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The Prognostic Significance of Atrial Fibrillation and Left Atrium Size in Patients with Aortic Stenosis

Aim	Aortic stenosis increases left atrial (LA) pressure and may lead to its remodeling. This can cause supraventricular arrhythmia. The aim of this study was to determine if the size of the LA and the presence of atrial fibrillation are related to the prognosis of patients with aortic stenosis.
Material and methods	Clinical evaluation and standard transthoracic echocardiographic studies were performed in 397 patients with moderate to severe aortic stenosis.
Results	In all patients, LA dimension above the median (≥43 mm) was associated with a significantly higher risk of death [HR 1.79 (CL 1.06–3.03)] and a LA volume above the median of 80 ml was associated with a significantly higher risk of death [HR 2.44 (CI 1.12–5.33)]. The presence of atrial fibrillation was significantly associated with a higher risk of death (p <0.0001). The presence of atrial fibrillation [HR 1.69 (CI 1.02–2.86)], lower left ventricular ejection fraction [HR 1.23 (CI 1.04–1.45)], higher NYHA heart failure class [HR 4.15 (CI 1.40–13.20)] and renal failure [HR 2.10 (CI 1.31–3.56)] were independent risk factors of death in patients in aortic stenosis.
Conclusion	The size and volume of the LA and the occurrence of atrial fibrillation are important risk factors for death in patients with aortic stenosis. The presence of renal dysfunction, low left ventricular ejection fraction, high NYHA functional class and atrial fibrillation are independent risk factors of poor prognosis in patients with aortic stenosis.

Keywords	Aortic stenosis; left atrium; atrial fibrillation; echocardiography; aortic valve
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Introduction

Aortic stenosis (AS) is the most common acquired heart valve disease. It is estimated that one in eight people over 74 yrs of age has at least moderate AS [1]. Increased valvular resistance causes pressure overload of the left ventricle (LV), resulting in increased LV end-diastolic pressure, myocardial hypertrophy, and diastolic and systolic dysfunction. As a consequence, left atrial (LA) pressure increases, leading to LA remodeling and supraventricular arrhythmia, including atrial fibrillation (AF) [2, 3]. It is still unclear whether the size of the left atrium (LA) and the presence of AF are significantly related to the prognosis of patients with AS. Rusinaru and co-researchers demonstrated that LA enlargement in patients with sinus rhythm appears to be a significant predictor of mortality risk [4]. Another study performed by Safaryan et al. showed that the LA size and the E/e ratio seemed to be related with poor outcome in patients with unoperated AS [5]. The current study assessed the significance of atrial fibrillation and LA size in the Krakow registry of patients with aortic stenosis (KRAK-AS).

Material and methods

The Krakow KRAK-AS registry was completed from July to October 2016 in the echocardiographic laboratories of the associated departments and outpatient clinics and

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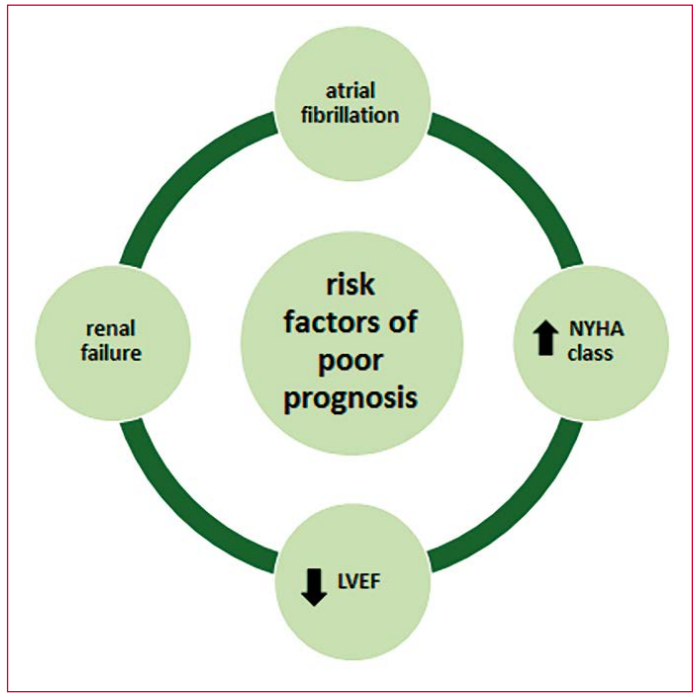
included 397 patients, who were included in the study. This was a prospective observational study performed as part of the registry of patients with aortic stenosis. The study was performed after obtaining approval from the Ethics Committee of the Jagiellonian University Collegium Medicum in Krakow (ethic statement number: 122.6120.66.2015 dated April 30, 2015). Patients with concomitant moderate or severe disease of other than the aortic value were excluded from the study. The study included all consecutive patients in whom at least isolated, moderate AS was diagnosed, i.e., mean gradient ≥ 20 mmHg and/or aortic valve area indexed to the body surface area (AVAi) below 0.80 cm^2/m^2. Only 1% of eligible patients did not agree to participate in the study. All included patients gave written, informed consent.

