

# Impact of transcatheter aortic valve implantation in patients with reduced ejection fraction

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## Abstract

**Background:** Aortic stenosis increases with age. According to guidelines, left ventricular systolic dysfunction is an indication for aortic valve replacement, even in asymptomatic patients. There is no clear data on the application of transcatheter aortic valve implantation (TAVI), which is a method showing continuous improvement in recent years, in patients with reduced ejection fraction (REF) having a poor prognosis for surgical aortic valve replacement. We therefore aimed to investigate the effect of TAVI on left ventricular ejection fraction (LVEF) and also its efficacy and safety in patients with REF.

**Methods and results:** The study included 104 patients who underwent transfemoral TAVI in our clinic. The patients were divided into two groups: LVEF ≤ 45% (REF group, n = 28) and LVEF > 45% (preserved ejection fraction [PEF] group, n = 76). Follow-up measurements were performed at baseline, discharge, 1<sup>st</sup>, 6<sup>th</sup> and 12<sup>th</sup> months. No statistical difference was found between the groups with respect to complications and mortality rates. A statistically significant difference was detected in LVEF after TAVI, either in all patients (53.9 ± 14.6, 57.0 ± 11.4, 59.4 ± 8.4, 60.4 ± 6.8, 63.2 ± 3.9, respectively, at baseline, discharge, 1<sup>st</sup>, 6<sup>th</sup> and 12<sup>th</sup> months, p < 0.001) or in the groups separately. A statistically significant increase in LVEF (p < 0.001) was determined at discharge, 1<sup>st</sup>, 6<sup>th</sup> and 12<sup>th</sup> months, whereas LVEF increased in all follow-ups of the PEF group, however this elevation reached a statistical significance only at the 1<sup>st</sup> month (p = 0.04).

**Conclusions:** Our study has shown the positive effect of TAVI on LVEF and its effective and safe applicability in patients with REF. (Cardiol J 2015; 22, 1: 108–114)

**Key words:** transcatheter aortic valve implantation, reduced ejection fraction, heart failure

## Introduction

Severe aortic stenosis (AS) is a common valvular heart disease that leads to a high morbidity and mortality rate. Aortic valve replacement (AVR)

is recommended in patients with severe AS that are symptomatic or asymptomatic accompanied by left ventricular ejection fraction (LVEF) < 50% [1]. Surgical replacement of the narrowed aortic valve (s-AVR) is performed with a low operative morta-

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Received: 31.03.2014 Accepted: 17.04.2014

lity rate in the absence of severe co-morbid conditions. Patients given s-AVR show both improved symptoms and prolonged survival. Nevertheless, s-AVR cannot be applied in 30% of patients because of left ventricular dysfunction, advanced age, or co-morbid conditions [2, 3]. Since s-AVR shows a high pre-operative risk, a conservative approach is preferred in patients with LVEF (reduced ejection fraction [REF]). S-AVR is also associated with operative mortality in patients with severe AS and REF [4, 5]. Transcatheter aortic valve implantation (TAVI) is an effective method for patients with severe AS that present a higher surgical risk or who cannot undergo s-AVR [6, 7]. Some studies have shown an improved effect of TAVI on LVEF [8]. However, the efficacy and safety of TAVI in patients with REF is not clearly proven. Consequently, guidelines accept LVEF < 20% as a relative contraindication for TAVI [1]. We have also aimed in our study to investigate the effect of TAVI on left ventricular function in addition to its applicability, efficacy, and safety in patients with REF.

