ORIGINAL ARTICLE

Clinical Characteristics and Mid-Term follow-up of Elderly Patients with Severe Aortic Stenosis not Eligible for TAVI

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Abstract

Background: The treatment for symptomatic severe aortic stenosis (AS) is the correction of valve stenosis by surgical valve replacement and more recently by transcatheter aortic valve implant (TAVI). However, in some high risk surgical patients, TAVI is not possible for technical or clinical reasons or due to the unavailability of the endoprosthesis.

Objective: The aim of this study was to evaluate a mid-term follow-up of symptomatic severe AS patients who are not eligible for TAVI trials, as well as to identify the clinical features of these patients.

Methods: This was an observational, retrospective study conducted with 475 symptomatic severe AS patients, evaluated by the Heart Team between 2000 and 2017. Inclusion criterias were: patients considered not to be eligible for TAVI. The Shapiro-Wilk test was applied to evaluate normality. Non-paired t and Mann-Whitney tests were applied for continuous variables, while the chi-squared and Fischer exact tests were applied for categorical variables, with a level of significance of p<0,05.

Results: The heart team evaluated 475 patients: 25 (5.26%) died before any intervention could be proposed; 326 (68.3%) were submitted to TAVI, so the study population consisted of 124 patients not eligible for TAVI. Of these, 31 (25%) underwent surgery and 93 (75%) remained in clinical treatment. In a mean 56 months- follow-up the mortality in clinical group was 46.2%. In the surgical group the mortality was 23.9% (in-hospital 12.9% and late mortality 11% in a mean 47.4 months follow-up). The patients that died presented a significantly lower left ventricle ejection fraction (LVEF), a smaller valve area, and a larger end-systolic diameter of the LV.

Conclusion: The mortality of the clinical group's patients was significantly higher than the surgical mortality (46.2% vs. 12.9%; p=0.021). The patients of the clinical group were older, weighed less, and had a higher incidence of renal failure and a higher STS score.

Keywords: Aortic valve stenosis, TAVI, transcatheter prosthesis implant, aortic valve replacement.

Introduction

Degenerative aortic stenosis (AS) is the most common form of valve disease in the Western world, especially in the population over 75 years of age,[1-3] with a progressive increase in prevalence with advancing age.[3,4] It merits particular attention for its clinical importance and its growing socio-economic impact.

The natural history of the disease consists of a prolonged latent period of low morbidity and mortality.[2] However, when symptoms of angina, syncope, or cardiac insufficiency develop, the average survival drops, and there is a progressive increase in the risk of sudden death.[2] However, in clinical practice, at least 30% of patients with symptomatic AS aged 75 or older do not undergo surgery due to their advanced

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age and comorbidities that increase the risk of surgery.[5] Without surgery, the rate of survival after three years of severe symptomatic AS is 30%.[6,7] Patients in their 80s who remain in clinical treatment have a survival rate of 65.8% at one year and 41.8% at two years, regardless of the associated symptoms.[8]

Transcatheter aortic valve implantation (TAVI) has gained prominence among the treatment options for AS. Studies have shown an increasing role of this method. In high-risk patients, TAVI is not inferior to conventional surgery.[9-12] In the intermediate-risk patients, TAVI, and surgical treatment have been shown to have equal mortality rates, though TAVI can have better results than surgery when transfemoral access is possible.[13-15] In low-risk patients, TAVI is also comparable or even better than surgery in patients with mean age of 73 years.[16,17]

It is still the case that the vast majority of patients who are referred for TAVI are those for whom surgery presents a high risk. However, some are not clinically or anatomically fit to undergo any intervention at all, surgical or percutaneous.

Besides, TAVI is not available to patients in Brazilian hospitals belonging to the Unified Health System (SUS) except for those included in research trials. Therefore, for patients who are excluded from such trials, for those that surgical treatment is clinically or technically contraindicated or for those who do not agree to undergo surgery, clinical management is the only possible option.

