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RESEARCH ARTICLE

Prevalence, characteristics and prognostic impact of aortic valve disease in patients with heart failure and reduced, mildly reduced, and preserved ejection fraction: An analysis of the ESC Heart Failure Long-Term Registry

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Aims To assess the prevalence, clinical characteristics, and outcomes of patients with heart failure (HF) with or without moderate to severe aortic valve disease (AVD) (aortic stenosis [AS], aortic regurgitation [AR], mixed AVD [MAVD]).

Methods and results Data from the prospective ESC HFA EORP HF Long-Term Registry including both chronic and acute HF were analysed. Of 15 216 patients with HF (62.5% with reduced ejection fraction, HFrEF; 14.0% with mildly reduced ejection fraction, HFmrEF; 23.5% with preserved ejection fraction, HFpEF), 706 patients (4.6%) had AR, 648 (4.3%) AS and 234 (1.5%) MAVD. The prevalence of AS, AR and MAVD was 6%, 8%, and 3% in HFpEF, 6%, 3%, and 2% in HFmrEF and 4%, 3%, and 1% in HFrEF. The strongest associations were observed for age and HFpEF with AS, and for left ventricular end-diastolic diameter with AR. AS (adjusted hazard ratio [HR] 1.43, 95% confidence interval [CI] 1.23–1.67), and MAVD (adjusted HR 1.37, 95% CI 1.07–1.74) but not AR (adjusted HR 1.13, 95% CI 0.96–1.33) were independently associated with the 12-month composite outcome of cardiovascular death and HF hospitalization. The associations between AS and the composite outcome were observed regardless of ejection fraction category.

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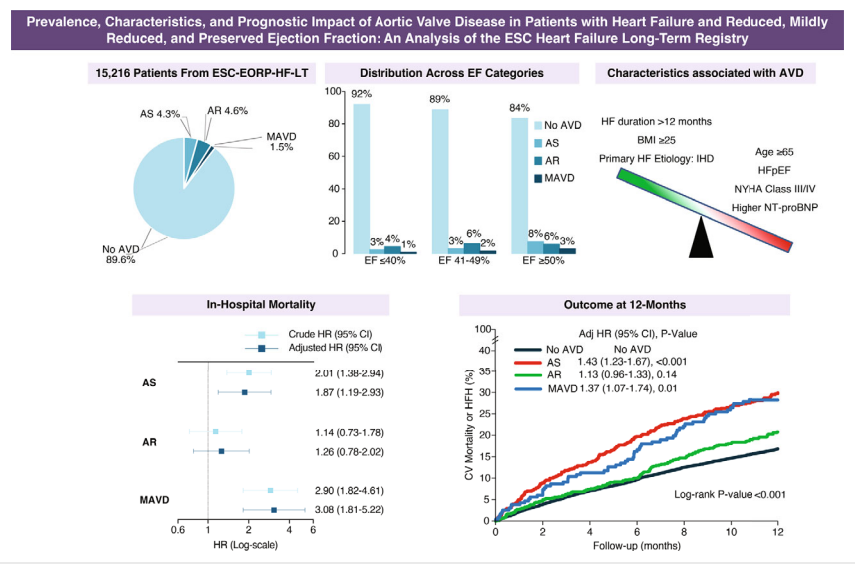
Conclusions In the ESC HFA EORP HF Long-Term Registry, one in 10 patients with HF had AVD, with AS and MAVD being especially common in HFpEF and AR being similarly distributed across all ejection fraction categories. AS and MAVD, but not AR, were independently associated with increased risk of in-hospital mortality and 12-month composite outcome, regardless of ejection fraction category.

Graphical Abstract



Aortic valve disease in patients with heart failure and reduced, mildly reduced and preserved ejection fraction: The ESC Heart Failure Long-Term Registry. AR, aortic regurgitation; AS, aortic stenosis; AVD, aortic valve disease; BMI, body mass index; CI, confidence interval; EF, ejection fraction; HF, heart failure; HFpEF, heart failure with preserved ejection fraction; HR, hazard ratio; IHD, ischaemic heart disease; MAVD, mixed aortic valve disease; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association. [Correction added on 26 July 2023, after first online publication: Graphical Abstract caption has been added in this version.]

Keywords Aortic valve disease • Aortic regurgitation • Aortic stenosis • Mixed aortic valve disease • Heart failure • Ejection fraction

Introduction

Heart failure (HF) is a leading cause of mortality and hospital readmissions.[1] With the ageing of the population, HF and aortic valve disease (AVD) including aortic stenosis (AS), aortic regurgitation (AR) and concomitant AS and AR (mixed AVD [MAVD]), frequently coexist and are expected to increase in prevalence in the next years.[2] HF is categorized by left ventricular ejection fraction (EF) into HF with preserved EF (HFpEF), HF with mildly reduced EF (HFmrEF), and HF with reduced EF (HFrEF).[1] In HF, it has been shown that comorbidity profiles, prognosis and treatment decisions differ with regard to these categories.[3–6] HFmrEF is on average more similar to HFrEF, including male sex, lower age, higher prevalence of ischaemic heart disease (IHD) and primarily cardiovascular (CV) outcomes.[7,8] HFpEF appears more distinct, with predominantly female sex, higher age, more commonly hypertension, and more commonly non-CV outcomes.[3] However, little is known about the prevalence and consequences of AVD in HF and across these three EF categories. AS certainly may cause left ventricular hypertrophy and HFpEF, but if progressive may also cause HFrEF. It has been proposed that AS and HFpEF may share underlying mechanisms involving chronic inflammation,[9–11] while AR might be more strongly related to the left ventricular dilatation that typically accompanies HFrEF.

Data on prevalence of, associations with, and consequences of AVD in HF is mainly from single centre studies,[9,10] clinical trials with narrowly selected populations[12–16] or population-based studies in which patients were not yet diagnosed with HF.[17,18] Furthermore, in single centre studies, patients are usually treated for acute HF but the role of AVD in patients with HF may differ in acute versus chronic HF. Since the hypertrophic and non-compliant left ventricle in AS and MAVD has reduced capacity to accommodate increased

stroke volumes,[14] the volume overload in acute HF might therefore be less well-tolerated in AS and MAVD compared with isolated AR. Finally, these studies have not performed within-cohort comparisons of the characteristics and consequences of all AVDs and in HFpEF versus HFrEF versus HFmrEF.

To address these gaps in knowledge, we performed a comprehensive comparative assessment of the prevalence of AVD in acute and chronic HF and across EF categories (aim 1), associated characteristics (aim 2) as well as the impact of AVD on 12-month outcomes (aim 3) of CV mortality and HF hospitalizations (HFH) and in-hospital mortality (aim 4) in the European Society of Cardiology (ESC) Heart Failure Association (HFA) EURObervational Research Programme (EORP) HF Long-Term (ESC-HF-LT) Registry.

