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ORIGINAL ARTICLE

The impact of atrial fibrillation on prognosis in aortic stenosis

Dorien Laenens [1], Jan Stassen [1], Xavier Galloo [1], See Hooi Ewe [2], Gurpreet K. Singh [1], Mohammed R. Ammanullah [2], Kensuke Hirasawa [1], Ching-Hui Sia [3], Steele C. Butcher [1,4], Nicholas W.S. Chew [3], William K.F. Kong [3], Kian Keong Poh [3], Zee P. Ding [2], Nina Ajmone Marsan [1] and Jeroen J. Bax [1,5,*]

[1]Department of Cardiology, Leiden University Medical Center, Albinusdreef 2, 2333 ZA Leiden, The Netherlands; [2]Department of Cardiology, National Heart Center Singapore, 5 Hospital Drive, Singapore 169609, Singapore, Singapore; [3]Department of Cardiology, National University Heart Center Singapore, 5 Lower Kent Ridge Rd, Singapore 119074, Singapore; [4]Department of Cardiology, Royal Perth Hospital, 197 Wellington St, Perth, WA 6000, Australia; and [5]Department of Cardiology, Turku Heart Center, University of Turku and Turku Unviersity Hospital, Kiinamyllynkatu 4-8, 20521 Turku, Finland

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Background Atrial fibrillation (AF) and aortic stenosis (AS) are both highly prevalent and often coexist. Various studies have focused on the prognostic value of AF in patients with AS, but rarely considered left ventricular (LV) diastolic function as a prognostic factor.

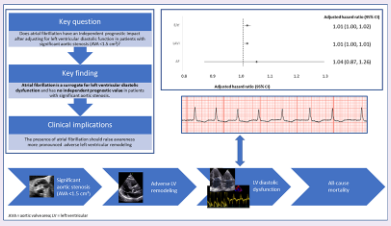
Objective To evaluate the prognostic impact of AF in patients with AS while correcting for LV diastolic function.

Methods Patients with first diagnosis of significant AS were selected and stratified according to history of AF. The endpoint was all-cause mortality.

Results In total, 2849 patients with significant AS (mean age 72 ± 12 years, 54.8% men) were evaluated, and 686 (24.1%) had a history of AF. During a median follow-up of 60 (30–97) months, 1182 (41.5%) patients died. Ten-year mortality rate in patients with AF was 46.8% compared to 36.8% in patients with sinus rhythm (SR) (log-rank $P < 0.001$). On univariable (HR: 1.42; 95% CI: 1.25–1.62; $P < 0.001$) and multivariable Cox regression analysis (HR: 1.19; 95% CI: 1.02–1.38; $P = 0.026$), AF was independently associated with mortality. However, when correcting for indexed left atrial volume, E/e' or both, AF was no longer independently associated with all-cause mortality.

Conclusion Patients with significant AS and AF have a reduced survival as compared to patients with SR. Nonetheless, when correcting for markers of LV diastolic function, AF was not independently associated with outcomes in patients with significant AS.

Graphical Abstract



Keywords Aortic stenosis • Atrial fibrillation • Diastolic dysfunction • prognosis

* Corresponding author: Department of Cardiology, Heart Lung Center, Leiden University Medical Center; Albinusdreef 2, 2300 RC Leiden, The Netherlands; Tel.: +31 71 526 2020; Fax: + 31 71 526 6809; Email: j.j.bax@lumc.nl

Introduction

Aortic stenosis (AS) is a common valvular heart disease, with prevalence increasing with age.[1] In addition, AS frequently coexists with atrial fibrillation (AF). AF is the predominant sustained arrhythmia in the general population, with a prevalence of 0.5–1%.[2] However, in patients with severe AS, AF is present in 15%[3] and up to 50% in patients undergoing transcatheter aortic valve replacement (TAVR).[4] Various studies have highlighted the prognostic value of AF in patients with AS,[5–12] with conflicting results. While many studies in different subgroups of AS have shown that AF is associated with worse outcomes,[5–11] a recent study in patients with severe AS did not show an independent relationship between AF and mortality.[12] The authors suggest that AF is a marker of underlying structural abnormalities associated with worse outcomes. It is well known that significant AS induces pressure overload, which leads to adverse left ventricular (LV) remodeling. An increased afterload is associated with LV hypertrophy,[13] LV diastolic dysfunction, increased LV filling pressures, and subsequent left atrial (LA) dilatation, which ultimately might cause AF.[14] Accordingly, the aim of the current study was to evaluate whether AF is only an epiphenomenon of the cardiac remodeling process or has an independent prognostic value in patients with significant AS. We hypothesized that LV diastolic dysfunction resulting from chronic LV pressure overload plays the key role in mediating prognosis and that AF is just a bystander.