Objectives

To evaluate the mid-term clinical follow-up of patients with severe symptomatic AS who are not eligible for TAVI research trials and to identify the clinical characteristics of these patients.

Methods

This is a retrospective observational study to evaluate patients with severe symptomatic AS who were attended in the valve disease outpatient clinic at a tertiary cardiac hospital between 2000 and 2017.

Severe AS were defined as an aortic valve area ≤ 1.0 cm^2, transaortic mean pressure gradient (ΔP) ≥ 40 mmHg or peak aortic jet velocity ≥ 4.0 m/s in the presence of normal or reduced left ventricle function. Patients with valve area ≤ 1.0 cm^2, a mean gradient lower than 40 mmHg and low ejection fraction (EF), were submitted to dobutamine stress transthoracic echocardiogram, in line with the criteria defined by the Brazilian Society of Valve Disease and the American Society Echocardiography.[18,19]

Clinical, epidemiological, laboratory, and echocardiography characteristics were evaluated, along with findings from tomography and cinecoronariography. The stratification of perioperative risk used scoring from the Society of Thoracic Surgeons (STS) and EuroSCORE II.

Inclusion criteria: patients with severe AS, symptomatic, considered not to be eligible for TAVI by the Heart Team and thus referred for aortic valve replacement surgery or conservative treatment due to anatomical difficulties or clinical criteria.

Exclusion criteria: patients with severe AS, symptomatic, considered to be eligible for TAVI by the Heart Team.

Statistical analysis

Statistical analysis was carried out using the program Statistical Package for Social Sciences (SPSS), version 19.0. The Shapiro–Wilk test was used to assess normality. Continuous variables with a normal distribution were described by their mean and standard deviation, while continuous variables with a non-normal distribution were described using their median and interquartile range. Significant differences were determined using the unpaired *t*-test for normally distributed variables and the Mann–Whitney test for non-normally distributed variables. Categorical variables were presented as percentages using the chi-squared and Fisher exact tests. Statistical significance was defined as $p < 0.05$.

Results

Between 2000 and 2017, a total of 475 patients with a diagnosis of severe AS were evaluated by the local heart team. Of these, 25 (5.26%) patients died before an intervention could be proposed, and 326 (68.3%) underwent TAVI. The remaining 124 patients who were not eligible for TAVI were included in this study. Thirty-one (25%) underwent valve replacement surgery and 93 (75%) remained in clinical treatment (Figure 1).

The main clinical characteristics of the 124 patients included in this study are provided in Table 1, while Table 2 provides echocardiographic results. The mean age was 80.66 ± 6.37 years, with women making up the majority of the study group and 44.5% were in functional class III. The mean STS score was 6.8 ± 5.27%, and the

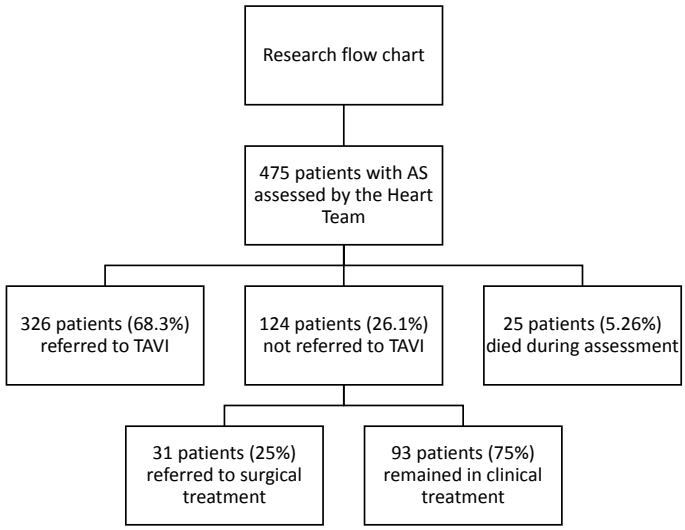

Figure 1 – Research flowchart

mean EuroSCORE II was 17.3 ± 11.03%. In addition, 31 (25.6%) patients had moderate to severe mitral insufficiency. Mean left ventricle ejection fraction (LVEF) was 53% ± 18.25% and mean creatinine clearance (CrCl) was 48.37 ± 17.67 mL/min.

