



## Evaluation of CA125 and NT-proBNP values in patients undergoing transcatheter aortic valve implantation

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### Abstract

**Background** Transcatheter aortic valve implantation (TAVI) is a minimally invasive, emerging therapy in surgically high risk, or inoperable patients. Parameters used for risk classification have some deficiencies in the selection of patients. The objective of this study is to evaluate the impact of TAVI on carbohydrate antigen 125 (CA125) and N-Terminal pro Brain-type Natriuretic Peptide (NT-proBNP) as biomarkers that have been used frequently in recent years, and also the relationship of these biomarkers to prognosis. **Methods & Results** Transcatheter aortic valve implantation was practiced on 31 patients in this study. Then, CA125 and NT-proBNP levels studied in patients prior to and after the TAVI were evaluated. The patients were also grouped in accordance with their left ventricular ejection fraction (LVEF) and CA125 levels (LVEF  $\geq$  40% and  $<$  40%; CA125  $\leq$  35 U/L and  $>$  35 U/L). The TAVI operation was successfully performed in all patients. There was no in-hospital mortality and substantial improvement in functional capacity was detected at follow ups. In addition, a statistically significant decrease was detected in post-TAVI CA125 and NT-proBNP levels of all patients (CA125  $83.8 \pm 18.1$  U/L vs.  $64.3 \pm 14.2$  U/L,  $P = 0.008$ ; NT-proBNP:  $4633.6 \pm 627.6$  pg/mL vs.  $2866.3 \pm 536.8$  pg/mL,  $P < 0.001$ ). In groups divided according to the CA125 levels, there was also statistically significant post-TAVI decline in CA125 levels. Within CA125  $>$  35 U/L and LVEF  $<$  40% groups, the permanent need for a pacemaker was required in one (3.2%) patient and mortality was observed in two (6.4%) patients after TAVI at follow up. **Conclusions** The results show that TAVI can be performed effectively and reliably in patients with high baseline levels of CA125 and NT-proBNP. These biomarkers are reduced substantially with TAVI, while high biomarker levels are associated with undesired events, and certainly, these biomarkers can be used for risk classifications in patient selection for TAVI.

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### 1 Introduction

Transcatheter aortic valve implantation (TAVI) is an effective treatment modality in patients that present severe aortic stenosis (AS) with a higher surgical risk, or that cannot undergo surgical aortic valve replacement (SAVR).<sup>[1,2]</sup> The risk scores currently used are those of the Society of Thoracic Surgeons (STS) and logistic EuroScore. These scoring methods are fundamentally used in the estimation of the risk for the patients undergoing open heart surgery, but

have exhibited some shortcomings. Moreover, as this patient population has many co-morbid diseases (complications), therefore, the results achieved with the help of TAVI may vary from patient to patient. To date, however, the use of biomarkers in the risk classification and estimation of prognosis after TAVI has not fully documented. The prognostic values of carbohydrate antigen 125 (CA125) and N-Terminal pro Brain-type Natriuretic Peptide (NT-proBNP) have been shown previously in heart failure and severe AS.<sup>[3–5]</sup> As a glycoprotein antigen, CA125 is found in the coelomic epithelium, amniotic fluid, pleura, peritoneum, pericardium, and bronchial/cervical secretions of normal adults. Additionally, CA125 is a well-established tumor marker to monitor the efficacy of ovarian cancer therapy and the early detection of recurrence,<sup>[6]</sup> and high levels of CA125 may be seen in other gynaecologic conditions without malignancy.<sup>[7]</sup> It has also been shown that CA125 is