Methods

Patient Selection and Covariates

From an ongoing multicentre registry of patients with AS (Leiden University Medical Center, Leiden, The Netherlands; National Heart Center, Singapore and National University Heart Center Singapore, Singapore), patients ≥18 years presenting between May 1994 and December 2019 with a first echocardiographic diagnosis of significant AS were included. Significant AS was defined as an aortic valve area (AVA) ≤1.5 cm^2.[15] Patients with previous aortic valve surgery, mitral valve replacement, congenital heart disease (except bicuspid aortic valve and aortic coarctation repair), dynamic LV outflow tract (LVOT) obstruction, moderate or severe mitral valve disease, or insufficient clinical data to determine the history of AF were excluded (*Figure 1*). Patients were retrospectively divided into two groups according to the history of AF [AF group and sinus rhythm (SR) group]. The definition of AF was based on a previous episode of AF, documented on ECG, rhythm monitoring, or cardiac implantable electronic devices before the index echocardiogram demonstrating significant AS. Baseline demographic and clinical data including age, sex, cardiovascular risk factors, comorbidities, symptoms, medication use, aortic valve replacement (AVR), and laboratory results were collected from medical records in the departmental electronic patient information system.

Patient Outcomes

All patients were followed-up for the occurrence of all-cause mortality, as ascertained by a review of hospital records linked to the governmental death registry database. Because of the retrospective design of the study, the ethics committees of the participating centres waived the requirement for written informed consent.

Transthoracic Echocardiography

All echocardiographic exams were performed according to current guidelines.[15–19] From the parasternal long-axis view, LV dimensions were assessed, and LV mass was calculated by the formula of Devereux.[16] LV end-diastolic and end-systolic volumes were assessed from the apical two- and four-chamber views, and the LV ejection fraction (LVEF) was calculated using the Simpson's biplane method.[16] LA volumes were calculated using the method of discs at end-systole in the apical two- and four-chamber views.[16] All volumes were indexed for body surface area (BSA), calculated by the formula of Du Bois. Pulsed wave Doppler recordings were obtained to measure LVOT velocity time integral from the apical three- or five-chamber views. Continuous wave Doppler recordings were obtained to estimate peak aortic jet velocity from the apical three-chamber, apical five-chamber, or parasternal right views, when feasible.[15] Mean aortic valve pressure gradient was calculated using the simplified Bernoulli equation.[15] Stroke volume was calculated using the LVOT velocity time integral and LVOT cross-sectional area, estimated by the LVOT diameter measured in the parasternal long-axis view, and was indexed for BSA. AVA was calculated using the continuity equation.[17] Diastolic function was assessed by pulsed-wave Doppler recordings of the transmitral flow to obtain peak early (E) and late (A) diastolic velocities.[18] Tissue

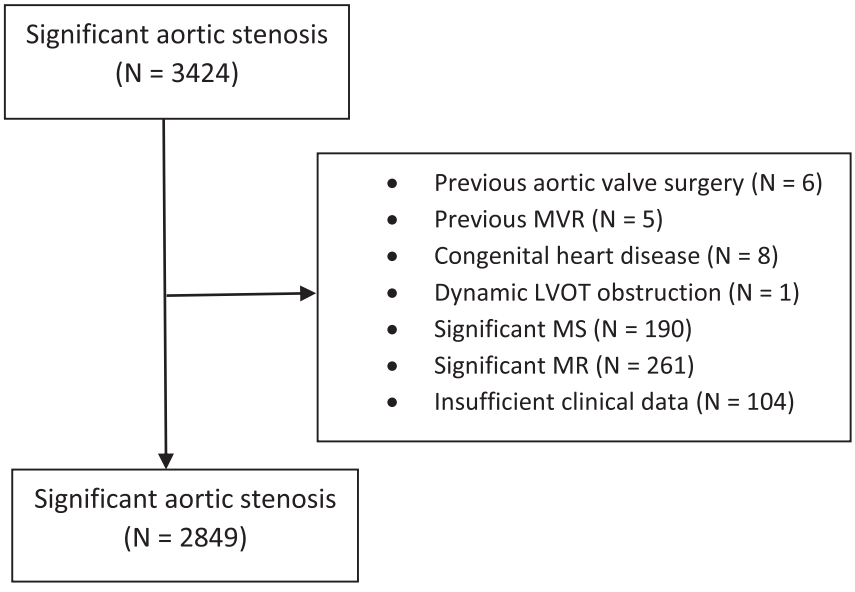


Figure 1 Patient selection. MVR = mitral valve replacement; LVOT = left ventricular outflow tract; MS = mitral stenosis; MR = mitral regurgitation.

