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Research article

Prognostic value of biological parameters in patients with severe aortic stenosis undergoing TAVI - results at six months

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Abstract: (1) Background: Aortic stenosis is the most common valvulopathy in elderly patients over 60 years of age. The absence of immediate surgical intervention through classic valve replacement or through a minimally invasive procedure, namely transcatheter implantation of the aortic valve (TAVI) leads to an increase in the risk of morbidity and mortality through the deterioration of the clinical condition. Since the first interventional transcatheter aortic valve implantation procedure was performed in 2012 and until now, the progression of medical technology and state-of-the-art valves have led to the refinement of the treatment strategy and the improvement of the prognosis of patients with aortic stenosis undergoing TAVI in the first 6 months after the procedure; (2) Methods: We conducted a prospective study in which 86 patients diagnosed with severe aortic stenosis underwent minimally invasive valve replacement by TAVI; (3) Results: The presence of preoperative anemia is associated with a negative prognosis both in the medium term and in evolution, and in addition to hematological parameters, we also evaluated a series of biochemical data, with special attention to renal function and lipid profile; (4) Conclusions: Biological parameters followed after TAVI may be predictors associated with a negative long-term prognosis.

Keywords: aortic stenosis; prognostic value; biological parameters; transcatheter aortic valve implantation

1. Introduction

Degenerative aortic stenosis (AS) is the most common valvular heart disease encountered in developed countries that requires an appropriate therapeutic approach [1, 2]. The clinical picture is marked by a long-term paucisymptomatic evolution that coincides with the typical clinical picture which, in the absence of procedural valve replacement treatment (surgical or minimally invasive), leads to a poor prognosis [3, 4]. Patients with severe, symptomatic AS who do not undergo surgical valve replacement or transcatheter aortic valve implantation (TAVI) are at high risk of morbidity and mortality, with a prognosis comparable to the survival rates of some neoplasms [5]. Transcatheter aortic valve implantation (TAVI) is recommended in patients with moderate to severe perioperative risk, as assessed by risk scores, as well as in low-risk patients over 75 years of age [6]. Clinical research on current TAVI attributes a superior prognosis compared to classical

surgical treatment in the short and medium term, regardless of the associated risk category [7, 8].

The aim of this study was to outline the clinical and biological picture of patients with severe AS undergoing TAVI and to highlight the importance of this minimally invasive procedure on symptomatology and the prognostic value of biological data at 6 months of follow-up.

2. Materials and Methods

2.1. Study design

We performed a prospective study in which 86 patients diagnosed with severe aortic stenosis underwent minimally invasive valve replacement with TAVI. Aortic stenosis diagnosis and multimodal evaluation prior to the minimally invasive procedure were performed according to current guideline recommendations using the European ESC guideline for valvular disease [9]. All patients enrolled in the study with severe aortic stenosis (with aortic peak velocity greater than 4 m/s, mean gradient greater than 40 mmHg, and aortic valve area less than 1 cm^2) underwent imaging analysis by echocardiography and cardiac computed tomography for the purpose of evaluating cardiac structure and function prior to TAVI with emphasis on prosthesis size or changes in local anatomy. Patients with severe AS requiring classical surgery or those with contraindications to minimally invasive procedures such as infective endocarditis, ascending aortic thrombosis, short annulus-to-coronary ostium distance, or annulus size less than 18 mm or greater than 29 mm were excluded. Demographic data, hemodynamic parameters, comorbidities, biological or echocardiographic parameters were obtained from the observation sheets both preoperatively and at the follow-up assessment 6 months after the procedure. Renal function assessment (serum creatinine and urea) was performed before TAVI, and electrocardiogram and vital parameters were monitored throughout the interventional procedure in the intensive care unit. None of the evaluated patients died 6 months after TAVI.

2.2. Statistical analysis

Descriptive analysis was performed using SPSS statistical software (version 26 for Windows; SPSS Inc., Chicago, IL, USA). Continuous variables were reported as mean ± SD and categorical variables as numbers (frequency and percentages). The Kolmogorov-Smirnov test was used to assess the normal distribution of the data. Continuous variables were compared using the t-test (parametric analysis). Categorical variables were compared using Fisher's exact test. Groups were compared using the $\chi 2$ or Fisher's exact test for categorical variables and Student's ANOVA/t test and Wilcoxon-Mann-Whitney U/Kruskal-Wallis tests for continuous variables, depending on their distribution. A p value ≤ 0.05 was considered statistically significant.