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strongly associated with the severity and adverse clinical results of heart failure (HF).<sup>[4,5]</sup> It was also suggested that high CA125 values were correlated with the severity of the disease in AS patients.<sup>[8]</sup> There is scarce data in the literature demonstrating the relationship between CA125 and TAVI. One cited source was obtained from the study of Husser, *et al.*<sup>[9]</sup> where they showed that CA125 levels were independent predictors of mortality and undesired events in the patients subjected to TAVI. As a recommended use in the diagnosis and treatment follow-up in current guidelines, Brain-type natriuretic peptide (BNP) is an amino acid protein synthesized by the myocardium that is cleaved into two fragments yielding BNP and NT-proBNP. Prognosis and clinical results for CA125 in AS was shown in many studies. The relationship of NT-proBNP is more economical with wider availability than CA125.<sup>[10-13]</sup>

In this study, we aim to evaluate the prognostic value of CA125 and NT-proBNP levels in patients with severe AS, as well as the effect of TAVI on CA125 and NT-proBNP levels.

## 2 Methods

### 2.1 Patients

Between July 2013 and December 2013, thirty one patients with severe symptomatic AS, who were at high risk or inoperable for SAVR due to co-morbid conditions, were included in our study. Their symptomatic status was assessed at baseline and at follow-ups, including the functional New York Heart Association (NYHA) classification. The echocardiographic criteria of severe stenosis were according to the current guidelines, such as aortic valve area (AVA)  $< 0.8 \text{ cm}^2$ , and/or mean transvalvular pressure gradient  $> 40 \text{ mmHg}$  and/or maximum transvalvular blood flow velocity  $> 4.0 \text{ m/s}$ . Dobutamine stress echocardiography was performed on the patients with low output and low gradient AS. The patients who could not be subjected to SAVR due to various co-morbid conditions, or STS score  $\geq 10\%$  and/or logistic EuroScore  $\geq 20\%$ , were considered for TAVI upon the evaluation of the heart team. Informed consents of all patients were obtained prior to the procedure and ethical approval of the ethics committee of our hospital was received for the study in question.

### 2.2 Preoperative preparations

Transthoracic echocardiography (TTE) Doppler tracings and 2D images were obtained from parasternal long and short axis, apical 4-chamber, and subcostal 4-chamber views. TTE were reviewed to assess the pericardium, valvular anatomy and function, and cardiac function. All pa-

tients were subjected to transesophageal echocardiography (TEE) and multi-slice computed tomography (MSCT) prior to the procedure. The valve morphology, aortic annulus, coronary ostium-annulus distance, calcification degree, the relevance of peripheral arteries and whether or not there was an additional pathology, were evaluated. Early post-procedural TTE was performed in all patients during their hospitalization and just before discharge. It was planned that the stable patients would be followed at the 1<sup>st</sup>, 6<sup>th</sup> and 12<sup>th</sup> month after discharge from hospital. During such follow-ups, their routine physical examinations, TTE and functional capacities were evaluated.

### 2.3 TAVI procedure

Balloon expandable Edwards SAPIEN XT (Edwards Lifesciences, Irvine, CA, USA) valves were implanted in all patients through the transfemoral route. A total of 29 (93.5%) of the patients underwent the procedure under local anaesthesia. During the procedure, the patients were heparinised in such a way that their activated clotting time would be 250–300 s. A percutaneous closure device (Prostar XL 10F system, Abbott Vascular, Redwood City, CA, USA) was used in 90.3% cases and the remaining cases were subjected to surgical cut-down.

### 2.4 CA125 and NT-proBNP measurements

Samples were drawn from the cubital vein into blood tubes and were immediately separated from the cells by centrifugation at 4000 r/min for 10 min, stored on ice at  $-80^\circ\text{C}$ , then analyzed. Serum NT-proBNP and CA125 levels were measured by a direct chemiluminescence assay within 24 h prior to procedure (defined as baseline levels), and before discharge ( $6.8 \pm 4.8$  days) after the procedure. A level of 35 U/L was considered the upper normal limit for CA125 levels. All patients were divided into two groups as LVEF  $\geq 40\%$  and  $< 40\%$  according to LVEF and as  $\leq 35 \text{ U/L}$  and  $> 35 \text{ U/L}$  according to CA125 level.