Table 1 Baseline characteristics

Variable	Overall population (n = 2849)	SR group (N = 2163)	AF group (N = 686)	P value
Demographic and clinical characteristics				
Age, years	72 (±12)	72 (±13)	75 (±9)	**<0.001**
Male sex, No. (%)	1561 (54.8%)	1181 (54.6%)	380 (55.4%)	0.93
Body mass index, kg/m^2	26.2 (±5.2)	26.2 (±5.4)	26.2 (±4.7)	0.94
Arterial hypertension, No. (%)	2137 (75.0%)	1605 (74.2%)	532 (77.6%)	0.22
Hypercholesterolemia, No (%)	1826 (64.1%)	1391 (64.3%)	435 (63.4%)	0.51
Diabetes mellitus, No (%)	835 (29.3%)	627 (29.0%)	208 (30.3%)	0.63
Coronary artery disease, No (%)	1218 (42.8%)	897 (41.5%)	321 (46.8%)	**0.03**
Smoking history, No. (%)	834 (29.3%)	621 (28.7%)	213 (31.0%)	0.34
COPD, No. (%)	258 (9.1%)	173 (8.0%)	85 (12.4%)	**0.001**
Stroke, No. (%)	383 (13.4%)	263 (12.2%)	120 (17.5%)	**0.001**
NYHA class, No. (%)				**<0.001**
* NYHA I	1433 (50.3%)	1132 (52.3%)	301 (43.9%)	
* NYHA II	831 (29.2%)	622 (28.8%)	209 (30.5%)	
* NYHA III	431 (15.1%)	287 (13.3%)	144 (21.0%)	
* NYHA IV	108 (3.8%)	77 (3.6%)	31 (4.5%)	
Angina, No (%)	427 (15.0%)	350 (16.2%)	77 (11.2%)	**0.001**
Syncope, No (%)	97 (3.4%)	76 (3.5%)	21 (3.1%)	0.51
Aortic valve replacement, No (%)	1464 (51.4%)	1108 (51.2%)	360 (52.5%)	0.77
TAVR, No (%)	784 (27.5%)	467 (21.6%)	214 (31.2%)	**<0.001**
SAVR, No (%)	681 (23.9%)	643 (29.8%)	141 (20.6%)	**<0.001**
Medication use				
Beta blocker, No (%)	1385 (48.6%)	978 (45.2%)	407 (59.3%)	**<0.001**
ACE-inhibitor/ARB, No (%)	1376 (48.3%)	995 (46.0%)	381 (55.5%)	**<0.001**
MRA, No (%)	145 (5.1%)	82 (3.8%)	63 (9.2%)	**<0.001**
Aspirin, No (%)	1211 (42.5%)	1015 (46.9%)	196 (28.6%)	**<0.001**
Oral anticoagulation, No. (%)	594 (20.8%)	160 (7.4%)	434 (63.3%)	**<0.001**
Statin, No (%)	1779 (62.4%)	1348 (62.3%)	431 (62.8%)	0.78
Diuretic, No (%)	971 (34.1%)	641 (29.6%)	330 (48.1%)	**<0.001**
Calcium channel blocker, No (%)	949 (33.3%)	727 (33.6%)	222 (32.4%)	0.38
Laboratory results				
eGFR MDRD, Mml/min/1,73 m^2	64.6 (±29.2)	65.7 (±29.5)	61.0 (±27.8)	**<0.001**
Hemoglobin, g/dl	14.7 (±4.8)	14.7 (±5.1)	14.7 (±3.6)	0.94

Bold values represent significant P values (i.e. <0.05).
Values are presented as mean ± SD or N (%).
COPD = chronic obstructive pulmonary disease; NYHA = New York Heart Association; TAVR = transcatheter aortic valve replacement; SAVR = surgical aortic valve replacement; ACE = angiotensin converting enzyme; ARB = angiotensin receptor blocker; MRA = mineralocorticoid receptor antagonist; and eGFR MDRD = estimated glomerular filtration rate by modification of diet in renal disease.