Methods

Study design, patient population and data collection

The ESC-HF-LT Registry has previously been described.[19] Briefly, it is a prospective, multicentre, observational study enrolling patients presenting with HF to 133 cardiology centres from 21 European and Mediterranean countries that are members of the ESC. Enrolment included (i) all outpatients with chronic HF diagnosed according to the clinical judgment of the responsible cardiologists at the participating centres; and (ii) all inpatients admitted to the hospital's cardiology ward or intensive cardiac care unit for acute HF, for whom an intravenous therapy for HF (inotropes, vasodilators, and/or diuretics) was needed. There are no specific exclusion criteria, with the exception of age that should be higher than 18 years. Follow-up data were collected at a mandatory visit at 12 months after study entry. The ESC-HF-LT Registry was approved by each local institutional review board in accordance with each country's legislation. Patients provided written informed consent.

For aims 1–3 of the present study to assess the prevalence, characteristics and prognostic impact of AVD, data were pooled for inpatients who had been treated for acute HF and outpatients with chronic HF. For inpatients, baseline data were collected at the time of hospital discharge after the patients had been treated for acute HF and for chronic HF patients collected at the time of the outpatient visit. For long-term outcomes, patients with acute HF were included only if they were discharged alive. The primary composite outcome consisted of time to first CV death or first HFH from the date of hospital admission or outpatient visit to 12-month follow-up. The secondary outcomes included the individual endpoints of the composite separately and in-hospital mortality. In-hospital survival was studied in inpatients only.

Biochemical blood measurements were determined using local standard laboratory procedures. A transthoracic echocardiography was performed at enrolment and presence of moderate/severe AVD was assessed. Patients were categorized into three EF groups: HFrEF (EF ≤40%), HFmrEF (EF 41–49%), and HFpEF (EF ≥50%).

Statistical analysis

Categorical variables are presented as percentages and compared by the chi-square test, and continuous variables are presented as median (Q1, Q3) and are compared by a non-parametric test (Kruskal–Wallis test). Baseline characteristics are reported and stratified according to AS, AR, MAVD, or no AVD.

To assess characteristics associated with AVD, univariable and multivariable logistic regression models were fitted including several independent variables, and each AVD category as dependent variable. Independent variables were selected based on clinical judgment including age (≥65 vs. <65 years), sex (female vs. male), heart rate (≥70 vs. <70 bpm), systolic blood pressure (≥100 vs. <100 mmHg), EF category, N-terminal pro-B-type natriuretic peptide (NT-proBNP) (≥ vs. < median), New York Heart Association (NYHA) class (III–IV vs. I–II), HF duration >12 months, previous HFH, IHD as primary aetiology, coronary artery disease (CAD), atrial fibrillation (AF), diabetes mellitus (DM), peripheral vascular disease (PVD), chronic obstructive pulmonary disease (COPD), stroke/transient ischaemic attack (TIA), anaemia (haemoglobin <13 g/dl in males and <12 g/dl in females), chronic kidney disease (CKD) (estimated glomerular filtration rate [eGFR] <60 ml/min/1.73 m^2), body mass index (BMI) (≥25 vs. <25 kg/m^2), sodium (<135 vs. ≥135 mmol/L) and left ventricular end-diastolic diameter (LVEDD) (≥60 vs. <60 mm).

Cumulative incidence curves were constructed for time to CV mortality/first HFH, and CV mortality and first HFH separately (with censoring for death) stratified on the presence of AVD and compared using the log-rank test. Subsequently, survival analyses were performed separately in the three EF subgroups (≤40%, 41–49% and ≥50%) according to the presence of AVD.

Univariable and multivariable Cox regression models were performed to assess the association between AVD and in-hospital mortality and time to 12-month outcomes of CV mortality or HFH as well as CV mortality and HFH separately. The models were adjusted for the same variables adopted in the logistic regression analysis. The proportional hazards assumption was investigated using the scaled Schoenfeld residuals. HF duration and NYHA class exhibited non-proportional hazards and were included as strata variables in the model.

To avoid bias due to data missing not at random, missing baseline covariates were handled by multiple imputation by chained equations[20] for 15 datasets and 15 iterations. Variables included in the imputation model are indicated in *Table 1*. The primary outcome, CV death or first rehospitalization for HF at follow-up, was included as the Nelson–Aalen estimator. Valve disease was not imputed. For patients with hospitalization during follow-up but missing information on date, the time to hospitalization was imputed with half the time to last follow-up.

Results

Study population

Between March 2011 and September 2018, 25 621 inpatients and outpatients were enrolled in the registry of whom 15 216 (60%) were included in the present analysis with complete information on AVD, 12-month follow-up data and no loss to follow-up (online supplementary *Figure S1*). Among these 15 216 patients, 5502 were inpatients (36.2%) treated for acute HF and 9714 outpatients (63.8%) with chronic HF. The median age was 67.0 (Q1 58.0, Q3 76.0), 31.2% were female, 23.5% had HFpEF, 14.0% had HFmrEF, and 62.5% had HFrEF. Baseline characteristic of the total population including inpatients and outpatients are shown in *Table 1*. Characteristics of inpatients treated for acute HF are also presented separately in online supplementary *Table S1*.

Table 1 Baseline characteristics of the total population (inpatients and outpatients)