## Methods

Between July 2011 and July 2013, 104 patients who were inoperable or at high risk for s-AVR due to severe calcified AS and co-morbid conditions were selected for TAVI in our clinic. The patients were divided into two groups, the group with preserved LVEF (PEF) and the group with reduced LVEF (REF). The REF group included a total of 28 patients. Five patients in the REF group were in the low-flow/low-gradient class (mean gradient < 40 mm Hg). The diagnosis of severe AS was confirmed following dobutamine stress echocardiography (DSE) performed with these patients. Transthoracic echocardiography (TTE) Doppler and 2-dimensional images were obtained from parasternal long and short axis, apical 4-chamber, and subcostal 4-chamber images. TTE was reviewed to assess the pericardium, valvular anatomy and function, and cardiac function. All patients underwent multi-slice computed tomography and transesophageal echocardiography before the procedure. Valve morphology, aortic annulus, coronary ostium-annulus distance, calcification, suitability of peripheral arteries, and the possibility of an additional pathology were also analyzed. Echocardiography (Philips iE33) was performed prior to TAVI and at hospital discharge, 1<sup>st</sup>, 6<sup>th</sup> and 12<sup>th</sup> months follow-ups. Doppler echocardiographic measurements included left ventricular end-diastolic volume, where LVEF was calculated with the

Simpson method, transvalvular pressure gradient was determined by the Bernoulli formula, and aortic valve area was calculated by the continuity equation. All echocardiography parameters were evaluated according to guidelines of the American Society of Echocardiography [9]. Echocardiography evaluations were performed by a single author. This is our limitation but intra-observer variability was evaluated by performing re-measurements in 15 patients. Intra-observer variability was found to be 5.5% by echocardiographic measurements. Because of these patients have frailty we could not use the other methods for measurement of LVEF like magnetic resonance imaging or nuclear scintigraphy.

TAVI was performed through the subclavian artery, via a supra-aortic approach and by transfemoral access in 5, 1, and 98 patients, respectively. TAVI was performed under general anesthesia in 5 and 12 patients from the REF group and PEF group, respectively, while all other patients were given local anesthesia. A vascular closure device was used in 77 patients while surgical closure was used in the remaining patients. Patients were heparinized to achieve an activated clotting time of 250–300 s. TAVI was performed using Edwards Sapien XT (Edwards Lifesciences, Irvine, CA, USA) balloon-expandable prostheses. Three valve sizes of 23, 26, and 29 mm expanded diameter were available. As a result, the cardiac surgery team agreed to apply TAVI. All patients were informed before performing the procedure with the approval of the Ethics Committee of our hospital. Stable patients were discharged and follow-ups at the 1<sup>st</sup>, 6<sup>th</sup> and 12<sup>th</sup> months were planned. During the follow-ups, routine physical examinations, echocardiography and functional capacities were evaluated.

## Statistical analysis

All analyses were performed using SPSS Statistics Version 17.0. Continuous variables are presented as mean and standard deviation and were compared by means of a 2-sided Student's t-test. Categorical data are expressed as frequency (percentages) and compared using the  $\chi^2$  and Fisher's exact tests. Echocardiography data obtained at baseline, discharge, 1<sup>st</sup>, 6<sup>th</sup> and 12<sup>th</sup> months were compared by repeated measures ANOVA. Continuous variables were compared between patients before and after TAVI using the paired Student's t-test (for normally distributed variables) or the Wilcoxon test (for non-normally distributed variables). Significance was accepted as  $p < 0.05$ .

## Results

Of the 104 patients, 69 were female and their mean age was 78.2 years. Among the patients, 28 (26.9%) were in the REF group and the rest were in the PEF group. The mean valve area was 0.62 cm<sup>2</sup> and the average mean gradient was 52.5 mm Hg by echocardiography. Mean and maximal gradients were statistically significantly lower in the REF group (mean gradient values of REF and PEF groups were, respectively, 46.9 ± 13.7 and 54.6 ± 13.2, *p* = 0.01). Of the patients in the REF group, 64.2% had LVEF ≤ 35%. Also 4 of these patients had LVEF ≤ 20%. Of the patients with LVEF ≤ 35%, only 5 were in the low-flow/low-gradient class. DSE performed in these patients revealed contractile reserve.