The clinical reasons for inegibility for TAVI–trials were as follows: presence of a thrombus in the left ventricle, severe chronic obstructive pulmonary disease (COPD), coronary disease with indication for surgery, symptomatic carotid disease, contraindication for antiplatelet drugs and life expectancy less than one year (16.5%).

The anatomical contraindications for TAVI included inadequate vascular access due to severe calcification, reduced arteries diameters or severe aortic/iliofemoral tortuosity, insufficient height of the coronary arteries relative to the valvar plane and bicuspid aortic valve.

Of these 124 patients, 31 (25%) underwent conventional valve replacement and 93 (75%) remained in clinical treatment. The main reasons for patients did not go for surgery are: life expectancy less than one year and refusal of surgical procedures.

Table 3 shows the characteristics of clinical and surgical patients. In the clinical group the patients were older, weighed less, had a lower CrCl, and higher STS risk score. There was no difference between the groups in terms of the EuroSCORE. Patients referred to surgery had more symptoms. The mean LVEF, mean gradient and mean aortic valve area were similar between both groups, as well as the LV end-diastolic and end-systolic diameters.

The total mortality of the 124 non-TAVI eligible patients with severe AS was 39.5% (49 patients). Concerning the 93 patients who remained in clinical treatment, 42 (46.2%) died within 56 months of average follow-up. Meanwhile, the 30-day mortality among the operated patients was 12.9%. Late mortality within the surgical sub-group was 11% within an mean 47.4 months follow-up.

Patients who died had a lower LVEF and more severe AS, as indicated by valve area and end-systolic diameter of the left ventricle.

Discussion

In our midst there is few data on the patients outcomes with severe symptomatic AS, who remained in clinical treatment or underwent valve replacement surgery despite the high surgical risk. Evaluating these patients is of considerable importance since the Brazilian population is aging significantly, with the prevalence of aortic stenosis rising as a consequence.

The PARTNER I study showed that TAVI was more effective than clinical treatment for inoperable patients. The follow up showed a mortality of 38,9% in 3- to 5 years in the TAVI group, against a mortality of 66,7% in the clinical group. In addition, the clinical group had a higher rate of rehospitalization within five years (87.6% vs. 47.6%)[10].

Table 1 – Clinical characteristics of the study population (124 patients ineligible for TAVI)

Variable	Measurement
Age (years)	80.66 ± 6.37
Gender (%)	
Male	37%
Female	63%
Weight (kg)	65.88 ± 15.3
STS score (%)	6.8 ± 5.27
EuroSCORE (%)	17.3 ± 11.03
NYHA (n = 124)	
I	16%
II	33.6%
III	44.5%
IV	5.9%
Serum creatinine (mg/dL)	1.23 ± 0.48
Creatinine clearance (mL/min)	48.37 ± 17.67
Hemoglobin (mg/dL)*	12.75 (10.86 – 14.64)
Hematocrit (%)*	39.1 (33.34 – 44.86)
Atrial fibrillation (%)	0.7%
COPD (%)	9.2%
DAPT contraindication (%)	2.6%
Life expectancy of < one year (%)	16.5%
Symptomatic carotid disease (%)	7.6%
Neoplasia (%)	5.6%

STS: Society of Thoracic Surgeons. NYHA: New York Heart Association. COPD: Chronic Obstructive Pulmonary Disease. DAPT: Dual Anti-Platelet Therapy.
** Expressed as median ± interquartile range (Q1 – Q3).*