A standard transthoracic echocardiographic study was performed. This included the LA parameters: LA diameter obtained in a parasternal long axis view; LA volume (LAV) obtained in apical 4-chamber and 2-chamber views. The LA surface area indexed volume (LAVI) was calculated. The left ventricular (LV) ejection fraction (LVEF) was calculated by the Simpson method. AS severity was assessed based on the aortic valve area (AVA) and AVAi, with these areas calculated on the basis of the continuity equation for fluids. The mitral inflow pattern was also recorded. In patients with sinus rhythm, the parameters of the diastolic function of the VL were analyzed according to the guidelines of the American Society of Echocardiography (ASE) and the European Association of Cardiovascular Imaging (EACVI) [6]. The following parameters were used to assess the diastolic function: LAVI, peak velocities of the E and A waves of mitral influx, and the mitral annular velocity was assessed by tissue Doppler echocardiography (TDE) in 4-chamber apical view (e' medial and e 'lateral). The study endpoint was death from any cause at a 3-yr follow-up from the date of inclusion. The patients with moderate AS who developed a severe stage of the defect during follow-up were transferred to a severe AS group.

Statistical analysis was performed using JMP® software (version 16.2.0. SAS Institute Inc., Cary, NC, USA). $p<0.05$ was considered statistically significant. The Shapiro-Wilk test was used to evaluate the normality of the data distributions. Values of continuous variables with normal distribution are presented as mean ± standard deviation (SD), and values of variables with non-normal distribution are presented as median and interquartile range. The ranges of values of individual parameters of the LA size were initially divided using the median, and then, the cut-off points having the maximum sensitivity and specificity in predicting death were determined using the Receiver Operating Characteristic (ROC) curves method. To identify the p value for particular subgroups in Table 1, the Kruskal-Wallis test for continuous variables and likelihood-ratio test for nominal variables were used. The post hoc analyses were performed using the Steel-Dwass method and the Bonferroni correction for continuous and nominal parameters, respectively. Univariate and multivariate Cox survival analyses were performed, depending on the severity of AS and the treatment method, i.e., surgical or conservative. A Kaplan-Meier analysis of the risk of death in patients with sinus rhythm and atrial fibrillation was also performed.

Central illustration. The Prognostic Significance of Atrial Fibrillation and Left Atrium Size in Patients with Aortic Stenosis



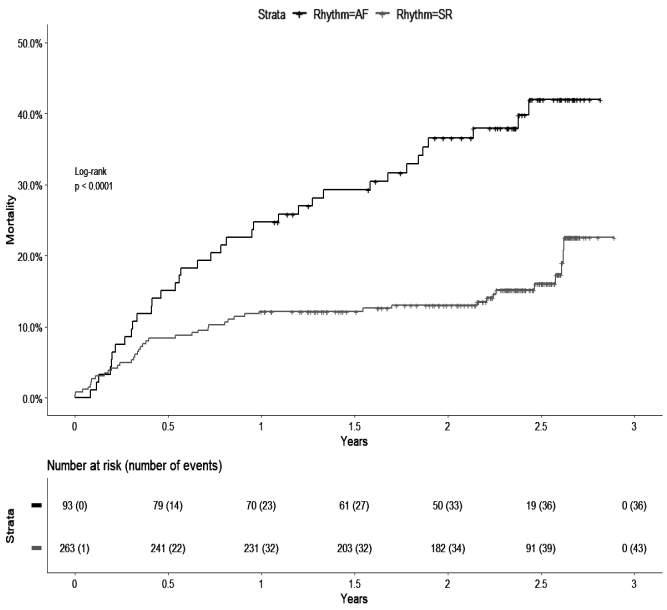
Chronic kidney disease was defined as kidney damage with eGFR <60 ml/min/1.73 m^2 that persisted for more than 3 months. The LV mass, mass of the LV indexed to the body surface area (LVMI) and relative wall thickness (RWT) were calculated and proved to be comparable in the group of patients with sinus rhythm and AF.