### 2.5 Statistical analysis

All analyses were performed using SPSS Statistics 17.0. Continuous variables are presented as mean  $\pm$  SD and were compared by means of two-sided Student's *t*-test. Categorical data are expressed as frequency, and were compared using the chi-square and Fishers exact tests. Data at baseline, discharge, and one month were compared by repeated measures ANOVA. All the factors that might have an influence on the CA125 and NT-proBNP levels were pooled from the whole cohort and the Pearson correlation rho (*r*) coefficient was calculated to examine the relationship between CA125 and NT-proBNP levels and these

variables. 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 set at  $P < 0.05$ .

### 3 Results

Eighteen of the patients were female, whereas 13 were male and the average age was 76.8 years. Mean AVA and mean gradient were found to be  $0.6 \pm 0.1 \text{ cm}^2$  and  $51.8 \pm 12.5 \text{ mmHg}$  in TTE, respectively. The average STS scores and average logistic EuroScores of the patients were  $6.8\% \pm 4.0\%$  and  $24.5 \pm 12.8\%$ , respectively. According to the risk model of the 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 (SurTAVI), 96.7% of patients were in the medium and high risk groups. Implant valves of 23 mm, 26 mm and 29 mm were used in 51.4%, 38.9% and 9.7% of the patients, respectively. Some 90% of the patients were in NYHA functional class III and IV, while 90.3% of them had coronary artery disease, 71% had hypertension, 38.7% had peripheral artery disease and 32.3% had diabetes mellitus. The STS score, basal CA125 and basal NT-proBNP were significantly higher in the LVEF  $< 40\%$  group while the mean gradient, AVA and LVEF were significantly lower in this group. When we reviewed data on CA125 groups, basal CA125 and basal NT-proBNP were significantly higher; whereas AVA and LVEF were significantly lower in the CA125  $> 35 \text{ U/L}$  group and statistically significant. Basal characteristics and procedural data of all patients and each group are presented in Table 1.

Mean discharge period after TAVI was  $6.8 \pm 4.8$  days and there was no statistically significant difference between the groups. The post-procedural mean gradient of the aortic valve of the patients was  $9.8 \pm 4.3 \text{ mmHg}$  and a significant decrease was noted in all groups. There was no moderate or severe paravalvular aortic regurgitation (AR) in any patient. Mild paravalvular AR was observed in 12.9% of the patients. Following the valve implantation, complete atrioventricular block developed in two patients (6.4%). One of them returned to the normal sinus rhythm at follow-up, while the other patient (in the group where LVEF  $< 40\%$  and CA125  $> 35 \text{ U/L}$ ) received a permanently implanted pacemaker. New atrial fibrillation (AF) developed in two patients after TAVI. When we examined vascular complications, hematoma in one patient and pseudo-aneurysm in another patient was observed. Another 12.9% of the patients

were subjected to  $\geq 2$  units of erythrocyte suspension transfusion. There was no in-hospital mortality after the procedure. Recovery in functional capacities was observed without any difference between the groups with 94.5% of the patients in NYHA functional class I and II in the 1<sup>st</sup> month. At follow-up, two patients died within a 30-day period due to non-cardiac reasons. Both mortalities were within the LVEF  $< 40\%$  and CA125  $> 35 \text{ U/L}$  groups. At follow up in the 1<sup>st</sup> month, NYHA functional class, AVA and LVEFs continued to increase while mean gradients continued to decrease. There were no complications and deaths at the follow up mean of 9 months.