Table 2 – Baseline echocardiographic findings

Variable	Measurement
LVEF (%)	55.84 ± 15.35
Mean aortic-valve gradient (mmHg)	53 (34.75–71.25)
Max. aortic-valve gradient (mmHg)	80.5 (51–110)
Aortic valve area (cm^2)	0.81 ± 0.27
LVEDD (mm)	51.43 ± 7.72
LVEDV (mL)	127.56 ± 45.96
LVESD (mm)	33.1 ± 8.32
LVESV (mL)	64.41 ± 23.35
Thrombus (%)	1.7%
Bicuspid valve (%)	4.3%
Mitral insufficiency	
Absent/Discrete	74.3%
Moderate	16.2%
Severe	9.4%

LLVEF: left ventricle ejection fraction. LVEDD: left ventricle end-diastolic diameter. LVESV: left ventricle end-systolic volume. LVESD: left ventricle end-systolic diameter. LVEDV: left ventricle end-diastolic volume.
**Expressed as median ± interquartile range (Q1–Q3).*

This study evaluated 475 elderly patients with severe and symptomatic AS. The institution's Heart Team was responsible for deciding between conservative treatment, transcatheter prosthesis implantation, or surgical treatment. In doing so, they considered both the inclusion protocols in use at the institution and the clinical and technical contraindications for TAVI.

It is well-known in cardiology that patients with severe and symptomatic AS have a reduced survival rate following the onset of the classic symptoms of heart failure, syncope, or angina.[2] The only treatment that reduces mortality is correcting the valve obstruction.[20] Until recently, the only option was valve replacement surgery. However, due to the age of patients with calcific AS and associated comorbidities, many symptomatic patients remain in clinical treatment. TAVI has recently emerged as an alternative to valve replacement surgery in patients of advanced age or patients with a technical contraindication to surgical intervention.[10]

In this study, 124 of 475 patients (26%) were ineligible for TAVI trials for technical or clinical reasons by the Heart Team decision. In the literature, the factors for which patients are not referred to valve replacement include age, left ventricular systolic dysfunction, and the presence of comorbidities, such as renal failure, COPD, and coronary disease. Of these factors, age and left ventricle function appear to have the greatest negative impact on the decision to operate.[20] In this study, the main reasons for choosing clinical treatment were the patient's refusal to undergo valve disease correction, associated comorbidities, technical contraindication, and low life expectancy (futile treatment). Some patients also had a

Table 3 – Comparison between clinical treatment and surgical treatment groups

	Clinical treatment (93 patients)	Surgical treatment (31 patients)	*p*
Age (years)	81.91 ± 6.1	76.87 ± 5.71	< 0.01
Sex (%)			
Male	34.1%	45.2%	0.272
Female	65.9%	54.8%	
Weight (kg)	64.2 ± 16.2	70.5 ± 11.6	0.011
STS score (%)	7.2 ± 5.23	5.7 ± 5.31	0.004
EuroSCORE (%)	17.8 ± 10.7	15.9 ± 12	0.206
NYHA (%)			
I - II	53.5%	38.7%	
III-IV	46.5%	61.3%	0.023
Serum creatinine (mg/dL)	1.26 ± 0.54	1.14 ± 0.28	0.674
Creatinine clearance (mL/min)	45.17 ± 17.5	56.6 ± 15.4	0.002
Hemoglobin (mg/dL)*	12.7 (11.3 – 14)	12.8 (11.2 – 4.3)	0.95
LVEF (%)	55.74 ± 15.92	56.1 ± 13.8	0.961
Mean aortic-valve gradient (mmHg)	45 (36 – 57)	50.5 (40.5 – 62.5)	0.249
Max. aortic-valve gradient (mmHg)	75.5 (60 – 88.7)	76.5 (69.7 – 95.5)	0.273
Aortic valve area (cm^2)	0.82 ± 0.24	0.79 ± 0.34	0.26
LVEDD (mm)	51.2 ± 7.9	52.14 ± 7.28	0.567
LVESD (mm)	33.22 ± 8.6	32.6 ± 7.08	0.975