Doppler imaging of the mitral annulus on the apical four-chamber view was used to measure e' at both the lateral and septal sides, and e' was averaged to calculate the E/e' ratio.[18] Pulmonary artery systolic pressure was calculated from the peak velocity of the tricuspid regurgitant jet using the Bernoulli equation, adding the right atrial pressure determined by the inspiratory collapse and diameter of the inferior vena cava.[16] Tricuspid annular plane systolic excursion (TAPSE) was measured from M-mode recordings to estimate the right ventricular (RV) systolic function.[16] Severity of aortic regurgitation was graded using a multiparametric approach.[19]

Statistical Analysis

Continuous variables are expressed as mean ± standard deviation or median and interquartile range (IQR), as appropriate. Categorical variables are presented as frequencies and percentages. Continuous variables were compared between groups using an independent t-test when normally distributed or Mann–Whitney U-test when not normally distributed. Categorical variables were compared using the Pearson χ^2 test. The cumulative survival curve was estimated by the Kaplan–Meier method, and differences between groups were compared using the log-rank test. Cox proportional hazard regression analysis was used to examine the association between AF and all-cause mortality. AVR was entered as a time-dependent covariate. Variables with a $P < 0.05$ on univariable analysis were included in the multivariable analysis, unless the amount of missing values exceeded 10% of the study population. A baseline model was constructed without AF and significant LV diastolic function parameters. First, AF was added to the baseline model. Next, AF and one significant LV diastolic function parameter were added. Finally, AF and all significant LV diastolic function parameters were added to the baseline model. The stability of this selection procedure was checked by investigating whether a

Table 2 Echocardiographic characteristics

Variable	Overall (*N* = 2849)	SR group (*N* = 2163)	AF group (*N* = 686)	*P* value
Left ventricle and atrium				
IVSD, mm	12.1 (±2.5)	12.0 (±2.5)	12.3 (±2.6)	**0.004**
PWT, mm	11.4 (±2.2)	11.3 (±2.1)	11.7 (±2.3)	**<0.001**
RWT	0.5 (0.4, 0.6	0,5 (0.4, 0.6)	0.5 (0.4, 0.6)	0.096
LV mass index, g/m^2	114.5 (93.0, 137.7)	113.1 (92.0, 135.8)	118.1 (95.3, 176.5)	**<0.001**
LVEDV index, ml/m^2	54.3 (43.3, 68.7)	54.7 (43.9, 69.0)	52.8 (40.8, 67.8)	**0.026**
LVESV index, ml/m^2	21.0 (15.6, 29.2)	20.6 (15.5, 28.8)	22.2 (15.8, 30.7)	**0.006**
LVEF, %	60 (52, 66)	61 (54, 67)	58 (47, 65)	**<0.001**
Stroke volume index, ml/m^2	44.5 (±12.9)	45.9 (±12.6)	42.2 (±13.5)	**<0.001**
LAVI, ml/m^2	35.2 (27.5, 45.5)	32.9 (25.9, 42.0)	43.6 (34.5, 57.3)	**<0.001**
E/e'	14.7 (11.0, 20.0)	14.5 (10.8, 26.3)	15.7 (11.7, 21.6)	**<0.001**
Aortic valve				
Anatomy				**<0.001**
Bicuspid, No (%)	309 (10.8%)	269 (12.4%)	40 (5.8%)	
Tricuspid, No (%)	2450 (86.0%)	1811 (83.7%)	639 (93.1%)	
Mean gradient, mmHg	27.0 (20.0, 37.9)	27.3 (20.0, 38.5)	26.0 (19.0, 35.1)	**0.003**
Peak velocity, m/s	3.4 (±0.8)	3.5 (±0.8)	3.3 (±0.8)	**<0.001**
AVA, cm^2	1.1 (0.9, 1.3)	1.1 (0.9, 1.3)	1.1 (0.9, 1.3)	0.98
AVA index, cm^2/m^2	0.6 (±0.2)	0.6 (±0.2)	0.6 (±0.2)	0.47
AR severity				0.57
Moderate or severe	244 (8.6%)	178 (8.2%)	66 (9.6%)	
Right ventricle				
PAPS, mmHg	31.4 (25.6, 38.8)	30.0 (25.0, 37.0)	34.8 (28.0, 42.6)	**<0.001**
TAPSE, mm	21.2 (± 4.7)	21.8 (± 4.6)	19.6 (± 4.8)	**<0.001**

Bold values represent significant *P* values (i.e. <0.05).
Values are presented as mean ± SD, median and IQR or *N* (%).
IVSD = interventricular septum diameter; PWT = posterior wall thickness; RWT = regional wall thickness; LVEDV = left ventricular end-diastolic volume; LVESV = left ventricular end-systolic volume; LVEF = left ventricular ejection fraction; LAVI = left atrial volume index; AVA = aortic valve area; AR = aortic regurgitation; PAPS = pulmonary artery systolic pressure; and TAPSE = tricuspid annular plane systolic excursion.