The mean Society of Thoracic Surgeons (STS) score of the patients was 7.4 and the mean logistic EUROScore values of the moderate and high risk groups were, respectively, 22.7% and 90.3% according to the SURTAVI risk model. STS (*p* < 0.001) and logistic EUROScore (*p* = 0.002) were found to be statistically significantly higher in the REF group than the PEF group, as expected. Similarly, pulmonary artery systolic pressure was statistically significantly higher (*p* = 0.04) while LVEF was lower (*p* < 0.001) in the REF group. Although the REF group had a severe level of chronic obstructive pulmonary disease, no other difference was found between the groups with respect to basal characteristics (age, gender, body mass index, New York Heart Association [NYHA] functional class, prevalence of diabetes or arterial hypertension, history of prior myocardial infarction or stroke, previous coronary artery bypass grafting, or prevalence of atrial fibrillation). The basal characteristics of the patients and TAVI data are shown in Table 1.

TAVI could be performed with a 100% procedural success. However, a second valve was used in 2 patients due to lower localization in 1 patient and valve embolization in the ascending aorta. After the procedure, a total of 5 intra-hospital mortalities were encountered because of right ventricular rupture due to rapid pacing (in 2 patients), left ventricular rupture due to wire in the left ventricle, postoperative bleeding via supra-aortic approach and left main coronary artery obstruction due to aortic cusp calcification. All of these 5 intra-hospital mortalities were in the PEF group. The follow-ups of the patients revealed mortalities in 2, 4 and 5 patients at respectively the 1<sup>st</sup>, 6<sup>th</sup> and 12<sup>th</sup> months, resulting in a total of 16 (15.3%) mortalities. Mortality rates of both groups were similar.

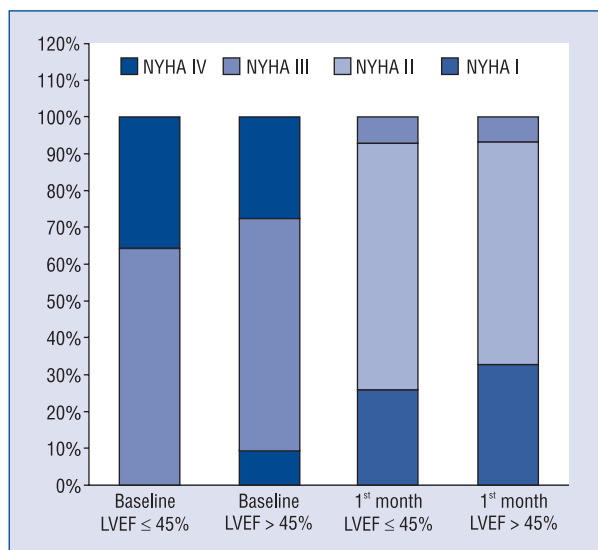
Echocardiographic follow-up was available for 95% and 85% of patients at discharge and at the 12<sup>th</sup> month, respectively. A statistically significant improvement was found in valve function (mean gradient, aortic valve area) at discharge and at follow-up after TAVI. Severe paravalvular aortic regurgitation developed in none of the patients after TAVI or in follow-ups. Both groups had similar rates of >+2 AR detected by TTE (15% vs. 24%, *p* = 0.29). There were no strokes in the hospital. Only 4 (3.8%) patients needed permanent pacemaker implantation because of atrioventricular block. Mean hospital stay was 7.3 ± 5.3 days and no difference was found between the groups (8.8 ± 7.1 days in the REF group, 6.8 ± 4.4 days in the PEF group; *p* = 0.09). At the follow-up, 92.8% and 92.9% of patients in the REF and PEF groups were found in class I and class II according to NYHA, respectively. An improvement in functional capacity proceeded during the 1<sup>st</sup> month follow-up (Fig. 1). No difference was found between the groups with respect to complications.

