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Sustained favourable haemodynamics 1 year after TAVI: improvement in NYHA functional class related to improvement of left ventricular diastolic function

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Aims Despite expected improvement in left ventricular (LV) systolic and diastolic function after transcatheter aortic valve implantation (TAVI), the complex relationship between pre-existent LV systolic and diastolic function and changes in LV haemodynamics and clinical symptoms have been scarcely investigated. This study investigated the presence of pre-operative LV diastolic dysfunction and its improvement over time after TAVI alongside improvement in New York Heart Association (NYHA) class in high-risk patients with severe aortic stenosis.

Methods and results The study population ($n = 358$) was divided into two groups according to baseline LV ejection fraction (LVEF): LVEF $< 50\%$ ($n = 96$) and LVEF $\geq 50\%$ ($n = 262$). We compared clinical and echocardiographic parameters between groups before TAVI, at 6 and 12 months follow-up. Grade III LV diastolic dysfunction was more frequent in patients with LVEF $< 50\%$ compared with patients with LVEF $\geq 50\%$ (50.0 vs. 16.3%, $P < 0.001$). Systolic and diastolic echocardiographic parameters improved after TAVI together with improvement in NYHA class both in patients with LVEF $< 50\%$ (diastolic dysfunction grade ≥ 2: baseline 100% of patients; 12 months 58.8%, $P < 0.001$; NYHA III/IV: baseline, 93.8%; 12 months, 9.7%, $P < 0.001$) and with LVEF $\geq 50\%$ (diastolic dysfunction grade ≥ 2: baseline, 87.1%; 12 months, 61.2%; NYHA III/IV: baseline, 74.5%; 12 months, 2.6%, $P < 0.001$). All-cause mortality was comparable between groups.

Conclusion TAVI exerts favourable effects on LV systolic and diastolic function with a remarkable improvement in LV diastolic function associated with improvement in NYHA functional class at follow-up. Prognosis at 1 year after TAVI was not influenced by baseline LV diastolic dysfunction both in patients with and without LV systolic dysfunction.

Keywords transcatheter aortic valve implantation • diastolic function • Doppler echocardiography

Introduction

In the last decade, transcatheter aortic valve implantation (TAVI) has shown to be a feasible and effective therapeutic alternative in patients with symptomatic severe aortic stenosis (AS) and contraindications or high risk for surgical aortic valve replacement.[1–3] Several studies have shown excellent, sustained transvalvular haemodynamics post-TAVI, together with a significant improvement in symptoms and quality of life.[4–6] However, the impact of TAVI on left ventricular (LV) systolic and diastolic function and their association with post-procedural improvement in quality of life and New York Heart Association (NYHA) functional class are not well characterized. Furthermore, despite significant LV mass regression and improvement in LV systolic and diastolic function after TAVI, the complex relationship among pre-operative LV systolic and diastolic function, LV filling pressures, and effects of TAVI on these parameters have

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been scarcely investigated.[7–9] These changes may have relevant clinical prognostic value. Specifically, most patients undergoing TAVI have symptoms related to heart failure and the patients who presented with dyspnoea have the worst diastolic function and the highest LV filling pressures, evidenced by largest left atrial (LA) volume and Doppler tissue imaging parameters.[10–13] Therefore, a comprehensive evaluation of changes of LV systolic and diastolic function after TAVI may add significant information regarding selection criteria for the procedure, follow-up, and prognosis.

The aims of this study were to evaluate in a large consecutive series of TAVI patients whether: (i) NYHA functional class before TAVI correlates with pre-operative LV diastolic dysfunction parameters; (ii) the improvement in NYHA functional class after TAVI depends on reduction of LV filling pressures and LV diastolic changes in patients both with normal or reduced LV systolic function; (iii) severe LV diastolic dysfunction at baseline precludes NYHA functional class improvement after TAVI; (iv) LV diastolic function in cases with normal or depressed LV systolic function impacts on prognosis.

Methods

Study population

This study prospectively recruited 358 patients with symptomatic severe AS who were referred for TAVI at Centro Cardiologico Monzino IRCCS (Milan, Italy). All patients had a NYHA functional class $\geq$II. Severe AS was defined as an aortic valve area (AVA) <1 cm^2 (or indexed 0.6 cm^2/m^2), a peak velocity >4 m/s, and a mean transaortic pressure gradient ≥ 40 mmHg.[14,15] All patients were considered at high operative risk or had contraindications for conventional surgical aortic valve replacement. Before the procedure, a detailed clinical evaluation included the assessment of operative risk based on the logistic EuroSCORE and identification of associated co-morbidities and physical frailty.

Invasive angiography or multi-detector computed tomography of the coronary/aorto-ilio-femoral arterial systems was performed in all patients. The indication for TAVI was evaluated by a multidisciplinary team approach. The 23-mm, 26-mm, or 29-mm Edwards Sapien or Sapien-XT transcatheter aortic valve prosthesis (Edwards Lifesciences, Inc., Irvine, CA, USA) was used in all cases and was implanted using either the transfemoral or transapical approach. The selection of the prosthesis size relies on the aortic annulus evaluation by transthoracic echocardiography (TTE), intra-operative transoesophageal echocardiography, and computed tomography. Patients who had other concomitant valvular disease of moderate or severe grade or atrial fibrillation or in whom LV diastolic function evaluation was not feasible were excluded.

The study was approved by the institutional ethics committee.

Echocardiography

Comprehensive TTE [M-mode, 2-dimensional (2D) and Doppler] was performed using commercially available equipment (iE33, Philips Medical System, Andover, MA, USA, or Vivid-7 or E9, GE Healthcare, Horten, Norway), prior to and after the procedure and at 6 and 12 months follow-up.