Cox regression model with backward elimination ($P = 0.1$) led to the same findings. To inspect for multicollinearity, the Pearson correlation coefficient was calculated between continuous variables, assuming no significant multicollinearity when the correlation coefficient was <0.5. Hazard ratios (HR) were presented with 95% confidence intervals (CI). A two-sided $P < 0.05$ was considered statistically significant. All analyses were performed using SPSS Statistics for Windows, version 25 (IBM, Armonk, New York, USA).

Results

Patient Population

In total, 2849 patients with significant AS (AVA < 1.5 cm^2) were selected (mean age 72 ± 12 years, 54.8% men) (*Figure 1*). One thousand ninety one patients (38.3%) had severe AS (i.e. AVA ≤ 1 cm^2, a mean aortic valve gradient ≥40 mmHg or peak aortic valve velocity ≥4 cm/s). A total of 686 (24.1%) patients had a history of AF. Baseline characteristics are shown in *Table 1* while echocardiographic variables are shown in *Table 2*. Patients in the AF group were older and had more comorbidities like coronary artery disease, chronic obstructive pulmonary disease, and stroke (*Table 1*). Patients in the AF group had more dyspnea [according to New York Heart Association (NYHA) class; $P < 0.001$], but less symptoms of angina compared to the SR group [350 patients (16.2%) in the AF group compared to 77 patients (11.2%) in the SR group, $P = 0.001$]. Both groups were equally treated with AVR [1108 patients (51.2%) in the SR group vs. 360 patients (52.5%) in the AF group, $P = 0.77$] and time to AVR was also similar between groups [5 months (IQR 0.0–20.0) in the SR group vs. 4.0 months (IQR 0.0–19.3) in the AF group; $P = 0.41$]. The patients in the AF group were more often treated with TAVR compared to the patients in the SR group (31.2% vs. 21.6%, $P < 0.001$). The patients in the AF group received more extensive heart failure medication (e.g. beta blockers, renin-angiotensin-aldosterone system blockade, and diuretics) compared to patients in the SR group. By echocardiography, patients in the AF group showed lower indexed stroke volume (42.2 ± 13.5 vs. 45.9 ± 12.6 ml/m^2, $P < 0.001$), lower LVEF [58.0% (IQR 47.2–64.6) vs. 61.0% (IQR 53.6–66.8), $P < 0.001$] and higher LV mass index [118.1 g/m^2 (IQR 95.3–176.5) vs. 113.1 g/m^2 (92.0–135.8), $P < 0.001$] (*Table 2*). Patients in the AF group had lower peak transaortic jet velocities and mean aortic valve gradients, whereas AVA was not significantly different between the patients in the AF group vs. the SR group. LV diastolic function [according to E/e', indexed left atrial volume (LAVi) and pulmonary artery systolic pressure] and RV systolic function (measured by TAPSE) were more often impaired in the patients in the AF group compared to the patients in the SR group.

Patient Outcomes

During a median follow-up of 60 months (IQR 30.0–97.0) 1182 (41.5%) patients died. Mortality rate was 11.1% at 1 year, 31.8% at 5 years, and 39.2% at 10 years of follow-up. Patients in the AF