Variable	Missing (%)	Overall (*n* = 15 216)	No AVD (*n* = 13 628; 89.5%)	AS (*n* = 648; 4.3%)	AR (*n* = 706; 4.6%)	MAVD (*n* = 234; 1.5%)	*p*-value
Characteristics							
Inpatient vs. outpatient		5502 (36%)	4619 (34%)	368 (57%)	365 (52%)	150 (64%)	<0.001
EF*, %	13%	36 [28, 48]	35 [28, 47]	46 [33, 60]	40 [30, 50]	47 [35, 57]	<0.001
≤40%		8295 (63%)	7699 (64%)	205 (41%)	319 (56%)	72 (42%)	
41–49%		1861 (14%)	1679 (14%)	59 (12%)	101 (18%)	22 (13%)	
≥50%		3120 (24%)	2654 (22%)	233 (47%)	154 (27%)	79 (46%)	
Age*, years		67 [58, 76]	66 [57, 75]	76 [70, 82]	71 [61, 79]	75 [68, 81]	<0.001
Female sex*		4746 (31%)	4129 (30%)	281 (43%)	240 (34%)	96 (41%)	<0.001
Heart rate*, bpm		74 [65, 89]	74 [64, 88]	79 [68, 93]	76 [66, 94]	80 [69, 96]	<0.001
Systolic BP*, mmHg	0.2%	124 [110, 140]	123 [110, 140]	130 [111, 149]	130 [110, 140]	130 [116, 145]	<0.001
NYHA class*	0.3%						<0.001
I		2922 (19%)	2680 (20%)	95 (15%)	104 (15%)	43 (18%)	
II		8298 (55%)	7491 (55%)	329 (51%)	360 (51%)	118 (50%)	
III		3617 (24%)	3130 (23%)	203 (31%)	215 (31%)	69 (30%)	
IV		334 (2.2%)	285 (2.1%)	19 (2.9%)	26 (3.7%)	4.0 (1.7%)	
HF diagnosis >12 months*	5.6%	6679 (47%)	6065 (47%)	244 (40%)	277 (43%)	93 (43%)	<0.001
Previous HFH*	0.4%	6325 (42%)	5685 (42%)	268 (42%)	271 (39%)	101 (44%)	0.379
Geographic region							<0.001
Eastern		4396 (29%)	3787 (28%)	210 (32%)	293 (42%)	106 (45%)	
Northern		750 (4.9%)	640 (4.7%)	42 (6.5%)	51 (7.2%)	17 (7.3%)	
Southern		6518 (43%)	5953 (44%)	273 (42%)	205 (29%)	87 (37%)	
Western		907 (6.0%)	828 (6.1%)	40 (6.2%)	33 (4.7%)	6 (2.6%)	
Middle East		664 (4.4%)	617 (4.5%)	32 (4.9%)	15 (2.1%)	0 (0%)	
North Africa		1350 (8.9%)	1203 (8.8%)	29 (4.5%)	103 (15%)	15 (6.4%)	
Other		631 (4.1%)	600 (4.4%)	22 (3.4%)	6 (0.8%)	3 (1.3%)	
Primary aetiology	0.1%						<0.001
IHD		7250 (48%)	6597 (48%)	255 (39%)	293 (42%)	105 (45%)	
Hypertension		1163 (7.6%)	1060 (7.8%)	43 (6.6%)	47 (6.7%)	13 (5.6%)	
Dilated cardiomyopathy		3614 (24%)	3427 (25%)	35 (5.4%)	138 (20%)	14 (6.0%)	
Valve disease		1517 (10%)	967 (7.1%)	272 (42%)	184 (26%)	94 (40%)	
Other		1662 (11%)	1567 (12%)	43 (6.6%)	44 (6.2%)	8 (3.4%)	
Comorbidities/conditions							
AF/flutter*		5898 (39%)	5124 (38%)	312 (48%)	352 (50%)	110 (47%)	<0.001
DM*		5139 (34%)	4681 (34%)	232 (36%)	162 (23%)	64 (27%)	<0.001
Stroke/TIA*		1534 (10%)	1301 (10%)	116 (18%)	72 (10%)	45 (19%)	<0.001
Peripheral vascular disease*	0.2%	1935 (13%)	1659 (12%)	145 (22%)	77 (11%)	54 (23%)	<0.001
CAD*	0.2%	7414 (49%)	6664 (49%)	315 (49%)	319 (45%)	116 (50%)	0.301
MI	0.1%	6867 (45%)	6169 (45%)	290 (45%)	299 (42%)	109 (47%)	0.461
Hypertension	0.1%	9384 (62%)	8311 (61%)	482 (74%)	433 (61%)	158 (68%)	<0.001
COPD*	0.2%	2359 (16%)	2029 (15%)	149 (23%)	125 (18%)	56 (24%)	<0.001
Chronic kidney disease	0.1%	3179 (21%)	2770 (20%)	163 (25%)	176 (25%)	70 (30%)	<0.001
Anaemia (haemoglobin <13 g/dl in males, <12 g/dl in females)*	16%	4889 (38%)	4233 (37%)	303 (54%)	259 (45%)	94 (48%)	<0.001
BMI*, kg/m^2	0.9%	28 [25, 31]	28 [25, 31]	27 [24, 31]	27 [24, 29]	27 [24, 30]	<0.001
Cancer	0.2%	691 (4.6%)	601 (4.4%)	37 (5.7%)	35 (5.0%)	18 (7.7%)	0.042
Depression	0.3%	1123 (7.4%)	975 (7.2%)	79 (12%)	40 (5.7%)	29 (12%)	<0.001
Smoking		2076 (14%)	1904 (14%)	60 (9.3%)	84 (12%)	28 (12%)	0.003
Intervention							
CABG		1880 (12%)	1718 (13%)	80 (12%)	64 (9.1%)	18 (7.7%)	0.006
PCI	0.1%	3525 (23%)	3260 (24%)	114 (18%)	130 (18%)	21 (9.0%)	<0.001
Valvular surgery		1261 (8.3%)	1081 (7.9%)	81 (13%)	77 (11%)	22 (9.4%)	<0.001
Devices	0.2%						<0.001
PM		915 (6.0%)	767 (5.6%)	69 (11%)	53 (7.6%)	26 (11%)	
CRT-P		243 (1.6%)	219 (1.6%)	6 (0.9%)	17 (2.4%)	1 (0.4%)	
CRT-D		1264 (8.3%)	1209 (8.9%)	17 (2.6%)	33 (4.7%)	5 (2.1%)	
ICD		1838 (12%)	1769 (13%)	22 (3.4%)	37 (5.3%)	10 (4.3%)	
ECG/echocardiographic data							
QRS duration, ms	11%	110 [92, 140]	110 [92, 140]	106 [90, 128]	110 [90, 136]	108 [90, 135]	0.001
QT duration, ms	19%	400 [370, 440]	400 [370, 440]	400 [372, 436]	400 [360, 437]	400 [374, 442]	0.002
LBBB,	6.6%	2566 (18%)	2316 (18%)	94 (15%)	110 (16.6)	46 (21%)	0.156
LVEDD*, mm	9.0%	60 [53, 66]	60 [53, 66]	54 [48, 61]	62 [55, 69]	58 [52, 66]	<0.001
Laboratory data							
eGFR*, ml/min/1.73 m^2	11%	68 [49, 87]	69 [50, 88]	58 [43, 77]	61 [44, 80]	56 [43, 77]	<0.001
Sodium*, mEq/L	15%	139 [137, 141]	139 [137, 141]	139 [137, 141]	139 [136, 141]	139 [136, 141]	0.002
Fasting glucose, mg/dl	27%	100 [89, 123]	101 [89, 123]	100 [88, 122]	97 [84, 113]	96 [85, 117]	<0.001

Table 1 (Continued)