When the effect of TAVI on left ventricular functions was considered, 37 (35.5%) patients and 28 (26.9%) patients had left ventricular dysfunction with LVEF ≤ 50% and LVEF ≤ 45%, respectively. No certain definition of patients with REF is present in the literature. LVEF can be accepted as ≤ 50%, ≤ 40%, ≤ 30% and ≤ 45% in identification of REF in different studies. We also assigned the patients into the REF group according to the most commonly used LVEF ≤ 45% value in the literature. A statistically significantly increased LVEF was found when all patients were evaluated (53.9 ± 14.6, 57.0 ± 11.4, 59.4 ± 8.4, 60.4 ± 6.8, 63.2 ± 3.9 at respectively, baseline, discharge, 1<sup>st</sup>, 6<sup>th</sup>, and 12<sup>th</sup> month; *p* < 0.001). When the REF and PEF groups were evaluated separately, a statistically significantly increased LVEF value (*p* < 0.001) was found at discharge, 1<sup>st</sup>, 6<sup>th</sup>, and 12<sup>th</sup> month in the REF group whereas LVEF increased in all follow-ups of the PEF group, however this elevation reached a statistical significance only at the 1<sup>st</sup> month (*p* = 0.04) (Fig. 2). Seventy percent of the patients in the REF group reached normal ejection fraction (LVEF > 50%) at the 6<sup>th</sup> month. Ejection fraction statistically significantly increased in all of the 4 patients with LVEF ≤ 20%, who had increased ejection fraction and reached > 45% at the end of the 1<sup>st</sup> month. In the multivariate analyses, there was statistically significant negative correlation between LVEF and STS score, Logistic EUROScore, functional capacity (NYHA), mitral regurgitation and pulmonary artery systolic pressure. But there

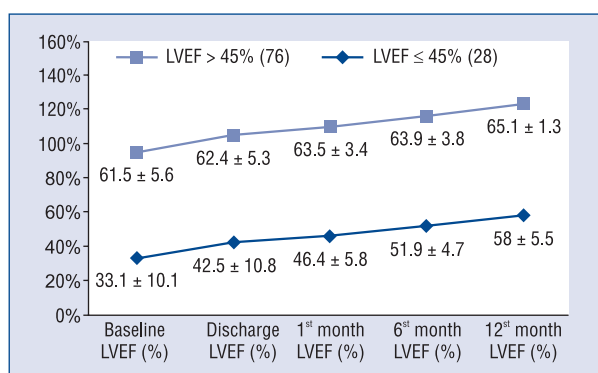
**Table 1.** Basal characteristics and procedural features.