3. Results

We enrolled in our study 86 patients diagnosed with severe AS undergoing TAVI who were evaluated by the heart team before and 6 months after the interventional procedure. Demographics, hemodynamic parameters, comorbidities and biological values at baseline and 6 months follow-up are shown in Table 1. Our study included predominantly women (53.3%), with a mean age of 75.8 ± 7, 44 years old.

Mean BMI was reduced (28.28 ± 3.19 kg/m2 vs. 27.09 ± 2 kg/m2), with statistical significance at 6 months after TAVI ($p < 0.001$). Two types of prostheses were used, with the Edwards Lifesciences Sapien 3 (64 patients, 74.4%) being the most frequently implanted. The transfemoral approach was used in 83.7% of patients (72 cases). The mean EUROSCORE value evaluated preoperatively was 8.92 ± 10.60. Multiple comorbidities were observed in the enrolled severe AS patients, including heart failure ($p < 0.001$), dyslipidemia (51.65%), coronary artery disease (48.84%), chronic kidney disease ($p = 0.692$), diabetes mellitus (31.40%) and hypertension (58.14%) being the most important.

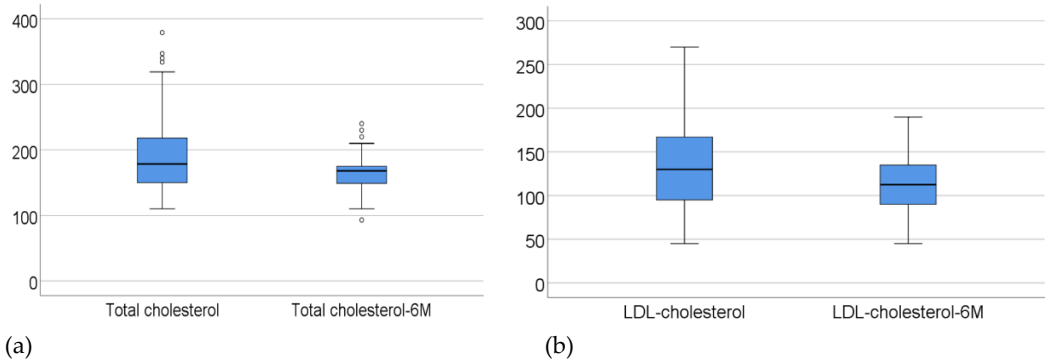
Prospective evaluation 6 months after TAVI included atrial fibrillation, heart failure, and chronic kidney disease. Thus, 97,7% of the patients presented a clinical picture of NYHA class II heart failure (84 patients), with the absence of cases of cardiac decompensation corresponding to NYHA class IV. At 6 months after TAVI, the incidence of G3 chronic kidney disease increased from 25.58% to 32, 37.2%.

Table 1. Demographics, resting hemodynamics, comorbidities and biological findings at baseline and at 6-months follow-up.