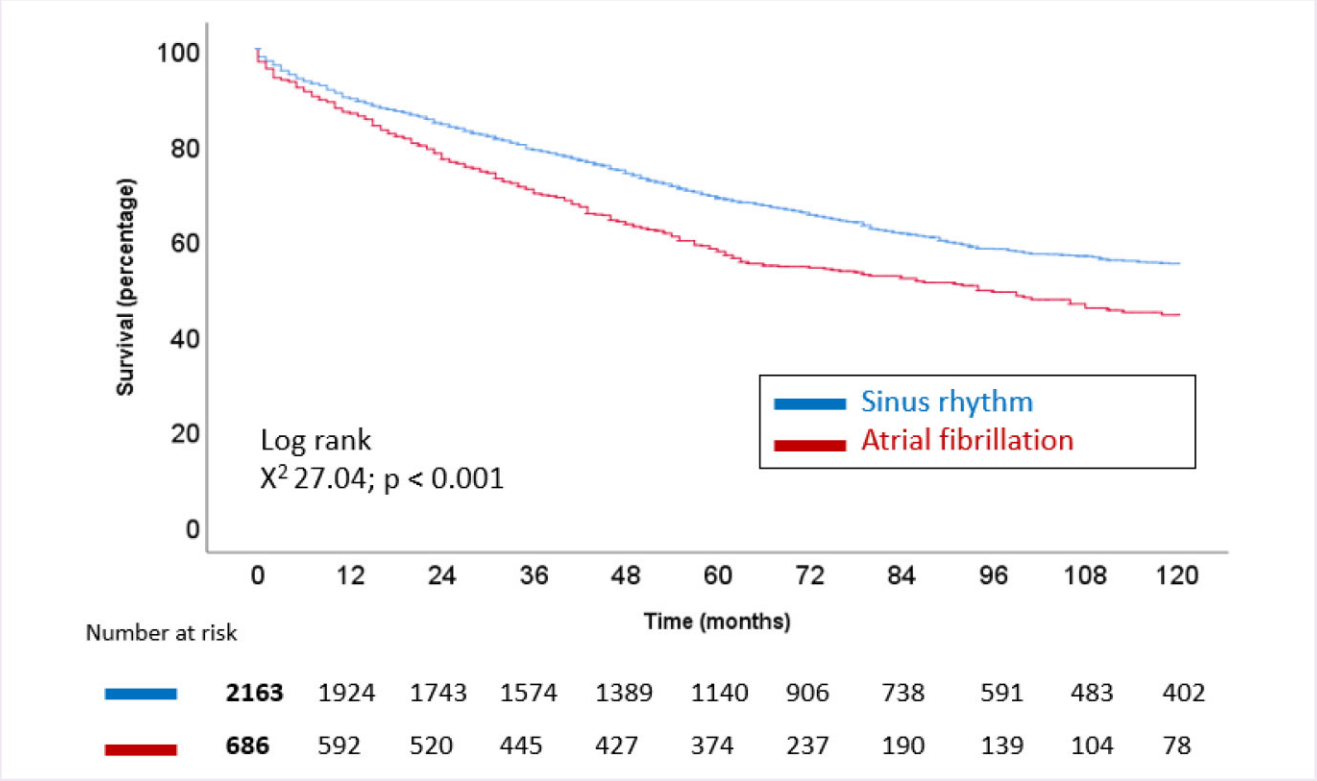


Figure 2 Kaplan–Meier curve for all-cause mortality.

group had a significantly higher 10-year mortality rate compared to patients in the SR group (46.8% vs. 36.8%; log-rank $P < 0.001$) (*Figure 2*). Uni- and multivariable Cox regression analysis for all-cause mortality are presented in *Tables 3* and *4*, respectively. On univariable analysis, AF was significantly associated with all-cause mortality (HR: 1.42; 95% CI: 1.25–1.62; $P < 0.001$) (*Table 3*). Subsequently, to investigate the independent prognostic value of AF with all-cause mortality, four multivariable models were created using a baseline model, which included the following variables: age, body mass index, arterial hypertension, diabetes mellitus, coronary artery disease, chronic obstructive pulmonary disease, kidney function, NYHA class III and IV, AVR as a time-dependent covariate, LV mass index, LV end-diastolic volume index, LVEF, mean aortic valve gradient, and TAPSE (*Table 4*). In the first model, only AF was added to the baseline model, whereas AF and LAVi were added in the second model, AF and E/e' in the third model, and AF, LAVi and E/e' in the fourth model. As such, the independent prognostic value of AF alone and after adjustment for LAVi and/or E/e' could be evaluated. In the first model, AF remained independently associated with all-cause mortality (HR: 1.19; 95% CI: 1.02 –1.38, $P = 0.026$). However, when correcting for LAVi (second model), E/e' (third model), or LAVi and E/e' (fourth model), AF was no longer independently associated with all-cause mortality (HR: 1.07; 95% CI: 0.90–1.26, $P = 0.45$ in the second model, HR: 1.12; 95% CI: 0.94–1.33, $P = 0.19$ in the third model and HR: 1.04; 95%CI: 0.87–1.26, $P = 0.66$ in the fourth model). In contrast, LAVi was independently associated with all-cause mortality in the second model (HR: 1.01; 95% CI: 1.00–1.01, $P < 0.001$), E/e' was independently associated with all-cause mortality in the third model (HR: 1.01; 95% CI: 1.00–1.02, $P = 0.009$) and LAVi and E/e' were both independently associated with all-cause mortality in the fourth model (HR: 1.01; 95% CI: 1.00–1.01, $P = 0.002$ and HR 1.01; 95%CI: 1.00–1.02, $P = 0.046$, respectively). To validate the stability of these findings, a multivariable Cox regression analysis model with backward elimination was performed, including all significant variables in univariable analysis. In this analysis, AF was removed from the model in the first step, resulting in a model that includes LAVI and E/e' as independent prognostic markers (Supplementary *Table 1*). When the Cox regression analysis with backward elimination was performed without LV diastolic function parameters (i.e. excluding LAVI and E/e'), AF remained significantly associated with outcomes. These findings imply that LV diastolic function is key to the prognosis of patients with significant AS, while AF has no independent prognostic value.