The 2D LV end-diastolic and end-systolic volumes indexed to body surface area were obtained from the apical view. The 2D LVEF was derived from the biplane Simpson method. Similarly, LA volume was measured using the biplane Simpson method.[16] Maximal aortic jet velocity was recorded from the apical, right parasternal, or suprasternal window that yielded the highest velocity signal. Peak and mean transaortic pressure gradients were measured using continuous-wave Doppler signal, and AVA was estimated pre- and post-implantation by the continuity equation, as described in the guidelines of the American Society of Echocardiography.[14,15] After the procedure, the presence of paravalvular and/or transvalvular aortic regurgitation was classified as trivial, mild, moderate, or severe.[17]

LV diastolic function was assessed using both conventional and novel diastolic parameters at each stage.[18] Transmitral LV filling velocities at the tips of the mitral valve leaflets were obtained from the apical four-chamber view using pulse-wave Doppler echocardiography. From the transmitral LV filling signal, the following variables were obtained: peak early (E) and late (A) transmitral velocities, *E/A* ratio, and E-wave deceleration time (DT). Tissue Doppler-derived early diastolic velocities (e') were recorded at the medial and lateral mitral annulus, and values were expressed as mean. The dimensionless index of E/e' was then calculated. In addition, pulmonary artery systolic pressure was measured according to previous studies.[19]

Grading diastolic dysfunction

LV diastolic dysfunction was graded as mild or Grade I (impaired relaxation pattern), moderate or Grade II (pseudonormal pattern), and severe (restrictive filling) or Grade III.[18] Criteria for the grading severity were (i) Grade I: mild diastolic dysfunction, *E/A* ratio <0.8, DT $>$ 200 ms, predominant systolic flow is seen in pulmonary venous flow, mean annular e' <8 cm/sec and E/e' ratio <8; (ii) Grade II: moderate diastolic dysfunction, mitral *E/A* ratio 0.8–1.5; E/e' ratio 9–12, $e' < 8$ cm/s, and systolic/diastolic flow ratio is <1; Grade II diastolic dysfunction represents impaired myocardial relaxation with mild to moderate elevation of LV filling pressures; (iii) Grade III, severe diastolic dysfunction, restrictive LV filling occurs, mitral *E/A* ratio >2, DT $<$ 160 ms, and average E/e' ratio $>$ 13 (or septal $E/e' > 15$ and lateral $E/e' > 12$).

Moreover, LA volume is increased in Grades II and III of diastolic dysfunction and, in the absence of pulmonary disease, increase in pulmonary artery pressure may be used to infer the presence of elevated LV filling.

Statistical analysis

Continuous data are presented as mean $\pm$ SD and categorical variables as frequencies (percentages), as appropriate. Differences between patients with LVEF $<$ 50% and those with LVEF $\geq$ 50% were assessed with unpaired Student's *t*-test or Mann-Whitney *U*-test for continuous variables, and with χ^2 test or Fischer's exact test for categorical variables, as appropriate. One-way ANOVA for repeated measures or Friedman test was used to analyse the repeated continuous data, and *post hoc* analysis for significant results was performed using the Bonferroni correction. Two-way ANOVA for repeated measures was used to analyse differences over time between patients with LVEF $<$ 50% and those with LVEF $\geq$ 50%. Survival was evaluated using the Kaplan–Meier analysis, and the log-rank test was used to test the differences between groups. A *P*-value <0.05 was considered statistically significant. All statistical analyses were performed using SPSS 20 (SPSS Inc., Chicago, IL, USA).

Results

A total of 358 patients underwent successful TAVI between March 2008 and February 2013. All patients received an Edwards SAPIEN valve via the transfemoral (73%) or the transapical approach (27%).

Complete follow-up data at both 6 and 12 months were available for 227 patients. Specifically, 15 patients did not have the echocardiographic examination at 6 months, 16 patients missed the

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12 months examination, and 37 patients were completely lost at follow-up. At 12 months, 48 patients (13.4%) had died including 14 patients (3.9%) who died within the 30 days after TAVI and 34 patients (9.5%) who died during the follow-up period (*Figure 1*).

Baseline clinical and echocardiographic findings

Of the total population, 96 patients (27%) had LV systolic dysfunction, defined as an LVEF < 50%, and the remaining patients (n = 262, 73%) had an LVEF ≥ 50% before TAVI. *Table 1* provides baseline clinical data according to LVEF. Compared with patients with LVEF ≥ 50%, patients with LV systolic dysfunction were more likely to be male, with lower body mass index, and more frequently had a history of coronary artery disease, previous myocardial infarction, percutaneous coronary intervention, atrial fibrillation, dyspnoea, and chronic renal dysfunction. Moreover, patients with baseline LVEF < 50% had a significantly higher logistic EuroSCORE and a greater proportion of patients in NYHA functional class III/IV.

Baseline echocardiographic characteristics of the study population stratified according to baseline LVEF are shown in *Table 2*. Patients with impaired LVEF had larger LV and LA volumes and greater LV mass index compared with their counterparts. Mean and peak aortic pressure gradient were lower, and AVA was smaller in patients with reduced LVEF compared with patients with LVEF ≥ 50%. A higher grade of diastolic dysfunction was found in patients with impaired baseline LVEF (LVEF < 50%: Grade II, 50.0%; Grade III, 50.0%; LVEF ≥ 50%: Grade I, 12.9%; Grade II, 70.8%; Grade III, 16.3%; P < 0.001).

NYHA class changes and echocardiographic outcomes

Figure 2 shows changes in the NYHA functional class and LV diastolic dysfunction grade over time in patients with LVEF < 50% and those with LVEF ≥ 50%. A significant improvement in the functional status was observed at 6 and 12 months in both groups together with a marked reduction in the degree of LV diastolic dysfunction. At 12 months follow-up, only few patients remained in LV diastolic dysfunction Grade III and in NYHA functional class III or IV.