Variable	Missing (%)	Overall (*n* = 15 216)	No AVD (*n* = 13 628; 89.5%)	AS (*n* = 648; 4.3%)	AR (*n* = 706; 4.6%)	MAVD (*n* = 234; 1.5%)	*p*-value
Haemoglobin, g/dl	16%	13 [12, 14]	13 [12, 15]	12 [11, 14]	13 [12, 14]	13 [11, 14]	<0.001
BNP, pg/ml	90%	307 [124, 764]	294 [117, 720]	451 [290, 1149]	456 [268, 960]	651 [296, 1419]	<0.001
NT-proBNP, pg/ml	76%	1410 [559, 3609]	1360 [538, 3451]	2503 [1067, 5516]	2776 [1103, 8442]	2592 [958, 5425]	<0.001
Medications							
RAASi/ARNi		12 962 (85%)	11 736 (86%)	459 (71%)	591 (84%)	176 (75%)	<0.001
Beta-blockers		12 889 (85%)	11 693 (86%)	490 (76%)	537 (76%)	169 (72%)	<0.001
MRA		9059 (60%)	8150 (60%)	341 (53%)	427 (61%)	141 (60%)	0.003
Oral diuretics		12 465 (82%)	11 136 (82%)	537 (83%)	606 (86%)	186 (80%)	0.031
Ivabradine		1102 (7.2%)	1022 (7.5%)	21 (3.2%)	49 (6.9%)	10 (4.3%)	<0.001
Digitalis		3404 (22%)	2993 (22%)	141 (22%)	209 (30%)	61 (26%)	<0.001
Anticoagulants		7450 (49%)	6535 (48%)	370 (57%)	403 (57%)	142 (61%)	<0.001

AF, atrial fibrillation; AR, aortic regurgitation; ARNi, angiotensin receptor–neprilysin inhibitor; AS, aortic stenosis; AVD, aortic valve disease; BMI, body mass index; BNP, B-type natriuretic peptide; BP, blood pressure; CABG, coronary artery bypass graft; CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; CRT, cardiac resynchronization therapy; CRT-D, cardiac resynchronization therapy-defibrillator; CRT-P, cardiac resynchronization therapy-pacemaker; DM, diabetes mellitus; ECG, electrocardiogram; EF, ejection fraction; eGFR, estimated glomerular filtration rate; HFH, heart failure hospitalization; ICD, implantable cardioverter-defibrillator; IHD, ischaemic heart disease; LBBB, left bundle branch block; LVEDD, left ventricular end-diastolic diameter; MAVD, mixed aortic valve disease; MI, myocardial infarction; MRA, mineralocorticoid receptor antagonist; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; PCI, percutaneous coronary intervention; PM, pacemaker; RAASi, renin–angiotensin–aldosterone system inhibitor; TIA, transient ischaemic attack.
*Included in the multiple imputation models and logistic/Cox regressions.

Prevalence of aortic valve disease in heart failure and across ejection fraction categories

Aortic regurgitation was present in 706 patients (4.6%; 55.6% HFrEF, 17.6% HFmrEF and 26.8% HFpEF), AS in 648 (4.3%; 41.2% HFrEF, 11.9% HFmrEF, 46.9% HFpEF) and MAVD in 234 patients (1.5%; 41.6% HFrEF, 12.7% HFmrEF, 45.7% HFpEF). AS and MVD were more common in HFpEF than in HFmrEF or HFrEF while the distribution of AR across EF categories was similar (*Figure 1*).

Associations between baseline characteristics and aortic valve disease

Most baseline characteristics of the total population (both inpatients and outpatients) were differently distributed in patients with AS, AR, MAVD and those without AVD (*Table 1*). Compared with patients without AVD, patients with AVD were older, more often in NYHA class III/IV and had higher levels of NT-proBNP. CV risk factors and comorbidities were overall more common in AS and MAVD patients compared with AR and no AVD patients. HF attributed to valve disease was more common in AS (42.0%) and MAVD (40.2%) compared with AR patients (26.1%). History of valvular surgery was reported in 13% of patients with AS, 11% of patients with AR and 9% of patients with MAVD. In the subset of patients with acute HF, baseline characteristics differed similarly as in the total population among the AVD categories compared with patients without AVD (online supplementary *Table S1*).

Because of differences in baseline characteristics in age, sex and comorbidities among patients with and without AVD, we assessed odds ratios (OR) for unadjusted (*Figure 2*) and adjusted (independent) associations with the prevalence of AVD (online supplementary *Figure S2*). There were several characteristics associated with all AVDs with the strongest ones being age ≥65 years with an OR for AS of 4.43 (95% confidence interval [CI] 3.68–5.32), for MAVD of 3.62 (95% CI: 2.79–4.69), and for AR of 1.91 (95% CI 1.68–2.18) followed by HFpEF (vs. HFrEF) with an OR for AS of 2.83 (95% CI 2.41–3.34), for MAVD of 2.65 (95% CI 2.04–3.44) and for AR of 1.34 (95% CI 1.15–1.55). Others were female sex, HFmrEF (vs. HFrEF), NYHA class III/IV, AF, higher heart rate, lower sodium levels and anaemia. Some were also inversely associated with AVD such as higher BMI, IHD as aetiology of HF and longer HF duration (>12 months). LVEDD was only a predictor of AR while PVD, CAD, prior stroke/TIA and COPD were associated with AS and MAVD but not AR.

Twelve-month outcomes of the total population

The incidence rates for the composite outcome of CV mortality or HFH at 12 months were 34.2 per 100 patient-years in AS (adjusted hazard ratio [HR] 1.43, 95% CI 1.23–1.67), 24.2 per 100 patient-years in AR (adjusted HR 1.13, 95% CI 0.96–1.33), and 32.6 per 100 patient-years in MAVD (adjusted HR 1.37, 95% CI 1.07–1.75) compared to no AVD (*Figure 3*). AR was a significant predictor only of CV mortality alone (adjusted HR 1.31, 95% CI 1.02–1.69). Patients who were excluded from the present analysis due to lack of AVD assessment had similar outcomes compared with included patients (online supplementary *Table S2*).