Parameters	**Baseline**	**Six Months Follow-Up**	***p* Value**
Age, y	75.8 ± 7.44		
Females	46 (53.3%)		
BMI, kg/m²	28.28 ± 3.19	27.09 ± 2	<0.001
Type of aortic prosthesis			
Edwards Lifesciences Sapien 3	64 (74.4%)		
Medtronic Evolut R	22 (25.6%)		
Vascular approach			
Transfemoral	72 (83.7%)		
Transapical	14 (16.3%)		
EUROSCORE II	8.92 ± 10.60	4.72 ± 3.09	<0.001
Symptoms			
Angina pectoris	63 (73.3%)	12 (14%)	<0.001
Fatigue	83 (96.5%)	7 (8.1%)	<0.001
Comorbidities			
Atrial fibrillation	21 (24.4%)	20 (23.3%)	1.000
Heart failure	NYHA class III 62 (72.1%)	NYHA class II 84 (97.7%)	<0.001
	NYHA class IV 24 (27.9%)	NYHA class III 2 (2.3%)	
Dyslipidemia	47 (51.65%)		
Coronary artery disease	42 (48.84%)		
Peripheral artery disease	21 (24.42%)		
Stroke	7 (8.14%)		
COPD	14 (16.28%)		
Diabetes mellitus	27 (31.40%)		
Chronic kidney disease	G2 (53, 61.63%)	G2 (42, 48.8%)	0.692
	G3 (22, 25.58%)	G3 (32, 37.2%)	
	G4 (2, 2.33%)	G4 (1, 1.2%)	
Hepatopathy	20 (23.26%)		
Hypertension	50 (58.14%)		
Resting hemodynamics			
SBP, mmHg	149.07 ± 21.17	127.64 ± 11.94	<0.001
DBP, mmHg	82.72 ± 9.79	74.17 ± 7.35	<0.001
Heart rate, bpm	73.35 ± 11.68	65.83 ± 6.35	<0.001
Arterial oxygen saturation (%)	89.76 ± 2.62	98.43 ± 0.95	<0.001
Biological parameters			
Hemoglobin	12.54 ± 1.88	13.24 ± 0.84	<0.001
Red blood cells	4.10 ± 0.79	4.42 ± 0.42	<0.001
Leucocytes	6930.81 ± 229.20	6131.28 ± 1110.53	0.009
Fasting glucose	125.19 ± 46.56	105.86 ± 16.06	<0.001
Fibrinogen	481.69 ± 137.60	373.42 ± 46.45	<0.001
ESR	28.58 ± 24.13	12.87 ± 8.73	<0.001
Thrombocytes	207069.77 ± 85475.94	192058.14 ± 53308.72	0.094
Urea	53.50 ± 27.13	44.69 ± 14.83	0.002
Serum creatinine	1.04 ± 0.35	1.04 ± 0.28	0.554
eGFR	68.81 ± 18.11	67.26 ± 15.60	0.277
Total cholesterol	191.50 ± 56.21	162.50 ± 26.49	<0.001
LDL-cholesterol	135.38 ± 48.54	112.15 ± 30.70	<0.001
Triglycerides	114.24 ± 50.72	111.16 ± 36.92	0.919

All values are expressed as mean ± standard deviation (SD) or n (%); y: years; BMI: body mass index; NYHA: New York Heart Association; COPD: chronic obstructive pulmonary disease; SBP: systolic blood pressure; DBP: diastolic blood pressure; ESR: erythrocyte sedimentation rate; eGFR: estimated glomerular filtration rate; LDL-cholesterol: low-density lipoprotein cholesterol.

To investigate patients undergoing TAVI from a paraclinical point of view, biochemical and hematological tests were acquired both at hospital admission and 6 months after TAVI. The mean value of hemoglobin increased significantly 6 months after TAVI (12.54 ± 1.88 g/dl vs. 13.24 ± 0.84 g/dl, $p < 0.001$), together with red blood cells (4.10 ± 0.79 mil vs. 4.42 ± 0.42 g/dl. dl, $p < 0.001$) and platelets (207069.77 ± 85475.94/mm3 vs. 192058.14 ± 53308.72/mm3, $p = 0.094$). Conversely, the mean value of serum leukocytes decreased (6930.81 ± 229.20/mm3 vs. 6131.28 ± 1110.53/mm3, $p = 0.009$), together with the significant reduction of inflammatory syndrome parameters (erythrocytes $p < 0.001$).
Among the biochemical markers, increased importance was given to renal function and lipid profile. Therefore, the 6-month assessment showed a reduction in mean serum total cholesterol (191.50 ± 56.21 mg/dl vs. 162.50 ± 26.49 mg/dl, $p < 0.001$) and LDL cholesterol (135 .38 ± 48.54 mg/dl vs. 112.15 ± 30.70 mg/dl, $p < 0.001$). Mean serum creatinine was almost identical, with no associated clinical impact (1.04 ± 0.35 mg/dl vs. 1.04 ± 0.28 mg/dl, $p = 0.554$).



(a) (b)

Figure 1. Lipid profile: (a) Box-plot illustration of the evolution of total cholesterol from baseline to 6 months; (b) Box-plot illustration of the evolution of LDL-cholesterol from baseline to 6 months.

4. Discussion

Our study included a number of 86 patients with severe AS undergoing TAVI, and through the evaluation performed 6 months after the intervention we proved the satisfactory results of the interventional therapy on the clinical status (angina <p = 0.001> and fatigue <p < 0.001>) . In terms of demographic data, our study included predominantly female patients (53.3%), with a mean age of 75.8 ± 7.44 years.

The impact of age and gender of patients with severe AS on disease progression has been highlighted in the literature [10]. There is a directly proportional relationship between the evolution of clinical status, age and periprocedural risk associated with TAVI, with older age correlating with a higher risk of bleeding complications and therefore with a higher risk of post-procedural death predominantly among women [11].