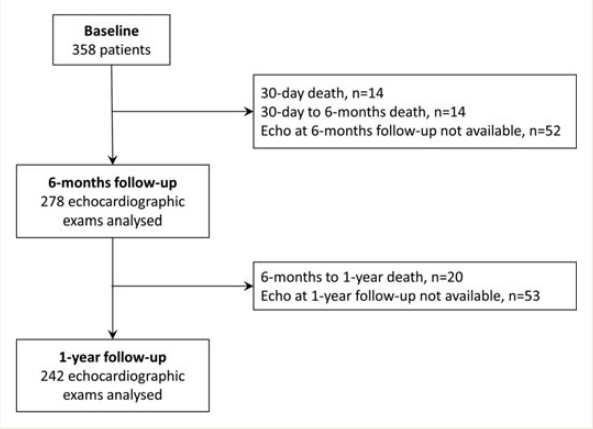

Figure 1 Echocardiographic exams at follow-up. Flow chart of the serial echocardiographic exams evaluated.

At 6 and 12 months after TAVI, an improvement in LVEF was observed together with a significant reduction of LV end-systolic volume and LV mass index both in patients with and without LV systolic dysfunction at baseline. Regardless of baseline LV systolic dysfunction, a trend towards a normalization of LV diastolic parameters together with a reduction in LA volume was observed at 6 and 12 months after TAVI (*Table 3*). An example of a patient with a significant improvement in LV diastolic function after TAVI is displayed in *Figure 3*. The most remarkable percentage changes (normalized to baseline value) were observed for A wave (LVEF < 50%: 35 and 37% at 6 and 12 months; LVEF ≥ 50%: 16 and 18%), DT (LVEF < 50%: 36 and 42%; LVEF ≥ 50%: 14 and 17%), e′ (LVEF < 50%: 27 and 32%; LVEF ≥ 50%: 21 and 23%), *E*/e′ ratio (LVEF < 50%: 18 and 25%; LVEF ≥ 50%: 5 and 5%), and LA volume (LVEF < 50%: 8 and 12%; LVEF ≥ 50%: 7 and 10%).

Focusing on LV diastolic parameters, on two-way ANOVA for repeated measures, *P*-values for the between-subjects effects clearly confirm that LA volume, E wave, A wave, *E*/*A* ratio, and *E*/e′ ratio were not influenced by baseline LV systolic function. Furthermore, *P*-values within-subjects effects (interaction between variable and group) show that both groups had similar changes over time for LA volume, A wave, and e′ (*Table 3*).

Moreover, we did not find a correlation between paravalvular regurgitation ≥2 and the diastolic dysfunction grade at follow-up.

Impact on survival

The causes of death during follow-up are detailed in *Table 4*. A similar proportion of patients with LV systolic dysfunction died at 30 days, 6, and 12 months compared with those without LV systolic dysfunction. There were no differences in causes of death between patients with LVEF < 50% and those with LVEF ≥ 50%.

Kaplan–Meier survival curves up to 12 months follow-up are shown in *Figure 4* according to LV systolic and diastolic dysfunction at baseline. Mortality rates were similar in patients with LV diastolic dysfunction ≥II and LV systolic dysfunction (no cases with systolic dysfunction and diastolic dysfunction <II were present in the study) and in patients with or without diastolic dysfunction ≥II and LVEF ≥ 50%.

A separate analysis of Kaplan–Meier survival curves according to patients with or without 1-year improvement of diastolic dysfunction is shown in *Figure 5*. In cases with baseline diastolic dysfunction grade = 2, no differences were found according to improvement in the diastolic dysfunction, in contrast a better survival was found in patients with baseline diastolic dysfunction grade = 3 which were found to improve at 1 year.

Discussion

The main findings of this study are that (i) NYHA functional class is associated with LV diastolic dysfunction at baseline in TAVI patients; (ii) TAVI results in significant improvement of LV systolic and diastolic function, reduces the LV filling pressures, and produces beneficial effects on clinical status at the follow-up; (iii) independently on baseline LV systolic function, severe LV diastolic dysfunction at baseline did not preclude NYHA functional class improvement after TAVI;

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Table 1 Baseline clinical characteristics of the overall population and comparison between patients with a baseline EF < 50% and those with EF ≥ 50%