Twelve-month outcomes across ejection fraction categories

Incidence rates and HRs for the composite endpoint and the individual endpoints of the composite across the EF categories are shown in online supplementary *Figure S2* and *Table S3*. AS and MAVD, but not AR, were associated with increased risk of the composite endpoint across all EF categories. The magnitude of the associations between AS or MAVD and outcomes were similar

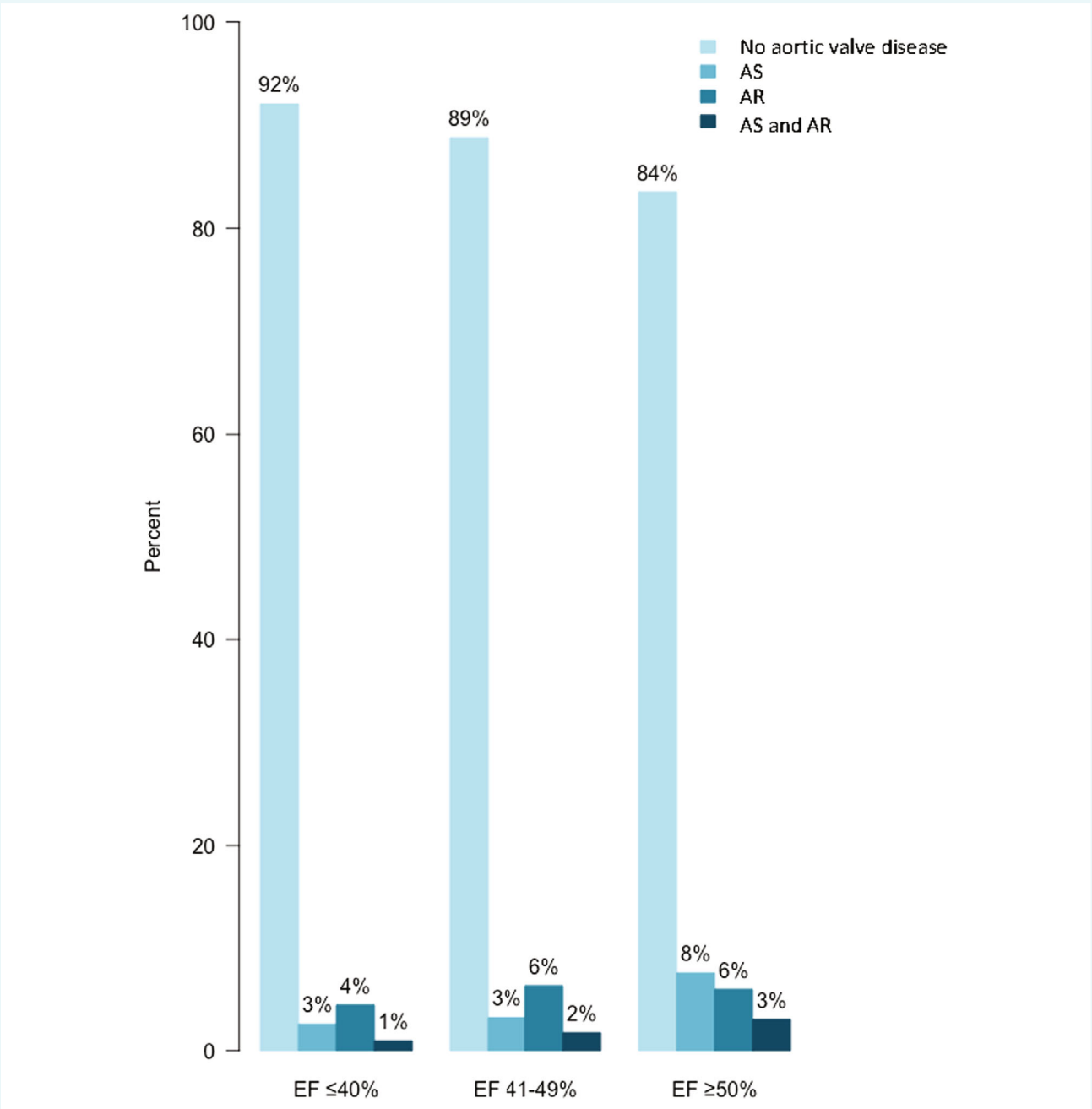


Figure 1 Proportions of aortic valve disease in heart failure with preserved, mildly reduced and reduced ejection fraction (EF). AR, aortic regurgitation; AS, aortic stenosis.

across the EF categories. AR was associated with increased risk of CV mortality alone in HFmrEF and HFrEF but not HFpEF.

Associations between aortic valve disease and in-hospital mortality in acute heart failure

Mixed AVD and AS, but not AR, were significantly associated with in-hospital mortality (adjusted HR 3.08, 95% CI 1.81–5.22; 1.87, 95% CI 1.19–2.93; and 1.26, 95% CI 0.78–2.02, respectively) (*Figure 4*).

Discussion

There were four main findings from the present analysis of the ESC-HF-LT registry, in which the prevalence, associated characteristics and prognostic impact of moderate to severe AVD in HF were examined: (i) one in 10 HF patients had AVD (AR 4.6%, AS