<b>Patient characteristics</b>	<b>All patients (n = 104)</b>	<b>LVEF ≤ 45% (n = 28)</b>	<b>LVEF &gt; 45% (n = 76)</b>	<b>P</b>
Male/female	35/69	13/15	22/54	0.10
Age [year]	78.2 ± 7.2	77.4 ± 7.9	78.5 ± 6.9	0.50
Body mass index [kg/m <sup>2</sup> ]	27.9 ± 7.5	28.1 ± 11.6	27.8 ± 5.5	0.89
NYHA class II	7	0	7	0.08
NYHA class III	66	18	48	
NYHA class IV	31	10	21	
STS	7.4 ± 5.3	11.8 ± 5.3	5.7 ± 4.2	<b>&lt; 0.001</b>
SURTA VI:				
Low risk	10	1	9	
Moderate risk	34	6	28	<b>0.03</b>
High risk	60	21	39	
EUROScore [%]	22.7 ± 15.8	30.2 ± 17.9	19.3 ± 14.1	<b>0.002</b>
<b>Associated comorbid conditions</b>				
Coronary artery disease	71.1%	64.2%	73.6%	0.41
Hypertension	81.7%	85.7%	80.2%	0.52
Diabetes mellitus	25.9%	28.5%	25.0%	0.71
Hyperlipidemia	45.2%	42.8%	46.0%	0.77
Smoker	19.2%	25.0%	17.1%	0.36
Chronic obstructive pulmonary disease:				
Mild	44.2%	21.4%	52.6%	
Moderate	30.7%	28.5%	42.1%	<b>&lt; 0.001</b>
Severe	23.0%	50.0%	13.1%	
Peripheral arterial disease	34.6%	46.4%	30.2%	0.12
Atrial fibrillation	27.9%	35.7%	25.0%	0.28
<b>Echocardiographic variables</b>				
Maximal gradient [mm Hg]	86.2 ± 21.5	76.5 ± 19.2	89.8 ± 21.3	<b>0.005</b>
Mean gradient [mm Hg]	52.5 ± 13.7	46.9 ± 13.7	54.6 ± 13.2	<b>0.01</b>
Aortic valve area [cm <sup>2</sup> ]	0.62 ± 0.17	0.60 ± 0.17	0.63 ± 0.17	0.42
LVEF [%]	53.9 ± 14.5	33.0 ± 10.1	61.5 ± 5.6	<b>&lt; 0.001</b>
Peak SPAP [mm Hg]	47.8 ± 13.6	52.3 ± 15.8	45.9 ± 12.1	<b>0.04</b>
Aortic regurgitation:				
Low	17	5	12	
Moderate	4	2	2	0.58
Severe	1	0	1	
Mitral regurgitation:				
Low	62	19	43	
Moderate	6	4	2	<b>0.009</b>
Severe	3	1	2	
Femoral vascular closure	85.5%	85.7%	85.5%	0.68
Valve diameter [mm]:				
23	59	11	48	
26	43	15	28	<b>0.01</b>
29	2	2	0	
Contrast used [cc]	201.5 ± 55.7	217.4 ± 48.6	195.6 ± 57.3	0.08
Duration of discharge after procedure [day]	7.3 ± 5.3	8.8 ± 7.1	6.8 ± 4.4	0.09

NYHA — New York Heart Association, STS — Society of Thoracic Surgeons; SURTA VI — Safety and Efficacy Study of the Medtronic CoreValve® System in the Treatment of Severe, Symptomatic Aortic Stenosis in Intermediate Risk Subjects Who Need Aortic Valve Replacement risk model; LVEF — left ventricular ejection fraction; SPAP — systolic pulmonary artery pressure



**Figure 1.** Changes in New York Heart Association (NYHA) functional class at 1<sup>st</sup> month in patients undergoing transcatheter aortic valve implantation according to left ventricular ejection fraction (LVEF) ≤ 45% or > 45%.



**Figure 2.** Left ventricular ejection fraction (LVEF) on baseline, improvement during the in-hospital phase, and after a mean follow-up duration of 12 months.

positive correlation between LVEF and mean gradient of aortic valve.

### Discussion

We have shown in our study that TAVI improves left ventricular function in the short and moderate periods. We have proven that LVEF, functional capacity and clinical results of patients with REF improved after TAVI and presented a similar prognosis when compared with patients in the PEF group. Our results also indicate that TAVI may be safe for patients in the REF group; similar to patients in the PEF group, and that TAVI may

be unassociated with an increased per procedural risk. It has been shown in the same manner that complication rates of patients in the REF group are comparable to those in the PEF group. Although the incidence of patients with left ventricular dysfunction among all patients (35.5% and 26.9% according to LVEF ≤ 50% and LVEF ≤ 45%, respectively) was high, similar or better clinical results than literature studies have been obtained.