Variables	All patients (n = 358)	LVEF < 50% (n = 96)	LVEF > 50% (n = 262)	P
Age (years)	81 ± 6	81 ± 6	81 ± 6	0.941
Male	118 (33.0%)	45 (46.9%)	73 (27.9%)	0.001
Body surface area (m^2)	1.7 ± 0.2	1.7 ± 0.2	1.7 ± 0.2	0.505
Body mass index (kg/m^2)	25.4 ± 4.7	24.4 ± 3.6	25.8 ± 5.0	0.003
Log EuroSCORE	20.5 ± 11.6	27.5 ± 14.2	18.0 ± 9.3	<0.001
NYHA functional class				
I–II	73 (20.4%)	6 (6.2%)	67 (25.6%)	<0.001
III–IV	285 (79.6%)	90 (93.8%)	195 (74.4%)	
Diabetes mellitus	89 (24.9%)	32 (33.3%)	57 (21.8%)	0.025
Dyslipidaemia	212 (59.6%)	56 (58.3%)	156 (60.0%)	0.776
Hypertension	313 (87.4%)	82 (85.4%)	231 (88.2%)	0.487
Current smoking	95 (27.6%)	38 (40.4%)	57 (22.8%)	0.001
Coronary artery disease	194 (54.2%)	65 (67.7%)	129 (49.2%)	0.002
Previous myocardial infarction	64 (17.9%)	34 (35.4%)	30 (11.5%)	<0.001
Previous PCI	89 (24.9%)	35 (36.5%)	54 (20.6%)	0.002
Previous CABG	51 (14.2%)	19 (19.8%)	32 (12.2%)	0.069
Peripheral vascular disease	162 (45.3%)	35 (36.5%)	127 (48.5%)	0.043
Heart rhythm				
Sinus rhythm	292 (81.6%)	69 (71.9%)	223 (85.1%)	0.004
Atrial fibrillation	64 (17.9%)	27 (28.1%)	37 (14.1%)	0.002
Pacemaker	39 (10.9%)	13 (13.5%)	26 (9.9%)	0.330
Angina	120 (33.5%)	28 (29.2%)	92 (35.1%)	0.291
Dyspnoea	331 (92.5%)	94 (97.9%)	237 (90.5%)	0.018
Syncope	71 (19.8%)	14 (14.6%)	57 (21.8%)	0.132
COPD	101 (28.2%)	31 (32.3%)	70 (26.7%)	0.299
eGFR (mL/min)	49.2 ± 21.7	42.7 ± 19.1	51.6 ± 22.2	0.001
eGFR < 60 mL/min	262 (73.4%)	82 (85.4%)	180 (69.0%)	0.002
Treatment				
β-Blockers	159 (45.3%)	52 (55.3%)	107 (41.6%)	0.023
ACEi/ARB	215 (61.3%)	50 (53.2%)	165 (64.2%)	0.061
Diuretics	271 (77.2%)	88 (93.6%)	183 (71.2%)	<0.001
Spironolactone	83 (23.6%)	35 (37.2%)	48 (18.7%)	<0.001
Calcium antagonists	85 (24.2%)	11 (11.7%)	74 (28.8%)	0.001
Statins	136 (38.7%)	38 (40.4%)	98 (38.1%)	0.696
Anticoagulants	63 (17.9%)	28 (29.8%)	35 (13.6%)	<0.001

PCI, percutaneous coronary intervention, CABG, coronary artery bypass graft surgery; COPD, chronic obstructive pulmonary disease; eGFR, estimated glomerular filtration rate; ACEi, angiotensin-converting enzyme inhibitors; ARB, angiotensin II receptor blockers.

(iv) prognosis at 1 year after TAVI is similar in patients with severe LV diastolic dysfunction and impaired LV systolic function and in patients without severe LV systolic or diastolic dysfunction at baseline.

Cardiac haemodynamics have been extensively studied in patients with AS.[10–12] AS correction affects LV hypertrophy and LV function to different extents. While LV hypertrophy regression and LV diastolic function normalization may take years after surgical aortic valve replacement,[20] few studies suggest an early LV remodelling after TAVI.[6,8] This, in conjunction with favourable haemodynamics, may explain the improvement of health-related quality of life after TAVI. However, the impact of TAVI on LV systolic and diastolic function is still scarcely investigated, and the understanding of these mechanisms is crucial for indication to TAVI, patients selection, and prognosis.

Previous studies on TAVI haemodynamics focused more on LV systolic function. Patients with severe LV systolic dysfunction showed significant improvement in LVEF after TAVI.[7,21,22] However, the rate and extent of post-operative changes in LVEF are largely variable and have not yet been entirely defined. LV function may display substantial changes in the immediate post-operative period due to acute decrease of afterload and also intermediate and long-term changes related to several chronic adaptations including regression of LV hypertrophy and increase in myocardial blood flow.[21,22] This latter mechanism has been also described in the immediate

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Table 2 Baseline echocardiographic characteristics

Variables	All patients ($n = 358$)	LVEF < 50% ($n = 96$)	LVEF > 50% ($n = 262$)	P
LVEDV index (mL/m^2)	59 ± 21	80 ± 24	51 ± 14	<0.001
LVESV index (mL/m^2)	28 ± 17	49 ± 18	20 ± 8	<0.001
LVEF (%)	56.1 ± 12.3	39.2 ± 6.7	62.3 ± 7.0	<0.001
LV mass index (g/m^2)	150 ± 41	170 ± 41	143 ± 38	<0.001
Left atrial volume index (mL/m^2)	57 ± 25	65 ± 21	55 ± 26	<0.001
AVA (cm^2)	0.64 ± 0.15	0.60 ± 0.16	0.65 ± 0.15	0.007
AVA index (cm^2/m^2)	0.38 ± 0.09	0.36 ± 0.09	0.39 ± 0.09	0.003
Mean aortic pressure gradient (mmHg)	51 ± 15	43 ± 15	54 ± 14	<0.001
Peak aortic pressure gradient (mmHg)	83 ± 22	71 ± 24	88 ± 20	<0.001
IVST (mm)	14 ± 2	13 ± 2	14 ± 2	0.006
PWT (mm)	12 ± 2	12 ± 2	12 ± 2	0.090
PASP (mmHg)	42 ± 11	46 ± 11	40 ± 11	<0.001
E (cm/s)	98 ± 33	101 ± 36	96 ± 32	0.200
A (cm/s)	100 ± 32	84 ± 36	105 ± 30	<0.001
E/*A* ratio	1.1 ± 0.6	1.4 ± 0.9	1.0 ± 0.5	0.002
e′ (cm/s)	5.3 ± 1.6	4.8 ± 1.5	5.5 ± 1.7	0.001
E/e′ ratio	19 ± 7	22 ± 8	18 ± 6	<0.001
Deceleration time (ms)	240 ± 81	202 ± 82	253 ± 77	<0.001

LV, left ventricular; EDV, end-diastolic volume; ESV, end-systolic volume; EF, ejection fraction; AVA, aortic valve area; IVST, interventricular septum thickness; PWT, posterior wall thickness; PASP, pulmonary artery systolic pressure.