CA125 and NT-proBNP levels decreased significantly in all patients after TAVI (CA125:  $83.8 \pm 18.1 \text{ U/L}$  vs.  $64.3 \pm 14.2 \text{ U/L}$ ,  $P = 0.008$ ; NT-proBNP:  $4633.6 \pm 627.6 \text{ pg/mL}$  vs.  $2866.3 \pm 536.8 \text{ pg/mL}$ ,  $P < 0.001$ ). It was found that CA125 levels decreased significantly in the groups of CA125  $\leq 35 \text{ U/L}$  and  $> 35 \text{ U/L}$  after TAVI (CA125  $\leq 35 \text{ U/L}$ :  $19.8 \pm 6.2 \text{ U/L}$  vs.  $14.9 \pm 5.2 \text{ U/L}$ ,  $P < 0.001$ ; CA125  $> 35 \text{ U/L}$ :  $150.7 \pm 97.9 \text{ U/L}$  vs.  $121.3 \pm 78.1 \text{ U/L}$ ,  $P = 0.022$ ). In the LVEF groups, on the other hand, CA125 levels decreased; however, this decrease was not statistically significant (LVEF  $\geq 40\%$ :  $50.9 \pm 66.1 \text{ U/L}$  vs.  $39.4 \pm 56.9 \text{ U/L}$ ,  $P = 0.054$ ; LVEF  $< 40\%$ :  $128.6 \pm 120.0 \text{ U/L}$  vs.  $106.9 \pm 90.6 \text{ U/L}$ ,  $P = 0.105$ ).

A statistically significant decrease was observed in NT-proBNP levels in all groups after TAVI (CA125  $\leq 35 \text{ U/L}$ :  $2420.5 \pm 2150.1 \text{ pg/mL}$  vs.  $1224.0 \pm 999.0 \text{ pg/mL}$ ,  $P = 0.002$ ; CA125  $> 35 \text{ U/L}$ :  $7280.5 \pm 2398.6 \text{ pg/mL}$  vs.  $4761.2 \pm 3119.2 \text{ pg/mL}$ ,  $P = 0.003$ ; LVEF  $\geq 40\%$ :  $3318.0 \pm 3023.3 \text{ pg/mL}$  vs.  $1639.8 \pm 2045.4 \text{ pg/mL}$ ,  $P = 0.007$ ; LVEF  $< 40\%$ :  $7047.6 \pm 2602.7 \text{ pg/mL}$  vs.  $5091.1 \pm 2976.8 \text{ pg/mL}$ ,  $P = 0.013$ ). All patients also showed a statistically significant increase in LVEF ( $50.9 \pm 17.3 \text{ U/L}$  vs.  $55.4 \pm 14.0 \text{ U/L}$ ,  $P = 0.003$ ) after the procedure. A statistically significant LVEF increase was observed in the high risk groups where LVEF  $< 40\%$  and CA125  $> 35 \text{ U/L}$  respectively, LVEF  $< 40\%$ :  $28.9\% \pm 10.1\%$  vs.  $38.1\% \pm 11.6\%$ ,  $P = 0.036$ ; CA125  $> 35$ :  $37.6\% \pm 17.6\%$  vs.  $46.8\% \pm 16.0\%$ ,  $P = 0.017$ ). As in prior to TAVI, a statistically significant difference between the LVEF and levels of CA125 and NT-proBNP among the LVEF groups continued after TAVI ( $P < 0.001$ ,  $P = 0.025$ ,  $P = 0.002$ , respectively). Similarly, it was ascertained that the statistical difference between the LVEF, level of CA125 and NT-proBNP among the CA125 groups continued after TAVI ( $P = 0.004$ ,  $P < 0.001$ ,  $P < 0.001$ , respectively). The variation in the parameters of all patients and each group after TAVI are presented in Table 2. In the correlation analysis performed, it was detected that the basal CA125 level had a negative correlation with LVEF and a positive correlation with logistic EuroScore and NT-proBNP levels.

It was also detected that basal NT-proBNP level had a negative correlation with AF, LVEF and AVA and a positive correlation with logistic EuroScore and CA125 levels (Table 3).