Results

Patients with severe AS, i.e., AVAi <0.60 cm^2/m^2 and/or mean gradient ≥ 40 mmHg, were identified as Group 1. Patients with moderate AS, i.e., AVAi between 0.60 and 0.80 cm^2/m^2 and/or mean gradient between 20 and 39 mmHg, were identified as Group 2. In each group, two subgroups were distinguished: patients who underwent surgical or transcatheter aortic valve implantation (Subgroups 1A and 2A) and patients treated conservatively (Subgroups 1B and 2B). In the group of 288 patients with severe AS, 205 were operated. Of the 109 patients with moderate AS, 31 patients were operated. The reason for aortic valve surgery at this stage of disease were severe symptoms attributed to AS, as other reasons were excluded, or concomitant coronary disease requiring coronary artery bypass grafting.

Table 1 presents the clinical characteristics of patients in each subgroup. AF patients are divided into 2 subgroups:

Figure 1. Kaplan–Meier analysis of the risk of death in patients with sinus rhythm (SR, light line) or with atrial fibrillation (AF, dark line; operated and non-operated subgroups combined)



paroxysmal AF or permanent AF (this subgroup consisted of patients with persistent and permanent AF). The patients who underwent surgery were younger compared to the patients treated conservatively (median age 69 (60–77) yrs vs. 81 (74; 85) yrs). The reasons for the conservative treatment were numerous comorbidities, frailty syndrome, or the patient's lack of consent to surgical treatment. In all groups, a comparable proportion of men and women was observed. Body surface area was also comparable in all groups. There were no significant differences between groups in the prevalence of hypertension and diabetes, while in conservatively treated patients, chronic kidney disease was more frequent (32%). The LV mass in patients with sinus rhythm was 238 g (193;301), LVMI was 128 g/m^2 (103;150), and RWT was 0.52 (0.44;0.59). Among patients with AF the LV mass was 231 g (193;306), LVMI was 127 g/m^2 (103;147), and RWT 0.51 (0.42–0.59).

The highest percentage of patients with AF, both paroxysmal and permanent, occurred in the group of patients with severe AS that was treated medically. These patients also had the highest median LA dimensions, i.e., LAV and LAVI.

In all patients, regardless of the severity of AS, a LA dimension greater than median (≥43mm), was associated with a significantly higher risk of death [hazard ratio (HR) 1.79 (95% confidence interval (CI) 1.06–3.03); p = 0.0303]. Similarly, LAV above the median of 80 ml was associated with a >2 fold higher risk of death [HR 2.44 (CI 1.12–5.33); p = 0.0253]. LAVI significance was at the borderline of significance [HR 1.02 (CI 1.00–1.03); p = 0.045].

In an analysis of the entire study group, the presence of AF (permanent or paroxysmal) was significantly associated with a higher risk of death. When AF was observed, mortality in the 3-yr follow-up reached 42%; when sinus rhythm was present, mortality was 22.5% (p <0.0001) (Fig. 1).

Analogous results were observed in the subgroups of operated and non-operated patients, but the results were only significant in the operated subgroup. In the operated subgroup, mortality was 31.3% in patients with AF and 21.8% in patients with sinus rhythm (p = 0.028). In the non-operated subgroup, mortality was 29.0% in patients with AF and 20.6% in patients with sinus rhythm (p = 0.53) (Fig. 2).

Of the entire study group. 47.9% of patients with AF and who had not been operated on died during the 3-yr follow up, while only 26.1% of patients with AF who underwent surgery