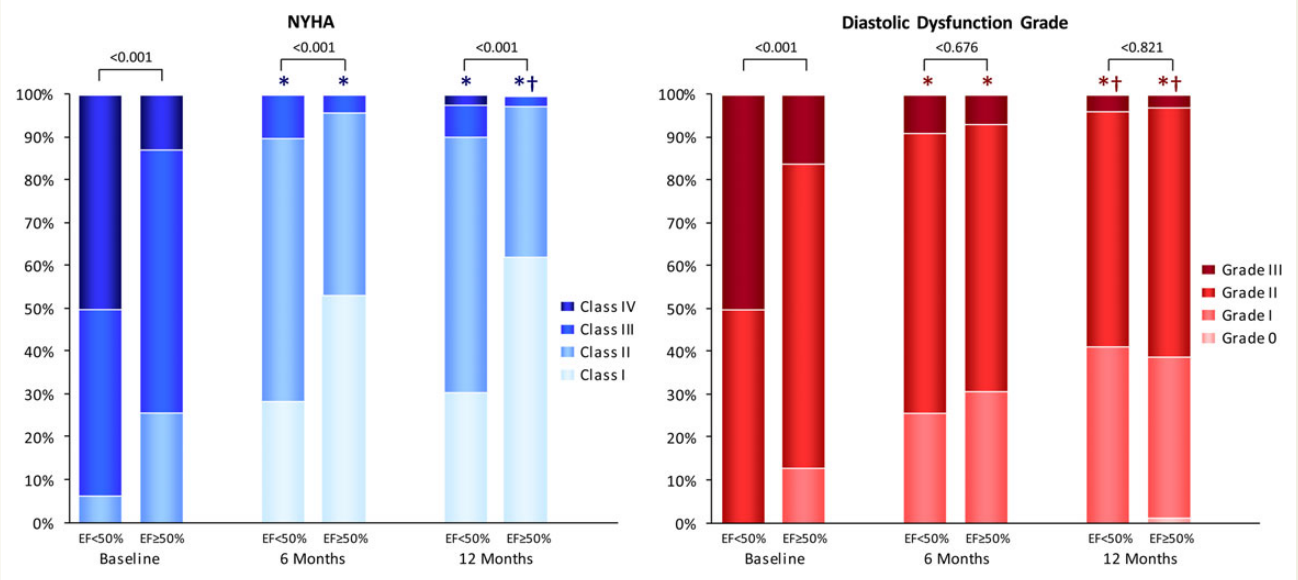

Figure 2 Comparison of New York Heart Association (NYHA) functional class (left) and of diastolic dysfunction grade (right) assessed at baseline, 6, and 12 months after transchateter aortic valve implantation for patients with EF < 50% and patients with EF ≥ 50%. *$P < 0.01$ vs. baseline in each group; †$P < 0.01$ vs. 6 months in each group.

post-operative phases of surgical aortic valve replacement and TAVI, as related to decrease in haemodynamic load, increase in diastolic myocardial perfusion, in systolic component of coronary flow and in sub-endocardial perfusion.[23] All these mechanisms may also significantly affect LV diastolic function and LV filling pressures.

In this study, we confirmed that in patients with LV systolic dysfunction, LVEF markedly improved after TAVI (from 38 to 51%) and remained stable in patients with normal LVEF at baseline. Moreover, to determine the effects of TAVI on LV systolic and diastolic function in the mid- and long-term follow-up of a large group of

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Table 3 Comparison of echocardiographic parameters at baseline, 6, and 12 months after TAVI for patients with EF < 50% and those with EF ≥ 50%

Variables	LVEF < 50% ($n = 57$)				LVEF > 50% ($n = 170$)				Two-way ANOVA for repeated measures	
	Baseline	6 months	12 months	P_1-v alue	Baseline	6 months	12 months	P_1-value	P_2-value	P_3-value
LVEDV index (mL/m^2)	79 ± 24	74 ± 23	70 ± 21*	0.005	52 ± 13	53 ± 14	52 ± 14	0.282	<0.001	<0.001
LVESV index (mL/m^2)	49 ± 19	38 ± 19*	36 ± 18*	<0.001	20 ± 8	20 ± 8	19 ± 8	0.413	<0.001	<0.001
LVEF (%)	38.7 ± 7.0	50.1 ± 9.9*	51.7 ± 11.9*	<0.001	62.6 ± 7.2	63.3 ± 6.9	64.4 ± 7.4*	0.015	<0.001	<0.001
LV mass index (g/m^2)	170 ± 44	145 ± 37*	143 ± 35*	<0.001	142 ± 35	124 ± 33*	119 ± 36*	<0.001	<0.001	0.652
Left atrial volume index (mL/m^2)	63 ± 21	56 ± 18*	54 ± 18*	<0.001	55 ± 29	50 ± 25*	49 ± 25*	<0.001	0.078	0.100
AVA (cm^2)	0.61 ± 0.15	1.82 ± 0.36*	1.79 ± 0.30*	<0.001	0.65 ± 0.15	1.83 ± 0.35*	1.82 ± 0.36*	<0.001	0.434	0.752
AVA index (cm^2/m^2)	0.36 ± 0.09	1.08 ± 0.20*	1.08 ± 0.20*	<0.001	0.39 ± 0.09	1.08 ± 0.20*	1.08 ± 0.20*	<0.001	0.334	0.830
Mean aortic pressure gradient (mmHg)	42 ± 15	11 ± 4*	11 ± 4*	<0.001	53 ± 13	12 ± 4*	13 ± 5*,†	<0.001	<0.001	<0.001
Peak aortic pressure gradient (mmHg)	69 ± 25	20 ± 7*	21 ± 7*,†	<0.001	87 ± 20	22 ± 7*	23 ± 8*,†	<0.001	<0.001	<0.001
IVST (mm)	13 ± 2	12 ± 2*	12 ± 2*	<0.001	14 ± 2	12 ± 2*	12 ± 2*	<0.001	0.151	0.026
PWT (mm)	11 ± 2	10 ± 2*	11 ± 2	0.004	12 ± 2	11 ± 2*	11 ± 2*	<0.001	0.221	0.003
PASP (mmHg)	46 ± 10	39 ± 11*	37 ± 11*	<0.001	40 ± 10	35 ± 8*	34 ± 9*	<0.001	<0.001	0.119
E (cm/s)	97 ± 36	90 ± 35	89 ± 41	0.128	94 ± 29	98 ± 28	97 ± 26	0.055	0.336	0.007
A (cm/s)	94 ± 36	114 ± 28*	114 ± 25*	<0.001	104 ± 30	114 ± 30*	117 ± 28*	<0.001	0.341	0.127
E/*A* ratio	1.1 ± 0.8	0.7 ± 0.3*	0.7 ± 0.2*	0.004	1.0 ± 0.5	0.9 ± 0.4	0.8 ± 0.3*	0.011	0.382	0.004
e′ (cm/s)	4.6 ± 1.3	5.7 ± 1.7*	5.9 ± 1.4*	<0.001	5.5 ± 1.7	6.3 ± 1.6*	6.4 ± 1.6*	<0.001	0.002	0.598
E/e′ ratio	21 ± 7	15 ± 5*	15 ± 6*	<0.001	18 ± 6	16 ± 5*	16 ± 5*	<0.001	0.408	<0.001
Deceleration time (ms)	202 ± 85	248 ± 73*	263 ± 82*	<0.001	255 ± 77	268 ± 64	277 ± 65*	0.006	0.001	0.024
Paravalvular regurgitation grade				0.655				0.102	0.254	0.366
<2		46 (80.7%)	45 (78.9%)			144 (84.7%)	140 (82.4%)			
≥2		11 (19.3%)	12 (21.1%)			26 (15.3%)	30 (17.6%)			