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

Patient characteristics	All patients, n = 31	LVEF ≥ 40%, n = 21	LVEF < 40% n = 10	P value	CA125 ≤ 35 U/L n = 17	CA125 > 35 U/L n = 14	P value
Male/Female, n	13/18	10/11	4/6	0.794	10/11	4/6	0.409
Age, yrs	76.8 ± 6.0	77.2 ± 5.6	76.5 ± 7.1	0.756	77.0 ± 5.6	76.5 ± 6.7	0.828
BMI, kg/m <sup>2</sup>	29.9 ± 11.0	28.7 ± 4.6	31.7 ± 8.5	0.513	31.8 ± 7.6	27.7 ± 7.0	0.317
NYHA II, %	9.7	14.4	10.0		11.8	7.1	
NYHA III, %	54.8	42.8	70.0	0.383	52.9	57.1	0.465
NYHA IV, %	35.5	42.8	20.0		35.3	35.7	
STS, %	6.8 ± 4.0	5.4 ± 2.8	9.5 ± 4.7	0.007	5.6 ± 2.9	8.1 ± 4.7	0.089
SurTAVI							
Low risk, n	1	3	1		3	1	
Moderate risk, n	7	7	2	0.383	7	2	0.383
High risk, n	19	11	7		11	7	
Logistic EuroScore, %	24.5 ± 12.8	22.1 ± 13.3	29.2 ± 11.4	0.166	21.5 ± 14.1	27.8 ± 10.6	0.187
Basal CA125, U/L	78.9 (9.6–398.7)	50.9 ± 66.1	128.6 ± 120.0	0.029	19.8 ± 6.2	150.7 ± 97.9	< 0.001
Basal NT-proBNP, pg/mL	4615.3 (111.0–9000.0)	3318.0 ± 3023.3	7047.6 ± 2602.7	0.002	2420.5 ± 2150.1	7280.5 ± 2398.6	< 0.001
Associated co-morbid conditions							
Coronary artery disease, %	90.3	95.0	80.0	0.610	94.1	84.6	0.695
Hypertension, %	71.0	75.0	60.0	0.398	82.4	57.1	0.124
Diabetes mellitus, %	32.3	35.0	30.0	0.784	35.3	28.6	0.690
Hyperlipidemia, %	48.4	60.0	30.0	0.121	52.9	42.9	0.576
Smoker, %	17.4	25.0	20.0	0.760	23.5	21.4	0.889
COPD, %							
Mild	35.5	45.0	20.0		41.2	30.8	
Moderate	37.6	35.0	40.0	0.336	35.3	38.5	0.826
Severe	26.9	20.0	40.0		23.5	30.8	
Peripheral arterial disease, %	38.7	60.0	60.0	1.00	47.1	30.8	0.367
Atrial fibrillation, %	29.0	25.0	30.0	0.770	17.6	42.9	0.124
Echocardiographic variables							
Maximal gradient, mmHg	84.4 ± 21.2	90.8 ± 22.5	72.8 ± 12.9	0.01	88.6 ± 17.5	81.8 ± 15.6	0.456
Mean gradient, mmHg	51.8 ± 12.5	55.2 ± 13.2	45.0 ± 7.7	0.013	55.3 ± 12.9	47.2 ± 10.8	0.079
AVA, cm <sup>2</sup>	0.6 ± 0.1	0.6 ± 0.1	0.5 ± 0.1	0.039	0.6 ± 0.1	0.5 ± 0.1	0.023
LVEF, %	50.9 ± 17.3	61.9 ± 5.4	28.9 ± 10.1	< 0.001	61.0 ± 7.7	37.6 ± 17.6	< 0.001
LVEDD, mm	4.6 ± 0.7	4.3 ± 0.5	5.2 ± 0.6	0.004	4.2 ± 0.5	5.0 ± 0.6	0.003
LVESD, mm	3.1 ± 0.8	2.6 ± 0.5	3.9 ± 0.8	0.001	2.5 ± 0.4	3.7 ± 0.8	< 0.001
IVSD, mm	1.3 ± 0.2	1.3 ± 0.1	1.3 ± 0.1	0.553	1.3 ± 0.1	1.3 ± 0.2	0.542
PWD mm	1.3 ± 0.2	1.3 ± 0.2	1.2 ± 0.1	0.489	1.3 ± 0.2	1.2 ± 0.2	0.828
Peak systolic pulmonary artery pressure, mmHg	54.5 ± 12.9	53.5 ± 12.1	56.0 ± 14.7	0.661	49.9 ± 12.3	58.5 ± 12.6	0.106
Aortic Regurgitation, %							
Moderate	3.2	5.6	10	0.235	6.7	5.5	0.706
Mitral Regurgitation, %							
Moderate	16.1	10.5	25	0.360	6.2	20.4	0.124
Femoral vascular closure, %	93.5	93.1	92.5	0.682	90.3	94.5	0.745
Valve diameter, %							
23 mm	51.4	52.6	55.6		50.4	50.0	
26 mm	38.9	47.4	11.1	0.014	43.8	35.7	0.094
29 mm	9.7	0	33.3		5.8	14.3	
Duration of discharge after the procedure, day	6.8 ± 4.8	8.8 ± 7.1	6.8 ± 4.4	0.863	6.7 ± 4.5	7.1 ± 6.1	0.812