Table 1. Clinical data of patients in each subgroup

Variable	Severe AS. Operated (1A, n=205)	Severe AS. Not operated (1B, n=83)	Moderate AS. Operated (2A, n=31)	Moderate AS. Not operated. (2B, n=78)	p*
Age (yrs)	71 (65–79) 1B	81 (74–85) 1A,2B,2A	69 (60–77) 1B	74 (58–81) 1B	<0.0001
Male	112 (55)	41 (49)	17 (55)	45 (58)	0.7593
Permanent AF	29 (15) 1B	22 (30) 1A, 2B	4 (14)	9 (12) 1B	0.0222
Paroxysmal AF	13 (7)	12 (16) 2A	0 (0) 1B	5 (7)	0.0126
LVEF (%)	60 (53–65) 1B,2B	55 (45–62) 1A,2B	60 (50–65)	63 (57–68) 1A,1B	0.0001
LA (mm)	42 (39–47) 1B	46 (41–53) 1A	43 (38–50)	43 (39–47)	0.0081
LAV (ml)	81 (53–104) 2A	86 (66–117) 2A,2B	36 (17–74) 1A,1B	62 (32–89) 1B	0.0005
LAVI (ml/m2)	45 (31–57)	52 (38–62) 2A,2B	26 (12–44) 1B	38 (25–53) 1B	0.0013
NYHA class	2 (2–3) 2B	2 (2–3) 2B	2 (1–3)	1 (0–2) 1A,1B	<0.0001
BSA (m2)	1.9 (1.7–2.0)	1.8 (1.7–2.0)	1.9 (1.8–2.0)	1.9 (1.7–2.0)	0.9449
Hypertension	149 (78)	62 (84)	18 (64)	55 (74)	0.1942
Diabetes mellitus	28 (14)	11 (13)	5 (16)	7 (9)	0.3311
Renal dysfunction	29 (15) 1B	24 (32) 1A,2A	2 (7) 1B	14 (19)	0.0057

Data are number (percentage) or median and interquartile range. *Among group p values were calculated using the Kruskal-Wallis test for continuous variables and likelihood-ratio test for nominal variables. 1A,1B,2A,2B subgroup number against which statistical significance was obtained by post hoc analysis. AF, atrial fibrillation; AS, aortic stenosis; BSA, body surface area; LA, left atrium; LAV, LA volume; LAVI, LA volume index; LVEF, left ventricle ejection fraction; NYHA class, New York Heart Association classification of heart failure.

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Figure 2. Kaplan-Meier analysis of the risk of death in patients with sinus rhythm (SR, light line) and atrial fibrillation (AF, dark line) in patients with AS that underwent surgery

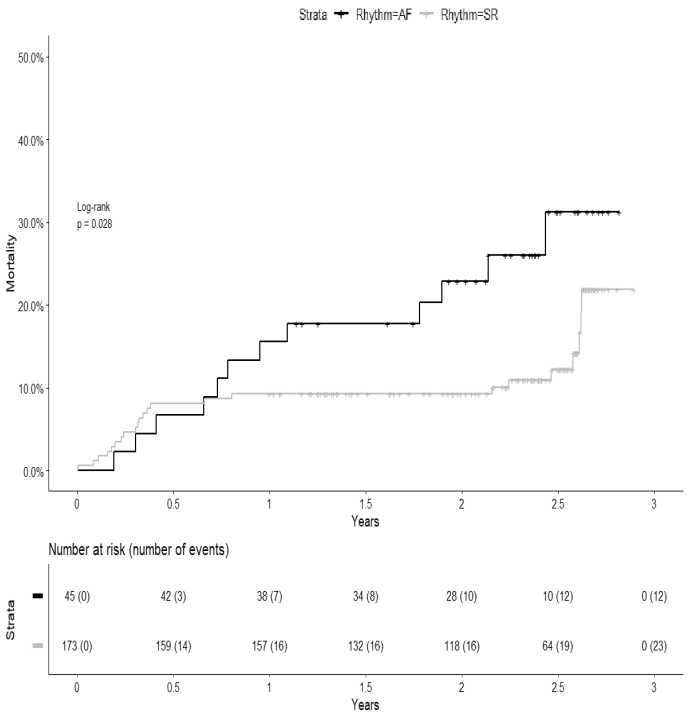


Table 2. Univariate analysis of the risk of death in patients with severe AS that underwent surgery

Variable	HR (95% CI)	p
Sinus rhythm	0.43 (0.21 - 0.89)	0.0219
Renal dysfunction	3.06 (1.47 - 6.36)	0.0028
RVSP ≥ 37.50mmHg	3.06(1.32 - 12.27)	0.0146
LAV ≥ 81ml	1.03 (1.01 - 1.06)	0.0124
LAVI ≥ 45ml/m2	1.05 (1.01 - 1.10)	0.0129
NYHA class (1 class increment)	1.91 (1.17 - 3.32)	0.0082
LVEF (10% decrement)	0.96 (0.94 - 0.99)	0.0043

HR, hazard ratio; CI, confidence interval; LAV, left atrium volume; LAVI, left atrium volume index; LVEF, left ventricle ejection fraction; NYHA class, New York Heart Association classification of heart failure; RVSP, right ventricular systolic pressure.