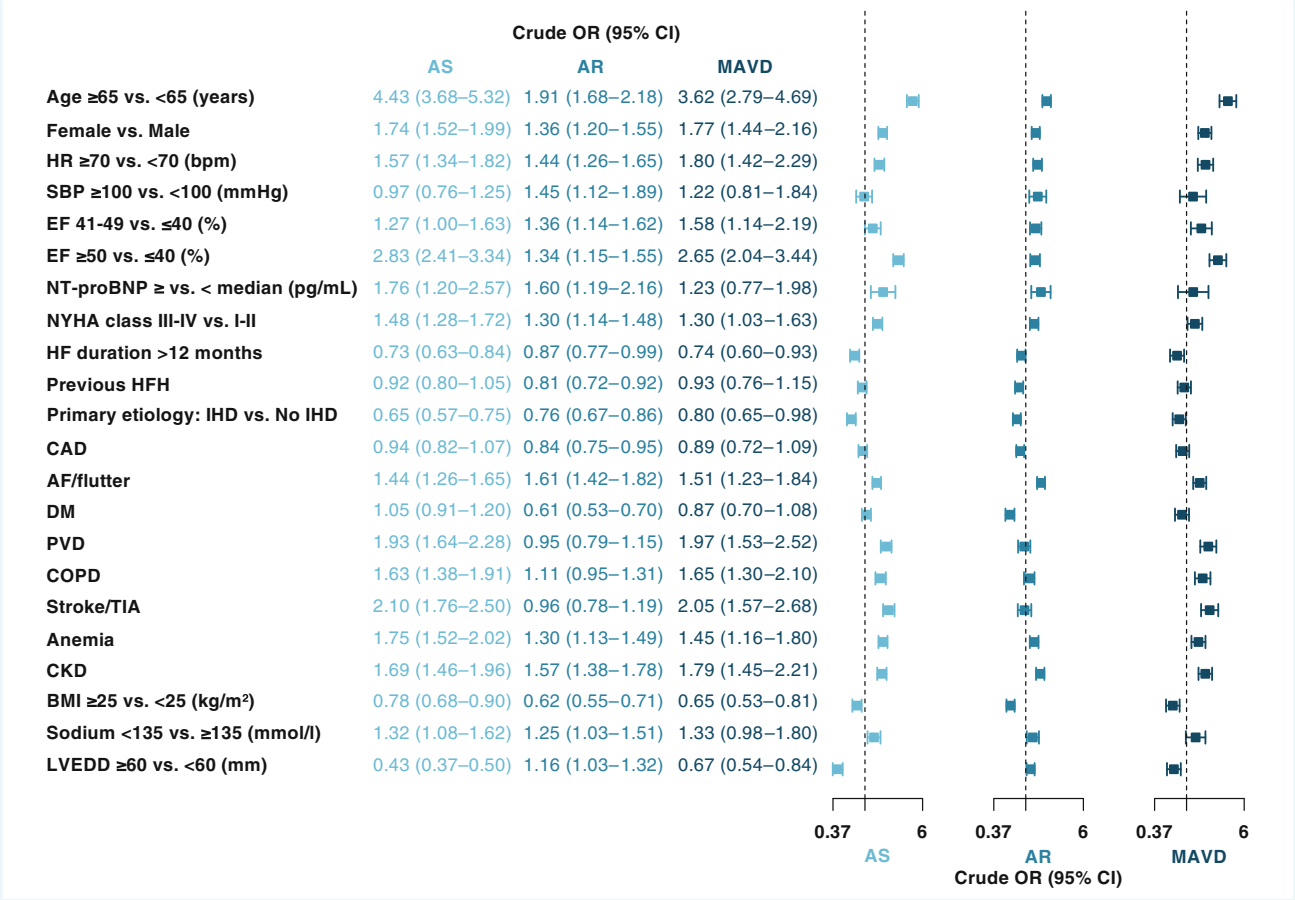
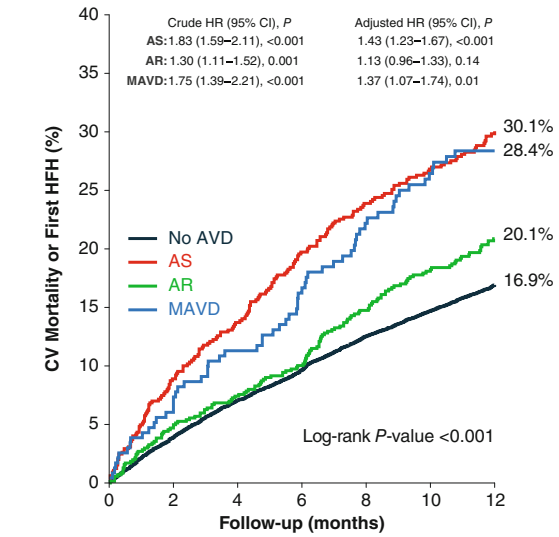


Figure 2 Associations between patient characteristics and type of aortic valve disease. AF, atrial fibrillation; AR, aortic regurgitation; AS, aortic stenosis; BMI, body mass index; CAD, coronary artery disease; CI, confidence interval; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; DM, diabetes mellitus; EF, ejection fraction; HF, heart failure; HFH, heart failure hospitalization; HR, heart rate; IHD, ischaemic heart disease; LVEDD, left ventricular end-diastolic diameter; MAVD, mixed aortic valve disease; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; OR, odds ratio; PVD, peripheral vascular disease; SBP, systolic blood pressure; TIA, transient ischaemic attack.

4.3% and MAVD 1.5%) and while AS and MAVD were more prevalent in HFpEF, AR was similarly distributed across HF categories; (ii) the strongest associations with AVD were observed for age and HFpEF and with a greater magnitude for AS and MAVD than for AR, while LVEDD was only associated with AR; (iii) AS and MAVD, but not AR, were independently associated with the composite endpoint of CV mortality or HFH and the associations between AS and outcomes were observed regardless of HF category; and (iv) AS and MAVD were independently associated with increased risk of in-hospital mortality (*Graphical Abstract*).

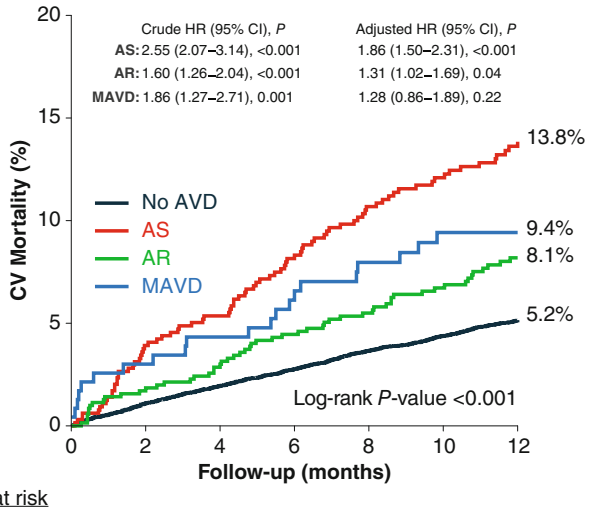
Prevalence of aortic valve disease in heart failure and across ejection fraction categories

Previous HF studies reporting on prevalence and associated factors of AVD were either single centre studies with limited sample sizes,[9,10] clinical trials[12–16] featuring narrowly selected patient groups that may not reflect more generalizable clinical settings[21] or population-based studies in which patients were not yet diagnosed with HF.[17,18] Several other limitations included not reporting on specific valvular lesions but rather 'valvular heart disease', not reporting on severity, and none of the studies performed a comparison across EF categories. These studies have also reported inconsistent findings. In the Prospective Comparison of ARNI with ARB Global Outcomes in HFpEF (PARAGON-HF) trial, among 844 patients, moderate to severe AS was found in 2% and mild AS in 10%[13] while the prevalence of mild AS in HFpEF was 30% in a single centre study ($n = 370$).[10] In the Irbesartan in Heart Failure with Preserved Ejection Fraction Study (I-PRESERVE) and Candesartan in Heart failure: Assessment of Reduction in Mortality and morbidity (CHARM) studies, the prevalence of valvular heart disease was 11% and 20%, respectively, but no subtypes of valvular heart disease were reported.[12] In a cohort study ($n = 79\,043$) involving people with suspected HF referred for echocardiography, moderate to severe AS was prevalent in 3.2% and AR in 2.1%.[17]