Data are presented as mean ± SD or percent unless other indicated. AVA: aortic valve area; BMI: body mass index; CA125: carbohydrate antigen 125; COPD: chronic obstructive pulmonary disease; IVSD: interventricular septum diameter; LVEDD: left ventricular end-diastolic diameter; LVEF: left ventricular ejection fraction; LVESD: Left ventricular end-systolic diameter; NT-proBNP: N-terminal pro brain-type natriuretic peptide; NYHA: New York Heart Association; STS: Society of Thoracic Surgeons; SurTAVI: Symptomatic Aortic Stenosis in Intermediate Risk Subjects Who Need Aortic Valve Replacement; TEE: transesophageal echocardiography; PWD: posterior wall diameter.

**Table 2. Post-procedural changing of parameters.**

Groups	Mean gradient, mmHg		P value	LVEF, %		P value	CA125, U/L		P value	NT-proBNP, pg/mL		P value
	preTAVI	postTAVI		preTAVI	postTAVI		preTAVI	postTAVI		preTAVI	postTAVI	
All patients, n = 31	51.8 ± 12.5	9.8 ± 4.3	< 0.001	50.9 ± 17.3	55.4 ± 14.0	0.003	83.8 ± 18.1	64.3 ± 14.2	0.008	4633.6 ± 627.6	2866.3 ± 536.8	< 0.001
LVEF ≥ 40%, n = 21	55.2 ± 13.2	10.7 ± 4.7	< 0.001	61.9 ± 5.4	63.5 ± 4.2	0.108	50.9 ± 66.1	39.4 ± 56.9	0.054	3318.0 ± 3023.3	1639.8 ± 2045.4	0.007
LVEF < 40%, n = 10	45.0 ± 7.7	7.8 ± 2.8	< 0.001	28.9 ± 10.1	38.1 ± 11.6	0.036	128.6 ± 120.0	106.9 ± 90.6	0.105	7047.6 ± 2602.7	5091.1 ± 2976.8	0.013
CA125 ≤ 35 U/L	55.3 ± 12.9	9.6 ± 4.1	< 0.001	61.0 ± 7.7	62.1 ± 7.5	0.277	19.8 ± 6.2	14.9 ± 5.2	< 0.001	2420.5 ± 2150.1	1224.0 ± 999.0	0.002
CA125 > 35 U/L	47.2 ± 10.8	10.1 ± 4.7	< 0.001	37.6 ± 17.6	46.8 ± 16.0	0.017	150.7 ± 97.9	121.3 ± 78.1	0.022	7280.5 ± 2398.6	4761.2 ± 3119.2	0.003

Data are presented as mean ± SD. CA125: carbohydrate Antigen 125; LVEF: left ventricular ejection fraction; NT-proBNP: N-Terminal pro B-type natriuretic peptide; TAVI: transcatheter aortic valve implantation.