Table 3. Multivariate analysis of the risk of death in patients with aortic stenosis (all groups combined)

Variable	Condition	HR (95% CI)	p
Renal dysfunction	present/absent	2.10 (1.31 - 3.56)	0.0024
LVEF (%)	10% decrement	1.23 (1.04 - 1.45)	0.0151
NYHA class	1 class increment	4.15 (1.40 - 13.20)	0.0126
Atrial fibrillation	present/absent	1.69 (1.02 - 2.86)	0.0429

LVEF, left ventricle ejection fraction; NYHA class, New York Heart Association classification of heart failure.

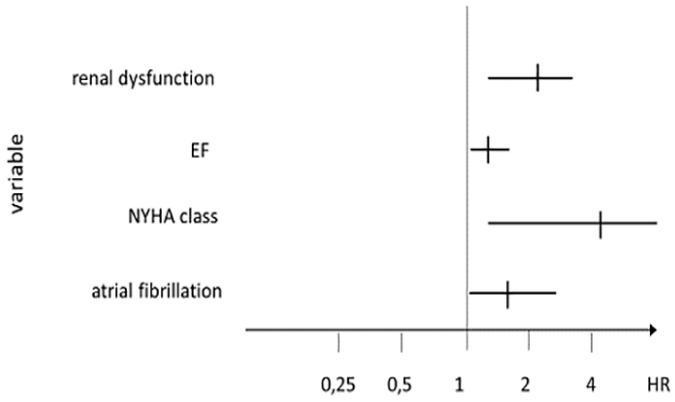
died during this period. Survival in the group with sinus rhythm was comparable regardless of type of treatment. The mortality rate in this group was 16.3% among patients not operated and 14.3% among those operated.

In all patients with sinus rhythm, both the LA dimension below the ROC cut-off point (45 mm) and the LAV below the ROC cut-off point (76 ml) were associated with a significantly lower risk of death in the 3-yr follow-up [HR 0.34 (CI 0.17–0.68); p = 0.002 and HR 0.23 (CI 0.06–0.83); p = 0.025, respectively].

In the subgroup of patients with severe AS who underwent surgical treatment (subgroup 1A), the presence of paroxysmal AF and the size of LAV and LAVI were associated with a greater risk of death. Moreover, the results showed that diagnosed chronic renal failure, right ventricular systolic pressure (RVSP) above the median (>37.5 mmHg), and the progressive degree of the New York Heart Association (NYHA) functional class of heart failure were factors that increased the risk of death. However, a greater LVEF was a factor that reduced the risk of death. The presence of sinus rhythm in patients with greater LVEF was an important protective factor (Table 2). Age has not been found to have a significant impact on the risk of death in this group of patients.

In the subgroup of patients with moderate AS who underwent surgery (subgroup 2A), the parameters of the LA size and the type of heart rhythm did not have a statistically significant prognostic importance.

Figure 3. Multivariate analysis of the risk of death in patients with aortic stenosis (all groups combined, see in the text for how variables were chosen). EF, left ventricle ejection fraction; NYHA class, New York Heart Association classification of heart failure



Multivariate analysis showed that the presence of AF, lower LVEF, higher NYHA class of heart failure, and renal failure were independent risk factors of death in these patients (Fig. 3, Table 3).

Diastolic dysfunction was found in 27 out of 108 patients with sinus rhythm (25%), and due to this small number of patients, a prognostic analysis was not performed.

Discussion

The incidence of both AS and AF typically increases with age. The object of this study was to determine the prognostic

significance of AF coexistent with AS. The study revealed that this is a common phenomenon. In a group of 397 patients in the KRAK-AS registry, AF was found in 23.6% (16.1% permanent, 7.5% paroxysmal); thus, the problem occurred in every fourth patient. Moreover, the prevalence of AF was higher in patients with a more advanced stage of AS. In patients with severe AS, 26.4% of patients had AF, compared to 16.5% of patients with moderate AS.

In other studies, AF was even more prevalent. Stortecky et al. showed that severe aortic stenosis accompanied AF in 33.7% of patients [7]. Other studies have shown that AF can coexist with AS in as many as 50% of cases [8, 9]. On the other hand, in a study by Philippart et al. that analyzed a group of patients with AF, 32% of the patients had concomitant AS [10].

The current results confirm that AF is a risk factor for death in long-term follow-up of AS patients, both in operated patients and in persons treated medically. The consequences of AF are not only deteriorating heart efficiency, worse exercise tolerance, chest pain, fainting, and stroke, but also increased risk of bleeding resulting from anticoagulation [11].