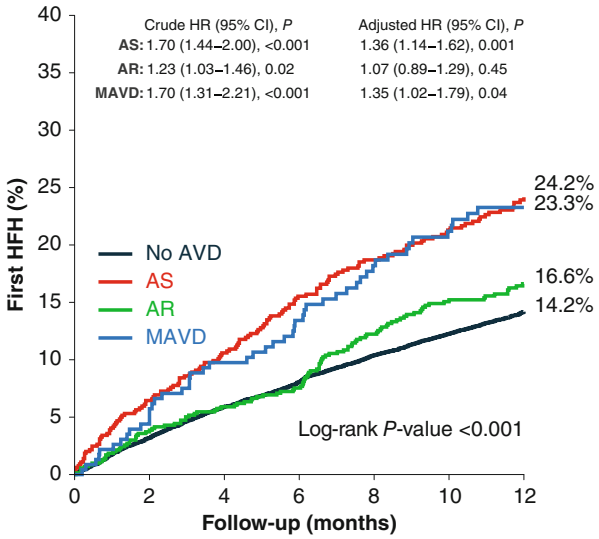
No. at risk

No AVD	13628	12998	12445	11957	11321	10649	8586
AS	648	573	534	490	452	416	328
AR	706	668	642	615	568	522	441
MAVD	234	215	199	187	166	153	133



No. at risk

No AVD	13628	13368	13112	12838	12435	11905	9651
AS	648	605	583	552	521	488	391
AR	706	688	672	650	625	590	496
MAVD	234	221	214	208	195	184	158



No. at risk

No AVD	13628	12998	12445	11957	11321	10649	8586
AS	648	573	534	490	452	416	328
AR	706	668	642	615	568	522	441
MAVD	234	215	199	187	166	153	133

Figure 3 Kaplan–Meier time-to-first event analyses according to aortic valve disease in heart failure patients. (*A*) Cardiovascular mortality or heart failure hospitalization (HFH). (*B*) Cardiovascular (CV) mortality. (*C*) HFH. AR, aortic regurgitation; AS, aortic stenosis; AVD, aortic valve disease; CI, confidence interval; HR, hazard ratio; MAVD, mixed aortic valve disease.

However, the prevalence of AS in the present study of 4.3% was more similar to the findings of a population-based study of 4.6% in individuals ≥75 years (in our study median age was 67 years).[18] The prevalence of moderate to severe AR of 4.6% in our study was, not surprisingly, higher than the 1.7% reported in the general population.[18] Data on the prevalence and impact of MAVD in HF are even more scarce. Here, MAVD had a lower prevalence (1.3%) than isolated AS or AR. However, in studies of patients undergoing transcatheter aortic valve implantation (TAVI), concomitant moderate to severe AR at baseline has been observed in 7–20%.[14–16] Our study provides a more accurate picture of the prevalence of each AVD in HF patients.

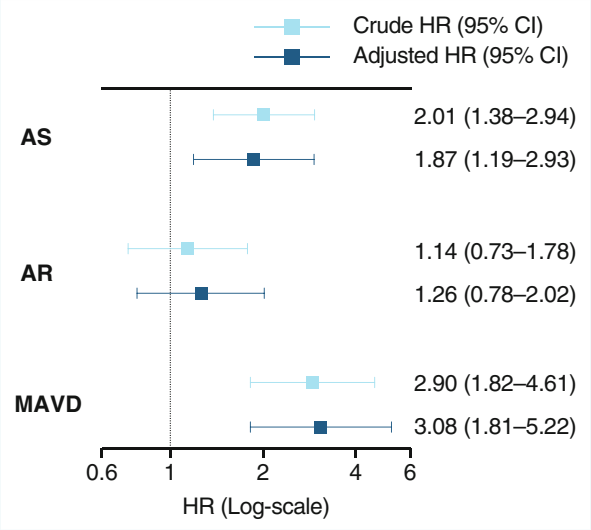


Figure 4 Association between aortic valve disease and in-hospital mortality. AR, aortic regurgitation; AS, aortic stenosis; CI, confidence interval; HR, hazard ratio; MAVD, mixed aortic valve disease.

Associations between clinical characteristics and aortic valve disease

Heart failure with preserved ejection fraction, after age, was the strongest predictor of AVD and, interestingly, the magnitude of this association was greater for AS and MAVD than AR. Since AS is now treatable even in the most frail patients, it is important to consider moderate to severe AS in patients with HFpEF. Several other associations were also present in AVD such as female sex, HFmrEF, CKD and AF. IHD as primary aetiology of HF was inversely related with all AVDs. The stronger link between AVD, specially AS and MAVD, and HFpEF adds novel information to a growing body of evidence suggesting that HFpEF is distinct from HFrEF and HFmrEF in, for example, the higher prevalence of female sex and higher age, as well as in most studies also higher prevalence of hypertension, AF and CKD, and lower prevalence of IHD. Given the emerging evidence suggesting that systemic inflammation is a central aspect of a 'HFpEF syndrome',[22,23] it is possible that AS and HFpEF are intertwined at a mechanistic level and develop in parallel from the same underlying drivers. In a recent study of HFpEF patients hospitalized due to acute HF, mild AS was present in over half of the patients and was associated with increased filling pressures and a smaller and stiffer left ventricle while mild AR coincided with a dilated left ventricle.[10] In addition, some associations were present in AR only including LVEDD while others in AS and MAVD such as PVD, CAD, prior stroke/TIA and COPD. A higher blood pressure was associated with AR and MAVD but not AS. These observations are not surprising since it has been shown previously that in addition to aging, AS is linked to atherosclerotic disease and AR to left ventricular dilatation and hypertension.[24] Finally, previous HFH and HFH duration>12 months were inversely associated with AVD. We speculate that, given the high risk of mortality in patients with moderate to severe AVD, survivor bias might underly these observations, that is, if HF is linked to or entails comorbid AVD, the HF may actually be of shorter duration.

Associations between aortic valve disease and outcomes

Both AS and MAVD were associated with the risks of the composite endpoint (CV mortality or HFH) and HFH alone that were twice as high compared to without AVD. Interestingly, we found no additive negative associations between AR and outcomes in the presence of AS (i.e. MAVD). If anything, the simultaneous presence of AR and AS appeared to a have positive role in outcomes, considering that AS alone, but not MAVD, was associated with significantly higher adjusted CV mortality. These findings contradict previous proposals that MAVD should be associated with worse outcomes than isolated AS or AR, based on the assumption that concomitant AR complicates the pathophysiology of AS by exposing the concentrically hypertrophied and non-compliant left ventricle to a superimposed volumetric overload.[25] Compatible with our results, some studies have reported lower mortality rates after transcatheter aortic valve replacement (TAVR) for MAVD than in isolated AS, suggesting that the existence of concomitant preoperative AR could, as a result of left ventricular adaptation to long-standing volume overload, act as a protective factor in patients who developed paravalvular regurgitation.[26]