Discussion

In this large cohort of patients with significant AS, AF is independently associated with outcomes when correcting for age, comorbidities, LV systolic function, LV mass, and RV systolic function. However, when additionally correcting for LV diastolic function (using E/e', LAVI, or both), AF is no longer an independent prognostic marker. These findings imply that AF is a surrogate for LV diastolic function and only plays a bystander role in the prognosis of patients with significant AS.

AF Is Closely Related to LV Diastolic Dysfunction

AF is the most prevalent cardiac arrhythmia in the general population and often coexists with valvular heart disease.[2,20] In the current study, AF was present in 24.1% of patients in line with the prevalence reported in the PARTNER I registry[21] and the FRANCE-2 registry.[22] The increasing prevalence with age of both AS and AF can explain why these entities frequently coincide.[23,24] Furthermore, the presence

Table 3 Univariable Cox regression analysis for all-cause mortality

Variable	Hazard ratio (95% CI)	*P* value
Age	1.04 (1.03, 1.04)	**<0.001**
Male sex	1.09 (0.97, 1.23)	0.15
Body mass index	0.97 (0.96, 0.98)	**<0.001**
Arterial hypertension	1.50 (1.29, 1.73)	**<0.001**
Diabetes mellitus	1.62 (1.43, 1.82)	**<0.001**
Coronary artery disease	1.33 (1.18, 1.50)	**<0.001**
AF	1.42 (1.25, 1.61)	**<0.001**
COPD	1.45 (1.20, 1.74)	**<0.001**
eGFR MDRD	0.98 (0.98, 0.98)	**<0.001**
NYHA class III and IV	1.69 (1.48, 1.93)	**<0.001**
Aortic valve replacement*	0.66 (0.58, 0.75)	**<0.001**
IVSD	1.00 (0.98, 1.02)	0.93
LV mass index	1.01 (1.00, 1.01)	**<0.001**
LV EDV index	1.01 (1.01, 1.01)	**<0.001**
LVEF	0.98 (0.98, 0.98)	**<0.001**
LAVI	1.01 (1.01, 1.01)	**<0.001**
Mean AS gradient	0.99 (0.98, 0.99)	**<0.001**
Peak AS velocity	0.72 (0.67, 0.78)	**<0.001**
AVA	1.04 (0.83, 1.29)	0.75
E/e'	1.02 (1.01, 1.02)	**<0.001**
PAPS	1.03 (1.02, 1.03)	**<0.001**
TAPSE	0.96 (0.95, 0.98)	**<0.001**

Bold values represent significant *P* values (i.e. <0.05).
COPD = chronic obstructive pulmonary disease; NYHA = New York Heart Association; eGFR MDRD = estimated glomerular filtration rate by Modification of Diet in Renal Disease; IVSD = interventricular septum diameter; LVEDV = left ventricular end-diastolic volume; LVEF = left ventricular ejection fraction; LAVI = left atrial volume index; AVA = aortic valve area; PAPS = pulmonary artery systolic pressure; TAPSE = tricuspid annular plane systolic excursion; and CI = confidence interval.
*entered as a time dependent covariate.

of LV hypertrophy, as a response to the higher afterload in patients with significant AS, also predisposes to AF. Consequently, impaired LV relaxation and reduced LV compliance reduce LV diastolic function. Elevated LV filling pressures induce elevated LA pressure that eventually will lead to LA dilatation. These maladaptive changes are associated with the development of AF.[14] Similarly, elevated LA pressure leads to AF in mitral valve disease[25] and congestive heart failure.[26] Accordingly, AF and LV diastolic dysfunctions are closely related. In addition, in the current study LV diastolic function was significantly more impaired in patients with AF as compared to patients with SR.