The increased incidence of AS in patients brings many co-morbid risk factors with age. One of these is left ventricular systolic dysfunction. LVEF may decrease due to after load mismatch or intrinsic contractile dysfunction [10]. If the increased LVEF is not caused by AS, aortic valve replacement may provide an improvement in LVEF. Aortic valve replacement is recommended for patients with REF, whether contractile reserve is present or not. DSE was required in only 5 of our patients and contractile reserve was sufficient in these patients. However, impaired left ventricular function is an independent risk factor for early and late mortality after s-AVR [11, 12]. Postoperative mortalities and complications are also at a high incidence even though left ventricular function improves after successful s-AVR in patients with REF [12, 13]. TAVI has developed rapidly over the last decade and has become an important treatment option for surgically inoperable or high-risk patients [6, 7]. Some previous as well as new studies indicate improved LVEF after TAVI [8, 14–20]. Especially studies conducted in recent years have evaluated the effect of TAVI on either LVEF or REF in patients. Clavel et al. [8] have compared 200 patients who underwent s-AVR with 83 patients who underwent TAVI for REF (according to LVEF ≤ 50%) and have shown a better improvement in the TAVI group in LVEF than the s-AVR group. Bauer et al. [14] found greater improvement at the 7<sup>th</sup> day in 31 patients with REF (according to LVEF ≤ 45%) who underwent TAVI compared to 21 patients receiving s-AVR. They found a similar improvement with respect to LVEF at the 3<sup>rd</sup> month. Pilgrim et al. [16] in their study obtained results similar to ours, having seen a rapid improvement in 30 patients with REF (according to LVEF ≤ 30%) after TAVI while no difference was found between patients with LVEF > 30% and the group with REF with respect to complications and mortality. Gotzmann et al. [20] divided patients into four groups based on LVEF (LVEF > 50% and ≤ 50%) and mean gradient (> 40 mm Hg and ≤ 40 mm Hg), as group 1, preserved LVEF/high gradient (n = 86), group 2, preserved LVEF/low gra-

dient (n = 27), group 3, reduced LVEF/high gradient (n = 45), and group 4, reduced LVEF/low gradient (n = 44). This study, which used the CoreValve® valve, found a statistically significant elevation in LVEFs. Nevertheless, this study showed that low gradient and/or low LVEF is associated with poor clinical results. We accepted LVEF ≤ 45% in our study and obtained successful clinical results in the patients with either REF or low gradient. Early and positive effects of TAVI on LVEF may be explained by several mechanisms. TAVI provides a lower transprosthetic gradient than s-AVR with its wider valve area, thus valve obstruction is completely released and pressure load on the left ventricle is removed. Improvement of LVEF is lower in patients with multivessel coronary artery disease who receive s-AVR concurrently with bypass whereas revascularization could be performed previously, when needed, if TAVI is preferred. Beside these points, other factors related to open surgery during s-AVR, which are irrelevant for TAVI, are ischemia, ischemia/reperfusion, inflammatory response, cardioplegia, surgical trauma, oxidative stress, cardiomyocyte apoptosis due to several factors and contractile dysfunction [21]. The pure percutaneous approach, local anesthesia and non-necessity of vasoactive drug-cardiac arrest-prolonged ventilation during TAVI is a protective characteristic for the pericardium [16]. Since risk scorings (STS, logistic EUROScore) used in patient selection and parameters of left ventricular dysfunction were not evaluated sufficiently, it comes to the forefront that when we consider these data, a scoring system specific for TAVI is necessary. TAVI should also be considered instead of s-AVR in patients with poor parameters of left ventricular function. It is obvious that a value of LVEF ≤ 20% is a relative contraindication criteria in the guidelines, which should be reevaluated and patient selection performed based on additional echocardiography criteria (contractile reserve, spackle tracking, left ventricular volume and etc.) and clinical criteria (fragility, functional capacity, age, gender etc.). It can be stated that the procedure can be performed with low complication and mortality rates using carefully conducted patient selection.

### Conclusions

We have shown that an improvement could be obtained using TAVI in left ventricular function and that TAVI could be performed successfully in the REF patient group, producing similar complication rates as the PEF patient group. It can be stated

according to this study that selecting TAVI may be necessary instead of s-AVR in patients with left ventricular dysfunction and that left ventricular functions are important parameters to be taken into account in patient selection. Consequently, more comprehensive and randomized studies of these procedures are necessary.

**Conflict of interest:** None declared

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