Importantly, the presence of AS regardless of HF category and symptoms, portended dramatically worse prognosis. The coexistence of AS and HFpEF could therefore have important implications for risk stratification of patients with AS undergoing valve interventions. Although TAVR could potentially induce a process of reverse remodelling leading to structural and functional improvements, most patients with preserved EF have substantial residual risk of readmissions for HF.[27] However, the prognostic implications of HFpEF in outcomes of valve interventions are currently not accounted for in clinical practice or by risk scores. Furthermore, despite HFpEF being the most frequent phenotype in AS, the prevalence of HFrEF was also high (41%) and these patients had worsened prognosis. Also, since aortic valve gradients can be underestimated in impaired left ventricular EF, these patients may, unfortunately, remain untreated.[28]

Patients with AR had overall similar outcomes as patients without AVD except for slightly higher CV mortality. In current clinical practice, patients with AR and a high burden of comorbidities (as in the present population) are treated conservatively with medical therapy. In recent years, there has been an increased interest in treating such high-risk HF patients with isolated AR using TAVI.[29,30] The present findings suggest that potential benefits may not be obvious, since HF patients with isolated AR had similar outcomes as patients without AVD (although patients with AR had a slightly higher CV mortality). The ongoing JenaValve Align AR[31] trials are expected to provide some data on whether TAVI in AR in high-risk HF populations will confer any clinical benefit.

Associations between aortic valve disease and in-hospital mortality

In patients with acute HF, AS and MAVD but not AR, were independently associated with increased risk of in-hospital mortality. However, this risk was slightly higher in patients with MAVD than AS. In MAVD, the left ventricle is exposed to unique haemodynamic challenges due to the presence of both pressure and volume overload leading to a concentric and non-compliant left ventricle which in addition suffers from increased stroke volumes.[25] Interestingly, we found that mean LVEDD in patients with MAVD was similar to that of patients with AS and smaller than in patients with AR. Since the left ventricular dilatation in the presence of AR is a sign of remodelling to adapt to and accommodate increased stroke volumes, our observation that LVEDD is smaller in MAVD than in isolated AR indicates reduced capacity of the left ventricle in MAVD to tolerate volume overload as in acute HF.

Limitations

Our study has limitations. Precise grading of the severity of AVD (moderate vs. severe) were not available in the present data set. Since very few patients had a history of valvular surgery, differences in characteristics or outcomes related to valvular surgery were not assessed. Furthermore, although it is not surprising that few patients had a history of surgery considering the high burden of comorbidities, some might have received TAVI (which was not recorded), especially during later years of the 2011–2018 study period. Given the advent of TAVI in the recent decade as an effective therapeutic option in patients at high surgical risk, outcomes might have differed in patients with versus without a history of TAVI. Echocardiography was performed in the context of routine clinical practice and not adjudicated. A substantial number of patients enrolled in the ESC-HF-LT registry were excluded from the present analysis due to lack of AVD assessment, 12-month follow-up data and loss to follow-up. However, outcomes of excluded and included patients were similar. The ESC-HF-LT registry included only patients from cardiology departments or specialized HF units. This is a likely explanation for the lower proportion with HFpEF, younger age and greater proportion of men, as compared to other more generalizable community settings.[32] Finally, there was no central event adjudication committee.

Conclusions

In this large, contemporary cohort of HF patients, one in 10 suffered from moderate-to-severe AVD. AS and MAVD, as compared to AR, were more prevalent in HFpEF and associated with increased risk of in-hospital mortality. AS and MAVD were associated with the composite outcome of CV mortality and HFH regardless of EF category while AR was associated with the individual endpoint of CV mortality. These findings highlight the common and detrimental role of AVD in HF regardless of EF category. Clinicians should pay attention to AVD in HF since AVD portends dramatically worsened prognosis and is now treatable even in elderly and frail patients. Also, ongoing trials will provide data on whether TAVI can improve prognosis in asymptomatic patients with moderate AS, in patients with moderate AS and HFrEF and in patients with HF and pure AR. Finally, these comprehensive data on AVD in different EF groups may serve as reference material when considering HF and AVD trial design and recruitment.

Clinical perspectives

Competency in medical knowledge

One in 10 patients had AVD with AS and MAVD being more common in HFpEF than HFmrEF and HFrEF but AR being similarly distributed across all HF categories. Age and HFpEF were strongly associated with AVD while LVEDD was only associated with AR. AS and MAVD, but not AR, were associated with increased risk of in-hospital mortality and the 12-month composite endpoint. AS was independently associated with worse prognosis in all HF categories.

Translational outlook

The role of AVD as a cause versus as a consequence of HF, and how this may vary depending on HF phenotype, requires further study.

Supplementary Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Conflict of interest: B.S. is supported by Region Stockholm clinical postdoctoral appointment (FoUI- FoUI-969 615), Swedish Heart-Lung Foundation (grants 20 220 524 and 20 190 322) and the Swedish Research Council (grant 2022–01472). M.A.: none related to the present work; utside the present work: speaker fees from Abbott Vascular and Medtronic. M.G.C.L. reports unrelated to the present work: consultancy or speaker's honoraria from Novartis, AstraZeneca, Boehringer Ingelheim, Abbott, Medtronic, CareDx, Astellas and Vifor Pharma. S.D.A. reports unrelated to the present work: grants or contracts: Vifor Int, Abbott Vascular; consulting fees: CVRx, Amgen, Respicardia, Novo Nordisk, Brahms, Novartis, Sanofi, Cordio; leadership or fiduciary role in other board: Abbott Vascular, AstraZeneca, Bayer AG, Bioventrix, Boehringer Ingelheim, Cardiac Dimension, Cardior, Impulse Dynamics, Janssen, Occlutech, Servier, Vifor Int, and V-Wave. A.J.S.C. reports unrelated to the present work: speaker's honoraria from AstraZeneca, Bayer, Boehringer Ingelheim, Edwards, Menarini, Novartis, Servier, Vifor, Abbott, Actimed, Arena, Cardiac Dimensions, Corvia, CVRx, Enopace, ESN Cleer, Faraday, Impulse Dynamics, Respicardia, and Viatris. M.L. is supported by Supported by Slovenian Research Agency [grant J3-3076] and reports unrelated to the present work: grants from Roche; consulting from Vifor, AstraZeneca, Bayer, Boehringer Ingelheim; speaker's honoraria from AstraZeneca, Novartis, Boehringer Ingelheim, Bayer. T.M. reports unrelated to the present work: speaker's honoraria from Abbott, AstraZeneca, Boehringer Ingelheim and Edwards. A.M. reports unrelated to the present work: grants or contracts from and consulting fees from Roche, 4TEEN4, Corteria; speaker's honoraria from MSD; Patents: S-Form Pharma. M.F.P. reports unrelated to the present work: consultancy, speaker's, institutional fees from AstraZeneca, Boehringer

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