STS: Society of Thoracic Surgeons. NYHA: New York Heart Association. LVEF: left ventricle ejection fraction. LVESD: left ventricle end-systolic diameter. LVEDD: left ventricle end-diastolic diameter.
** Expressed as median ± interquartile range (Q1–Q3).*

technical contraindication to surgery, such as porcelain aorta, or contraindications to TAVI such as significant peripherical artery disease or inadequate aortic annulus size. The Heart Team's evaluation considered invasive treatment to be futile in 16.5% of the patients analyzed; in this population, the life expectancy was less than one year.

Besides, this was a group with elevated risk of mortality, which was confirmed by the high incidence of death before an intervention could be proposed (5.26%). Since these patients were elderly and had severe and symptomatic AS, most of the 475 patients assessed by the Heart Team were referred for TAVI (68.3%), while 19,5% remained in clinical treatment for several reasons mentioned earlier, and only 6.5% could be referred for surgery. Despite the high surgical mortality (12.9%), it was significantly less than for patients who remained in clinical treatment (46,2%). In this sample, it is noteworthy that the surgical mortality was closer to the EuroSCORE projection (17.3 ± 11.03 %). Our data are consistent with the literature, which reports surgical mortality of up to 14% for octogenarians.[21]

The high mortality observed in the clinical sub-group is not a surprising finding. It is well established in the literature on the natural history of AS that shows a 2-3 year patient survival after symptoms begin (angina and dyspnea).[22]

TAVI is an innovative procedure that uses a minimally invasive technique, reduces symptoms and improves the quality of life in elderly patients with severe symptomatic AS.[10] However, this procedure is not yet covered by most private health insurance providers in Brazil nor by SUS, the country's publicly funded health care system .

Although the sample size of this study was fairly small, it represents the reality of elderly symptomatic aortic patients who remain in clinical treatment.

In this study, 26.1% of elderly patients with symptomatic aortic stenosis were ineligible for TAVI research trials, and only 6.5% could be referred to surgery. The authors would like to note that the patients who remained in clinical treatment may have indeed been able to undergo TAVI if the procedure had been available from SUS since the inclusion criteria in the research protocols were more rigid than those for TAVI in clinical practice.

Limitations

This retrospective and observational study evaluated patients with severe AS and high surgical risk who were not eligible for TAVI. It did not discuss the patients late follow-up who underwent TAVI, which could enrich the results obtained. However, since the SUS represents the healthcare reality for most of our country's population, it is important to study the patients' outcomes excluded from the research protocols.

Conclusion

Of the 475 patients with severe symptomatic AS evaluated by the Heart Team, 124 (26.1%) patients were ineligible for TAVI for technical or clinical reasons. Of these, 75% remained in clinical treatment, and 25% were referred to surgery. The clinical mortality was significantly higher than the surgical mortality (46.2% vs. 12.9%; p=0.021). The patients who remained in clinical treatment were older, weighed less, had a higher incidence of renal failure and higher STS risk score.

Author contributions

Conception and design of the research: Ramos AIO, Rezende MO. Acquisition of data: Rezende MO, Dos Santos NSS, Targino DVD, Francischini MS, Andrade AIA, Souza CS, Maldi CP. Analysis and interpretation of the data: Ramos AIO, Andrade AIA, Rezende MO. Statistical analysis: Ramos AIO, Andrade AIA, Rezende MO. Writing of the manuscript: Ramos AIO, Rezende MO, Andrade AIA, Dos Santos NSS, Siqueira DAA, Le Bihan David, Pinto IM. Critical revision of the manuscript for intellectual content: Ramos AIO.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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Study Association

This study is not associated with any thesis or dissertation work.

Ethics approval and consent to participate

This article does not contain any studies with human participants or animals performed by any of the authors.

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