The Prognostic Bystander Role of AF

Various studies have evaluated the prognostic value of AF in patients with AS.[5–12] In these studies, worse survival was noted in patients with AS and AF compared to patients with AS and SR, in line with the observations in the current study. In 1838 patients with severe AS who underwent AVR (32% with AF), *Kubala et al.*[8] showed that AF was independently associated with all-cause mortality. These results were in line with observations in other patient groups with AS, including medically managed severe AS,[6] moderate AS,[7] any severity of AS (AVA < 2 cm^2)[5,11] and low gradient severe AS.[9] On the contrary, in a large cohort of 1847 patients with severe AS (16% having AF), *Zhang et al.*[12] reported no independent relationship between AF and all-cause mortality. The authors highlighted the difference in underlying structural heart disease between patients with AF vs. patients with SR, suggesting that AF is a clinical marker of underlying cardiac abnormalities associated with worse outcomes. Of interest, most studies only adjusted for clinical variables and LV systolic function, but did not include markers of LV diastolic function. Besides *Zhang et al.*[12] and *Burup Kristensen et al.*,[11] no other studies included LAVI or E/e' in the multivariable Cox regression analysis. Compared to *Zhang et al.*, the current study includes a larger patient cohort with significant AS (AVA < 1.5 cm^2) and a higher prevalence of AF (24.1% vs. 16%). Patients with significant mitral valve disease were excluded to avoid confounding effects. The current study was focused on LV diastolic function to potentially explain why AF does not play an independent role in differences among outcomes. The most important finding of this study is that AF showed no incremental prognostic value when adjusting for markers of LV diastolic function, indicating a bystander role in the prognosis of patients with significant AS.

Clinical Implications

Incidences of both AS and AF are increasing in the ageing population. While the impact of AF on prognosis in patients with significant AS remained a matter of debate based on previous studies, the current study indicates that AF is a surrogate for underlying LV diastolic function. Nevertheless, the presence of AF should raise awareness of more pronounced adverse cardiac remodeling. Especially in asymptomatic patients with severe AS or symptomatic patients with low flow, low gradient severe AS, the presence of AF should trigger further diagnostic work-up. The use of exercise testing, dobutamine stress echocardiography, or cardiac computed tomography to determine the clinical relevance (severity) of the AS is required.

Table 4 Multivariable Cox regression analysis for all-cause mortality*

	Model 1 HR (95% CI)	*P* value	Model 2 HR (95% CI)	*P* value	Model 3 HR (95% CI)	*P* value	Model 4 HR (95% CI)	*P* value
AF	1.19 (1.02, 1.38)	**0.026**	1.07 (0.90, 1.26)	0.45	1.12 (0.94, 1.33)	0.19	1.04 (0.87, 1.26)	0.66
LAVI			1.01 (1.00, 1.01)	**<0.001**			1.01 (1.00, 1.01)	**0.002**
E/e'					1.01 (1.00, 1.02)	**0.009**	1.01 (1.00, 1.02)	**0.046**

Bold values represent significant *P* values (i.e. <0.05).
AF = atrial fibrillation; LAVI = indexed left atrial volume; HR = hazard ratio; and CI = confidence interval
*Adjusted for age, body mass index, hypertension, diabetes mellitus, coronary artery disease, chronic obstructive pulmonary disease, estimated glomerular filtration rate, New York Heart Association class III and IV, aortic valve replacement as a time-dependent covariate, mean aortic valve gradient, left ventricular mass index, left ventricular end-diastolic volume index, left ventricular ejection fraction, and tricuspid annular plane systolic excursion.

Limitations

The current study concerns a retrospective analysis, with inherent limitations. In addition, since 24-hour ambulatory monitoring was not systematically performed, the AF burden was unclear. The patient population includes a spectrum of AS severity, which may have affected the current results. Due to the retrospective design of the study, the outcome data are limited to all-cause mortality without distinction between cardiac and non-cardiac deaths. Data about heart failure hospitalizations, strokes, or bleeding were not routinely available.

Conclusion

This large retrospective analysis of patients with significant AS reveals that AF is not a prognostic marker once the patient population is adjusted for LV diastolic function. Although patients in the AF group have reduced overall survival as compared to patients in the SR group, AF was not independently associated with outcomes. Moreover, AF reflects underlying LV diastolic dysfunction and should raise awareness of more pronounced adverse cardiac remodeling induced by significant AS.

Supplementary Material

Supplementary material is available at *European Heart Journal—Quality of Care and Clinical Outcomes* online.

Disclosures

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Data Availability

The data underlying this article will be shared on reasonable request to the corresponding author.

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