LV, left ventricular; EDV, end-diastolic volume; ESV, end-systolic volume; EF, ejection fraction; AVA, aortic valve area; IVST, interventricular septum thickness; PWT, posterior wall thickness; PASP, pulmonary artery systolic pressure.
P_1-value, one-way ANOVA for repeated measures; *$P < 0.05$, vs. baseline; †$P < 0.05$, vs. 6 months.
P_2-value, between-subjects effects on two-way ANOVA for repeated measures.
P_3-value, within-subjects effects (interaction between variable and group) on two-way ANOVA for repeated measures.

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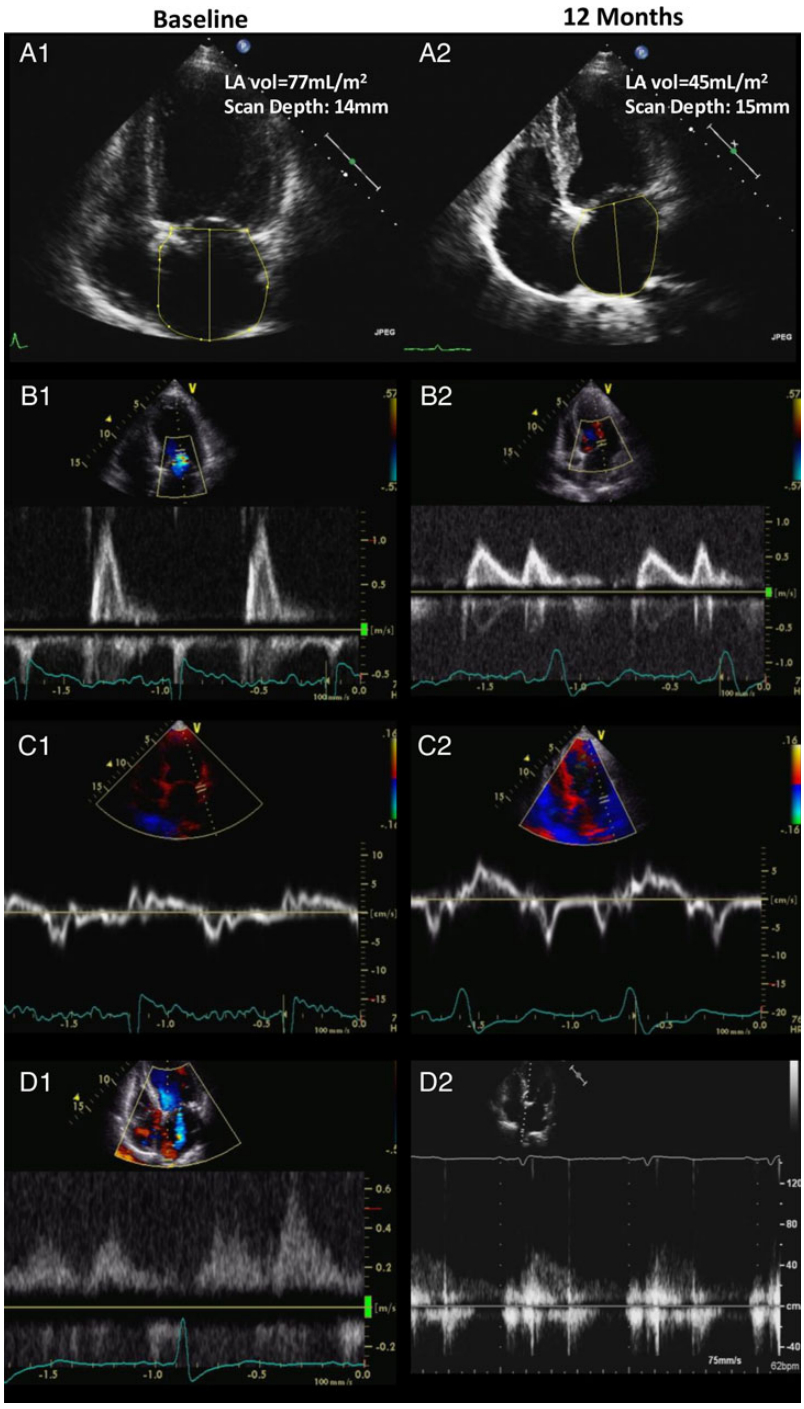