All variables used in the univariate analysis were taken to construct a multivariate Cox survival analyses. It is notable that when the size of the LA exceeded the median, even in sinus rhythm patients, this factor was associated in the univariate analysis with an increased risk of death among the entire group of patients. This was true regardless of the severity of AS and the treatment strategy. However, in the multivariate analysis, increased LA size was not been found to be an independent risk factor for death. This may have been due to the fact that atrial enlargement and AF are related, and the presence of rhythm type was a stronger predictor of death than LA size. Also, the RVSP variable appeared not to be statistically significant during multivariate analysis. This may have been due to the fact that this variable was not assessable in some patients.

Losi with colleagues examined the estimated LA volume (eLAVI) and showed that a high eLAVI was independently associated with an increased risk of adverse cardiovascular events [12]. Their study, however, was based only on patients with asymptomatic, mild, or moderate AS, while patients with severe AS or symptomatic were not included. In the study of Naito and colleagues, the relationship between LAVI and postoperative AF in patients with severe AS was analyzed [13]. They concluded that the LAVI assessment may be a useful tool to gauge the risk of AF occurrence after aortic valve replacement. However, the significance of this parameter in predicting other postoperative outcomes has not been clearly defined.

In a study by Morimoto et al., the minimum LA volume index (LAVImin) was assessed echocardiographically at the end of diastole, i.e., just before mitral valve closure, and the clinical symptoms in patients undergoing aortic valve replacement surgery due to severe stenosis were analyzed [14]. LAVImin after aortic valve replacement was significantly higher in symptomatic patients compared to asymptomatic patients. This confirms the association of AS severity with LA overload and dilatation. LA enlargement also correlates with the severity of LV diastolic dysfunction and is also a predictor of cardiovascular events, such as AF and stroke [15]. The study of Benjamin et colleagues also showed that the risk of death was significantly higher in case of previously diagnosed AF. Therefore, in the overall assessment of patients with AS, it is worth paying attention, not only to the leading heart rhythm, but also to the size of the LA and LV diastolic function. These may indicate risk of supraventricular arrhythmia and further complications, including an increased risk of death. These complications may affect both patients undergoing surgery and those treated medically.

LA dimensions may be related to the severity of the AS and the amount of LV remodeling and these may be mechanisms underlying the prognosis of AS. Increased valve resistance causes pressure overload of the LV, impaired LV relaxation, hypertrophy and fibrosis. As a result, gradually diastolic and systolic LV dysfunction occurs leading to increased LV end-diastolic pressure. The concomitant LA pressure increase causes both LA dilatation and dysfunction [16] [16]. Thus, LA anatomical and functional status can be a marker reflecting the severity and stage of the aortic stenosis syndrome. O'Connor et al analyzed 52 patients with severe AS and 20 healthy people matched for sex, heart rate, BSA, and blood pressure. Systolic and late diastolic LA strain were significantly reduced in patients with AS compared with controls [17]. Atrial fibrillation is a consequence of these above pathophysiological mechanisms, and, thus, it could be used as a simple, binary marker of the severity of AS. The results of the current study support the concept of using this marker as a part of a prognostic evaluation.

The advancement of the aortic valve defect, indirectly through left ventricular diastolic dysfunction, may play a role in the AF pathomechanism. AF, LV diastolic dysfunction, and LA enlargement are not currently considered in the European guidelines as markers of the clinical stage of AS, but LV diastolic dysfunction has appeared in American recommendations for AS stages assessment [18]. Further studies could provide additional evidence supporting inclusion of these parameters to the prognostic evaluation in patients with AS. This could become an additional argument in favor of surgery in moderate AS, before advanced changes in the atrial myocardium, arrhythmic consequences, and increased mortality risk occur.

Limitations of the study

The analyzed data were based on a registry. The registry includes reports of echocardiographic examinations performed in various laboratories. Thus, the data could have been affected by methodological differences in the measurements. The limited number of patients in some subgroups could also have decreased the significance of the analyses.

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Conclusions

The size and volume of the LA and AF are important risk factors for death in patients with AS. The presence of renal dysfunction, LVEF, a high NYHA functional class of heart failure, and AF are independent risk factors of poor prognosis in patients with AS. Further longitudinal studies are needed to assess if patients with moderate AS and a first episode of AF, along with the presence of diastolic dysfunction or moderate LA dilatation, could benefit from early invasive treatment.

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