**Table 3. Multivariate analysis of CA125 and NT-proBNP levels.**

Variables	CA125		NT-proBNP		LVEF		NYHA		STS		EuroScore		AVA		Mean gradient		AF	
	r	P	r	P	r	P	r	P	r	P	r	P	r	P	r	P	r	P
CA125	1		0.65	< 0.001	-0.58	0.001	0.128	0.491	0.17	0.367	0.41	0.021	-0.27	0.146	-0.27	0.136	-0.57	0.761
NT-proBNP	0.65	< 0.001	1		-0.54	0.002	0.176	0.344	0.25	0.183	0.35	0.043	-0.37	0.042	-0.18	0.326	-0.43	0.015

AF: atrial fibrillation; AVA: aortic valve area; CA125: carbohydrate antigen 125; LVEF: left ventricular ejection fraction; NT-proBNP: N-Terminal pro BrainB-type natriuretic peptide; NYHA: New York Heart Association; STS: Society of Thoracic Surgeons.

## 4 Discussion

As far as we know, this is the first study evaluating the effect of TAVI on both CA125 and NT-proBNP levels. The results obtained through our study are as follows: (1) TAVI can be performed in an effective and reliable way on the patients who have high CA125 and NT-proBNP levels; (2) the high CA125 and NT-proBNP levels measured before the TAVI procedure decreased significantly after TAVI; (3) it has been documented that CA125 and NT-proBNP levels have a negative correlation with LVEF and a positive correlation with the logistic EuroScore; (4) when we divided the patients into groups according to the CA125 levels and LVEF (CA125 ≤ 35 U/L, and CA125 > 35 U/L; LVEF ≥ 40%; and LVEF < 40%); it was found that the CA125 and NT-proBNP levels were higher in the groups of CA125 > 35 U/L and LVEF < 40% and complications and deaths occurred in these groups. Nevertheless, a statistically significant increase in LVEF was also observed in these groups; and (5) CA125 and NT-proBNP levels decreased in all individual groups after TAVI. Moreover, all groups also presented noticeable improvement in their NYHA functional class at follow up.

Severe degenerative AS is a disease whose frequency gradually increases in elderly people and which the possibility of survival rapidly decreases after the disease becomes

symptomatic. Its definite treatment is valve replacement. However, the rate of the patients who could not be subjected to SAVR due to the frequency of the co-morbid situations together with the advanced age is around 30%–40%.<sup>[14,15]</sup> The TAVI procedure was initially applied in people in the year 2002 and performed on a realistic basis with rapid development securing its place as an alternative to SAVR in the patients with high surgical risk in the last valve guideline of the European Society of Cardiology (ESC).<sup>[16]</sup> Risk estimation within the scope of TAVI is an important research subject in order to make a definition in the determination of which patients will benefit from it and which methods will be applied after the procedure and during the follow-up process. It was found that the STS and logistic EuroScore risk classifications, which are used in patient selection, underestimated the operative risk in this patient group involving many risk factors.<sup>[17]</sup> There has not been a current and reliable model through which we can measure the risk of mortality in the short and long term follow up of the prospective patients considered for TAVI.

Biomarkers have being frequently used in the diagnosis and follow-up treatment of cardiovascular diseases. The role of CA125 and NT-proBNP among these biomarkers has been clearly shown as advantageous in many cardiovascular diseases, particularly heart failure.<sup>[3-5,8,11,18]</sup> Their contributions to risk scorings and their prognostic values have been