Figure 3 Example of non-invasive haemodynamic improvement after TAVI. Changes after TAVI at 12 months in atrial volume (*A*1, *A*2), transmitral flow Doppler (*B*1, *B*2), mitral annular tissue Doppler imaging (*C*1, *C*2), and pulmonary vein flow Doppler (*D*1, *D*2) showing improvement of diastolic dysfunction grade.

symptomatic severe AS patients at high surgical risk, we evaluated several echocardiographic and Doppler parameters showing that improvement of symptoms in the follow-up was clearly correlated to changes in diastolic function and reduction of LV filling pressures independently on LV systolic dysfunction at baseline. Few studies investigated LV diastolic function after TAVI.[8,9] In our study, changes in diastolic dysfunction and LV filling pressures were assessed by comprehensive echocardiographic and Doppler parameters. In detail, the improvement of LV diastolic dysfunction and LV filling pressures was associated with LV reverse remodelling (reduction in LV

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Table 4 Causes of death during follow-up

	All patients ($n = 358$)	LVEF < 50% ($n = 96$)	LVEF > 50% ($n = 262$)	P
Intraprocedural mortality	6 (1.7%)	1 (1.0%)	5 (1.9%)	0.571
30-day mortality	14 (4.0%)	3 (3.1%)	11 (3.9%)	0.643
Death from any causes	2 (0.6%)	0 (0.0%)	2 (0.8%)	
Death from cardiovascular causes[a]	12 (3.4%)	3 (3.1%)	9 (3.4%)	
Death from stroke	0 (0.0%)	0 (0.0%)	0 (0.0%)	
6-month mortality	28 (7.8%)	8 (8.3%)	20 (7.6%)	0.827
Death from any causes	19 (5.3%)	7 (7.3%)	12 (4.6%)	
Death from cardiovascular causes[a]	26 (7.3%)	6 (6.2%)	20 (7.6%)	
Death from stroke	3 (0.8%)	1 (1.0%)	2 (0.8%)	
1-year mortality	48 (13.4%)	14 (14.6%)	34 (13.0%)	0.702
Death from any causes	19 (5.3%)	7 (7.3%)	12 (4.6%)	
Death from cardiovascular causes[a]	26 (7.3%)	6 (6.2%)	20 (7.6%)	
Death from stroke	3 (0.8%)	1 (1.0%)	2 (0.8%)	

[a]Deaths from unknown causes were assumed to be deaths from cardiovascular causes.

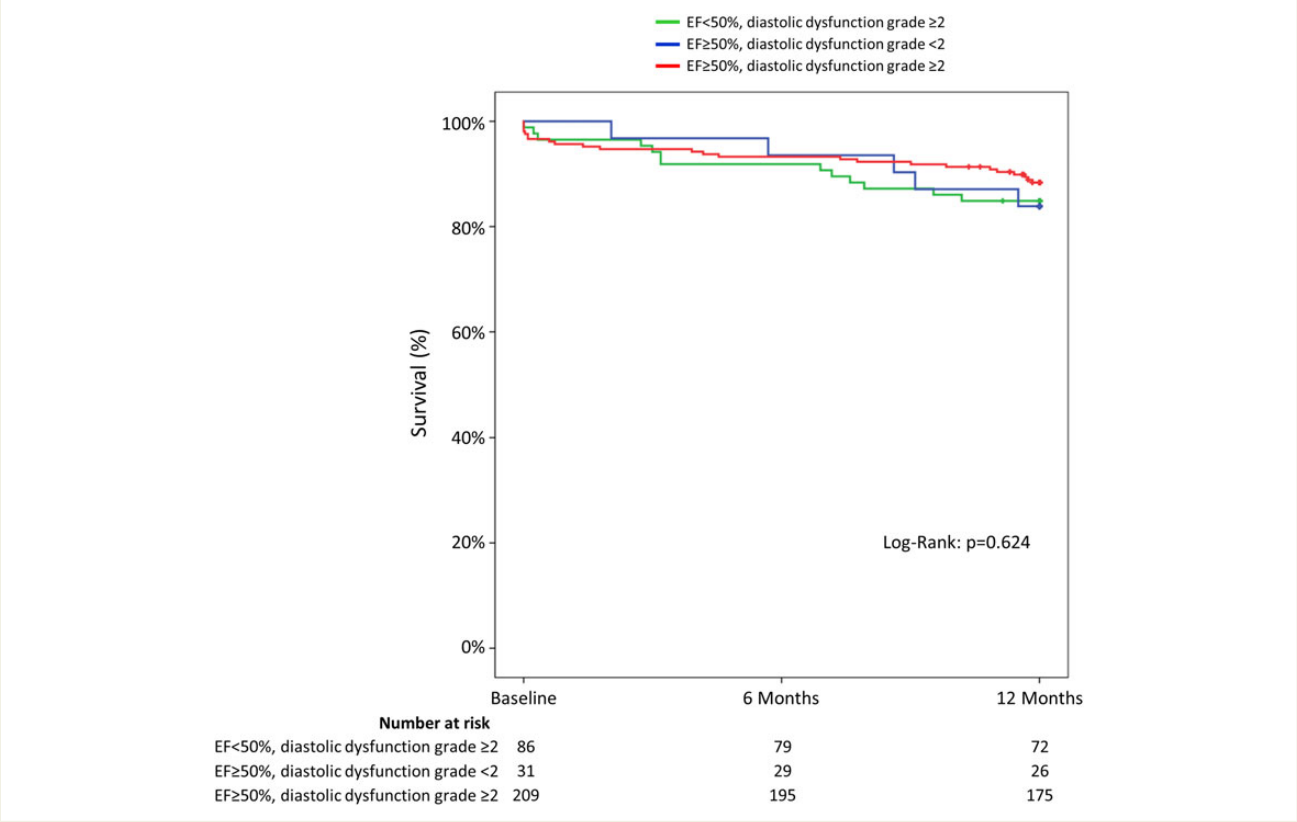

Figure 4 Freedom from all cause of mortality at 1-year follow-up. Kaplan–Meier curves of survival according to the left ventricular ejection fraction and to the grade of diastolic dysfunction at baseline.