TAVI correlates with a multitude of functional markers, predominantly echocardiographic, that outline the improvement of the clinical status in patients with severe AS. In our study, we found a reduction in the symptoms and functional class of heart failure New York Heart Association (NYHA) after 6 months after the procedure, thus the statistical analysis of evidence of the absence of functional class IV NYHA, and the patients who presented symptoms specific to the functional class. III NYHA significantly reduced from 72.1 to 2,3 % at 6-month follow-up ($p < 0.001$). Reductions in angina pectoris ($p < 0.001$) and fatigue ($p < 0.001$) were observed in more than three quarters of the enrolled patients. Multiple comorbidities were an important characteristic of the cohort in our study marking both peri-procedural risk and long-term outcome.

Dyslipidemia (51.65%), coronary artery disease (48.84%), chronic kidney disease ($p = 0.692$), diabetes mellitus (31,40%) and hypertension (58.14%) were part of a significant

percentage of patients, requiring management multidisciplinary with the role of reducing the risk of mortality. Clinical studies in the specialized literature quantify the importance and number of associated pathologies in assessing prognosis [5]. Barth et al. [1] concluded that patients undergoing TAVI who presented less than 6 comorbidities are associated with half the risk of death in the long term compared to patients with severe AS undergoing drug therapy alone ($p = 0.004$), a fact that requires management therapeutically enhanced.

The statistical analysis, in addition to the clinical markers, also analyzed the biological ones both at hospital admission and 6 months after TAVI. Serum hemoglobin ($p < 0.001$) and red blood cell ($p < 0.001$) levels improved markedly from anemic stage to an optimal level 6 months after TAVI. The presence of anemia has been reported in 42–67% [12] of patients with severe AS, and one year after TAVI is associated with increased mortality and a poor prognosis [13-15]. It was also observed that persistent anemia is associated with hospital readmission in the first year after TAVI (odds ratio 1.91, $p = 0.024$), having an impact on the clinical picture, through the persistence of clinical signs and symptoms of advanced heart failure (odds ratio. 0.49, $p = 0.034$) [12].

Takagi et al. [12] observed that preoperative anemia also correlates with a poor prognosis in evolution, a meta-analysis highlighting the directly proportional relationship between decreased serum hemoglobin levels and increased risk of short-term ($p = 0.003$) and medium-term ($p < 0.001$). Khadija et al. [16] demonstrated that the frequent thrombocytopenia encountered in patients undergoing TAVI, with more than 30%, correlates with severe bleeding, vascular complications, or death in the first 30 days after the procedure.

We paid more attention to kidney function and lipid profile. Our values of serum total cholesterol ($p < 0.001$) and LDL-cholesterol ($p < 0.001$) decreased 6 months after TAVI, similar to literature data. In a cohort of 119 patients undergoing TAVI presented in one study, low levels of serum LDL-cholesterol and high-density lipoprotein cholesterol were shown to be associated with an increased risk of acute cardiac or cerebrovascular events in the short term [15]. Inflammatory parameters are frequently present due to local lesions. Khadija et al. [17] showed that the duration of the intervention and the amount of contrast used is characteristic of an early inflammatory response in the first 24 hours after TAVI ($p < 0.01$). In our study we observed decreased serum levels of leukocytes ($p = 0.009$), fibrinogen ($p < 0.001$) and ESR ($p < 0.001$) compared to baseline levels, which confers a favorable prognosis in patients undergoing TAVI after 6 months.

Chronic kidney disease is often present in patients undergoing TAVI, with a special prognostic role [18]. Statistical analysis of biological parameters at 6 months revealed a persistence of renal dysfunction predominantly in the G3 stage. Advanced age, comorbidities, and incorrectly administered contrast agents can lead to acute kidney injury after TAVI, and in the long term lead to chronic kidney disease with a severe prognosis [19]. Most specialized studies note the improvement of renal function after TAVI [20 - 22].

Our study has some limitations due to the small number of patients enrolled and the subjective assessment of associated symptoms. Cases in which clinical-paraclinical data were not complete and those patients who did not show up for follow-up 6 months after TAVI, were excluded from the study.

5. Conclusions

In conclusion, we demonstrated in our study that the TAVI procedure presents a favorable role both on the clinical picture and on the hemodynamic parameters. Biological parameters observed 6 months after TAVI require follow-up in dynamics to identify reversibility or transformation into predictors associated with a severe long-term prognosis.

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