detailed. Pedrazzini, *et al.*<sup>[19]</sup> suggested that post-operative BNP levels were more accurate in estimating the results after SAVR than the logistic EuroScore. The relationship of NT-proBNP and BNP with TAVI showed that they were prognostic indicators and high levels were associated with negative results with the help of recent studies.<sup>[13,20–23]</sup> In the study carried out by Kefer, *et al.*<sup>[13]</sup> which is one of the first studies with regard to BNP and TAVI, it was concluded that BNP is a strong predictor of 30-day outcomes after TAVI, at both baseline and 24 hours after the procedure. In concurrence, BNP could be helpful in improving patient selection for TAVI. In the study conducted by Sherif, *et al.*<sup>[22]</sup> 56 patients subjected to TAVI and 36 patients subjected to SAVR were compared, and they showed that NT-proBNP decreased after TAVI and remained unchanged after SAVR. In another study,<sup>[21]</sup> it was established that basal and early-stage increasing NT-proBNP levels of 91 patients subjected to TAVI were the predictors of mortality. In the same study, it was seen that the NT-proBNP levels decreased at the early and late-stage for the patients subjected to transfemoral (TF) TAVI and at the late-stage for the patients subjected to transapical (TA) TAVI. Furthermore, within the scope of this study, an increase in the levels of NT-proBNP was observed at the early-stage in TA TAVI, and revealed that the TF TAVI procedure is also associated with a significant reduction in the early NT-proBNP levels to below baseline levels.<sup>[21]</sup> Another study with a large number of patients (373 patients) suggested an association between the baseline NT-proBNP levels and one year mortality in patients undergoing TAVI. As a result of this study, they suggested that NT-proBNP results in a higher predictive value for patient selection and should be included in the risk stratification of patients undergoing the TAVI.<sup>[23]</sup> On the other hand, in another recent study involving 340 patients, it was determined that high basal BNP levels were associated with increased peri-procedural and 30-day undesired events.<sup>[20]</sup> In a study highlighting the importance of the NT-proBNP levels in risk classification, the NT-proBNP levels of 85 patients were measured 24 h before the procedure and its effect on mortality was examined with the help of the logistic EuroScore. This study concluded that NT-proBNP plasma levels 24 h prior to the procedure is of similar, but of superior prognostic value compared with logistic EuroScore for the prediction of mortality at 30 days and long-term. NT-proBNP was also shown to be a strong independent predictor of death when included in an invariable model, while logistic EuroScore did not.<sup>[24]</sup>

Nevertheless, there is not sufficient data with respect to the TAVI and CA125 which is a more definitive biomarker than BNP and NT-proBNP. The reasons why CA125 is

more ideal include the facts that it better predicts the severity of heart failure and the rates of increased mortality and hospital admissions,<sup>[25,26]</sup> plasma levels are influenced less by patient characteristics,<sup>[8]</sup> and it is more economical in price and widely available.<sup>[9]</sup> Pre- and post-procedural CA125 levels of 228 patients for whom both balloon and self-expandable bioprosthetic valves were used in the first study concerning TAVI and CA125 were measured.<sup>[9]</sup> Through this study, it was concluded that CA125 was a strong predictor of mortality or major adverse cardiac event. At the same time, serial CA125 measurements after TAVI were significant predictors of both outcomes, even when modelled simultaneously with time-varying NT-proBNP, logistic EuroSCORE, baseline NYHA functional class III/IV, and device success. The other result was the patients with elevated baseline CA125 values (above the median) showed an independent increase of risk for all-cause mortality, or major adverse cardiac event after TAVI.<sup>[9]</sup> Our study also offers similar results with the above mentioned study and it was shown that CA125 levels decreased after TAVI. However, more comprehensive and randomized studies should be carried out on this regard.

In terms of limitations, the small size of the experimental group and small number of deaths are the limitations of the study. Large randomized controlled trials could provide more definitive evidence in the future.

In conclusion, TAVI is a developing and minimally invasive method that can be an alternative to SAVR in treatment of patients with severe AS. With this research, we have shown that TAVI can be successfully and safely practiced on patients with high baseline CA125 and NT-proBNP levels. These biomarkers can be used in the risk classification process, which TAVI significantly decreases CA125 and NT-proBNP levels and such decrease is associated with prognosis. However, the use of CA125 and NT-proBNP in TAVI, its preferential use in the risk calculation process and its relationship with prognosis will become clearer and more explicit through randomized and controlled studies involving larger patient populations requiring a long term follow-up process.

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