volumes and mass), LA reverse remodelling (reduction in LA volumes), and reduction of pulmonary artery systolic pressure. As the severity of LV diastolic function, particularly when it leads to elevated LV filling pressures, has been shown to correlate with symptoms of dyspnoea in AS patients,[10] the current study further demonstrated that improvement in functional status after TAVI is associated with improvement in LV diastolic dysfunction. Accordingly, at 12 months, few patients remained with severe LV diastolic

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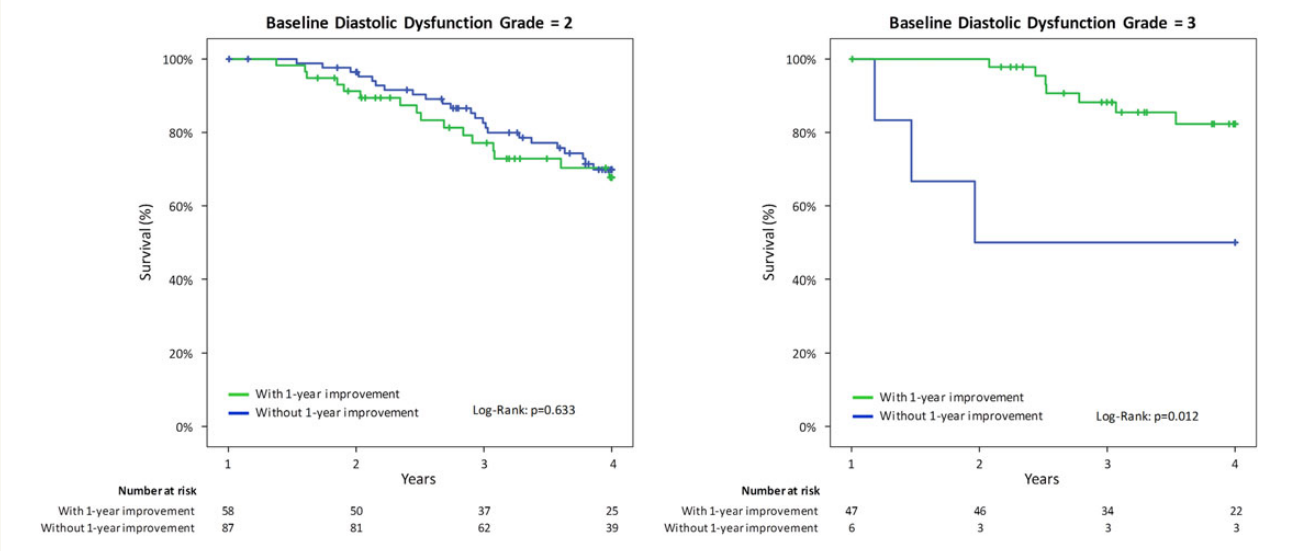

Figure 5 Survival Kaplan–Meier curves for baseline diastolic dysfunction Grade 2 (left panel) and 3 (right panel) stratified by patients with and without 1-year improvement in diastolic dysfunction grade.

dysfunction and in NYHA functional Class III or IV. Therefore, even the presence of severe LV diastolic dysfunction at baseline does not preclude marked functional improvement after TAVI, and this observation is not related to the co-existence of LV systolic dysfunction. These results may impact on selection criteria for TAVI and demonstrates the importance of this procedure also in advanced symptomatic AS cases.

Park *et al.*[11] studied a characteristic intra-cardiac haemodynamic profile for each presenting symptoms (syncope, dyspnoea, and chest pain) in patients with severe AS, despite a similar AVA and aortic valve mean pressure gradient. In our patients with severe AS, larger LA volume, lower cardiac output, lower stroke volume index, and higher E/e' ratio were independent determinants of the presence of symptoms (NYHA Class III/IV). The patients who presented with dyspnoea had the worst LV diastolic function and the highest filling pressure, evidenced by largest LA volume, lowest e', highest E wave, and highest E/e' ratio. In our study, the large majority of cases (80%) was in NYHA functional Class III or IV and had LV diastolic dysfunction, high LV filling pressures, evidenced by large LA volume, low e', high E wave, and high E/e' ratio in agreement with the study by Park and colleagues.[11] Thus, the baseline clinical and echo-Doppler characteristics of our patients represent the typical advanced haemodynamic scenario in this pathology leading to severe heart failure.

For many elderly patients, morbidity may be a greater concern than mortality. A marked and durable improvement in functional class and quality of life after TAVI has been well documented. The randomized PARTNER trials documented a marked reduction in re-hospitalization with transfemoral TAVI compared with medical management[24] and, in comparison with surgery, a significantly shorter length of stay as well as earlier improvement in functional status.[2] Our data not only show the link between functional status and LV systolic and diastolic function after TAVI, but also demonstrate that the co-existence of severe LV diastolic and systolic dysfunction has not a significant impact on 1-year mortality after TAVI. In fact, mortality was similar in cases with LV diastolic dysfunction $\geq$II associated with LV systolic dysfunction (no cases with systolic dysfunction and diastolic dysfunction $<$II were present in the study) and in cases with or without diastolic dysfunction $\geq$II, independently on LVEF $<$ or $\geq$50%. Therefore, TAVI may be largely beneficial in patients with advanced systolic and diastolic dysfunction and NYHA III and IV without a prohibitive procedural risk or 1-year mortality.

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