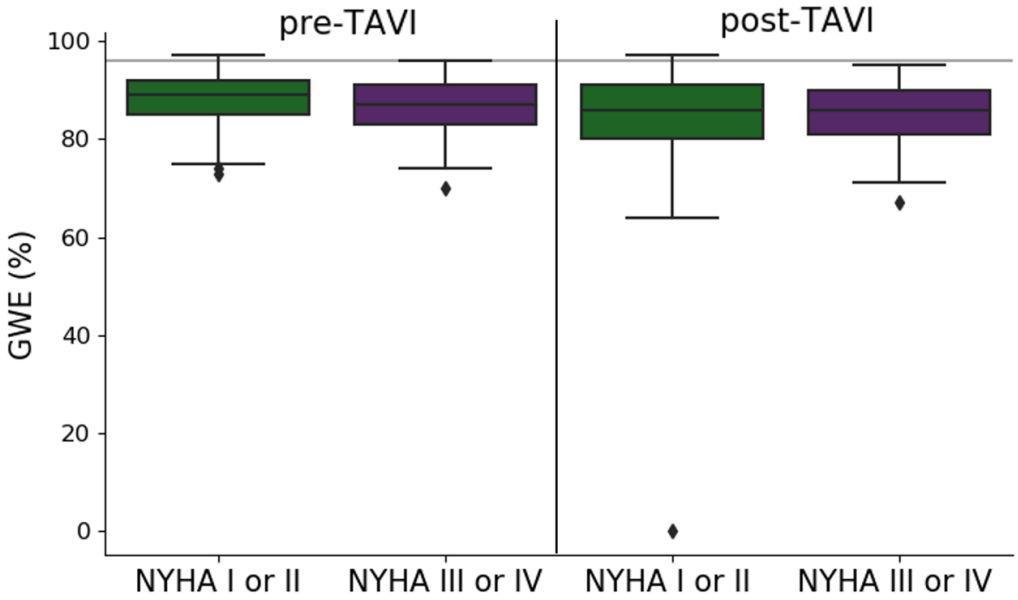


Fig. A.6. Evolution of global wasted work (GWW) after transcatheter aortic valve implantation (TAVI) based on pre-TAVI New York Heart Association (NYHA) stratification. Horizontal grey lines correspond to mean values and standard derivation in healthy population [15]. Relative change, defined as (post-TAVI measure minus pre-TAVI measure) divided by pre-TAVI measure, was not statistically significant in both subgroups (NYHA class I or II versus NYHA class III or IV).