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Association of Mortality With Aortic Stenosis Severity in Outpatients
Results From the VALVENOR Study

Augustin Coisne, MD, PhD; David Montaigne, MD, PhD; Samy Aghezzaf, MD; Hélène Ridon, MD; Stéphanie Mouton, MD; Marjorie Richardson, MD; Anne-Sophie Polge, MD; Patrizio Lancellotti, MD, PhD; Christophe Bauters, MD; for the VALVENOR Investigators

IMPORTANCE Modern data regarding incidence and modes of death of patients with aortic stenosis (AS) are restricted to tertiary centers or studies of aortic valve replacement (AVR).

OBJECTIVE To provide new insights into the natural history of outpatients with native AS based on a large regionwide population study with inclusion by all cardiologists regardless of their mode of practice.

DESIGN, SETTING, AND PARTICIPANTS Between May 2016 and December 2017, consecutive outpatients with mild (peak aortic velocity, 2.5-2.9 m/s), moderate (peak aortic velocity, 3-3.9 m/s), and severe (peak aortic velocity, ≥4 m/s) native AS graded by echocardiography were included by 117 cardiologists from the Nord-Pas-de-Calais region in France. Analysis took place between August and November 2020.

MAIN OUTCOMES AND MEASURES Natural history, need for AVR, and survival of patients with AS were followed up. Indications for AVR were based on current guideline recommendations.

RESULTS Among 2703 patients (mean [SD] age, 76.0 [10.8] years; 1260 [46.6%] women), 233 (8.6%) were recruited in a university public hospital, 757 (28%) in nonuniversity public hospitals, and 1713 (63.4%) by cardiologists working in private practice. A total of 1154 patients (42.7%) had mild, 1122 (41.5%) had moderate, and 427 (15.8%) had severe AS. During a median (interquartile range) of 2.1 (1.4-2.7) years, 634 patients underwent AVR and 448 died prior to AVR. Most deaths were cardiovascular (200 [44.7%]), mainly associated with congestive heart failure (101 [22.6%]) or sudden death (60 [13.4%]). Deaths were noncardiovascular in 186 patients (41.5%) and from unknown causes in 62 patients (13.8%). Compared with patients with mild AS, there was increased cardiovascular mortality in those with moderate (hazard ratio, 1.47 [95% CI, 1.07-2.02]) and severe (hazard ratio, 3.66 [95% CI, 2.52-5.31]) AS. The differences remained significant when adjusted for baseline characteristics or in time-dependent analyses considering AS progression. In asymptomatic patients, moderate and mild AS were associated with similar cardiovascular mortality (hazard ratio, 0.99 [95% CI, 0.44-2.21]).

CONCLUSIONS AND RELEVANCE While patients in this study with moderate AS had a slightly higher risk of cardiovascular death than patients with mild AS, this risk was much lower than that observed in patients with severe AS. Moreover, in asymptomatic patients, moderate and mild AS were associated with similar cardiovascular mortality.

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Supplemental content

Author Affiliations: University Lille, Inserm, CHU Lille, Institut Pasteur de Lille, U1011- EGID, Lille, France (Coisne, Montaigne, Aghezzaf, Ridon, Mouton, Richardson, Polge); University of Liège Hospital, GIGA Cardiovascular Sciences, Department of Cardiology, Heart Valve Clinic, CHU Sart Tilman, Liège, Belgium (Lancellotti); Gruppo Villa Maria Care and Research, Maria Cecilia Hospital, Cotignola, Anthea Hospital, Bari, Italy (Lancellotti); University Lille, Inserm, CHU Lille, Institut Pasteur, U1167, Lille, France (Bauters).

Group Information: The VALVENOR Investigators are listed in Supplement 2.

Corresponding Author: Augustin Coisne, MD, PhD, Department of Clinical Physiology and Echocardiography, Heart Valve Clinic, Institut Coeur Poumon, CHU Lille F59000, France (augustin.coisne@chru-lille.fr).

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Five decades have passed since Ross and Braunwald[1] described the natural history of aortic stenosis (AS). Although the clinical significance of severe AS has been consistently documented,[2,3] a few recent studies suggest that less advanced stages of severity (mild and moderate AS) are also associated with poor prognosis, eg, increased mortality in patients with moderate AS without reaching the burden of severe AS.[4-8] In 2019, Strange et al[9] reported that survival in patients with moderate AS could be superimposable to that of severe AS. The question of more timely interventions in moderate as well as severe AS to improve outcomes emerges at a time of low morbidity and mortality from surgical and transcatheter aortic valve replacement (AVR).[10] Importantly, previous studies dealing with the outcome of AS were based on limited data regarding the number of patients or lacked information regarding comorbid factors, modes of death, or progression in severity of AS.

In addition, most of the literature comes from tertiary centers and specialized heart valve clinics or focuses on AVR trials.[3] The aims of the present study were to provide new insights into (1) the natural history of AS based on a large regionwide population study with inclusion by all cardiologists regardless of their mode of practice and (2) incidence and modes of death in outpatients presenting with native valvular AS.

Key Points

Question What is the outcome of outpatients with aortic stenosis (AS) in the current era?

Findings In this cohort study including 2703 patients followed up by 117 cardiologists for a median of 2.1 years, patients with moderate AS had a slightly higher risk of cardiovascular death than patients with mild AS, but this risk was much lower than that observed in severe AS. Moreover, in asymptomatic patients, moderate and mild AS was associated with similar cardiovascular mortality.

Meaning Asymptomatic patients with moderate AS undergoing standard symptomatic and echocardiographic follow-up may not be exposed to an increased risk of mortality.

Methods

Study Population and Design

The VALVENOR (Suivi d'une Cohorte de Patients Présentant une Sténose Valvulaire Aortique en Région Nord-Pas-de-Calais) study was a multicenter study that enrolled 2830 outpatients with native valvular AS between May 2016 and December 2017. Patients with a peak aortic jet velocity of 2.5 m/s or more on transthoracic echocardiography (TTE) were prospectively included by 117 cardiologists from the Nord-Pas-de-Calais region (approximately 4 million inhabitants) in France during outpatient visits. Data on race and ethnicity were not collected. Patients younger than 18 years or with a documented history of AVR were excluded. We also excluded 110 patients with concomitant severe mitral or aortic regurgitation[11,12] or prior mitral valve intervention, leaving 2720 patients for the present analysis. Participating physicians were selected based on their geographic distribution to provide a representative sample of the current practice of all cardiology care in the region, including university public hospitals, nonuniversity public hospitals, and private practices. This study was approved by the French medical data protection committee (Le Comité Consultatif sur le Traitement de l'information en Matière de Recherche) and authorized by the Commission Nationale de l'Informatique et des Libertés for the treatment of personal health data. All patients orally consented to the study after being informed in writing of the study's objectives and treatment of the data, as well as on their rights to object, of access, and of rectification.

TTE

TTE was performed as part of routine clinical practice using commercially available systems. Peak aortic jet velocity was derived from transaortic flow, recorded with continuous wave Doppler. According to current diagnostic criteria,[13] patients were categorized as having mild AS (peak aortic jet velocity, 2.5-2.9 m/s), moderate AS (peak aortic jet velocity, 3-3.9 m/s), and severe AS (peak aortic jet velocity, ≥4 m/s).

Follow-up

Patients were followed up by their treating cardiologists. The number of outpatient visits was at the discretion of the cardiologists. Protocol-specified follow-up was performed at 2 years using a standardized case record form to report clinical events. To minimize follow-up bias, general practitioners and/or patients were contacted by a research technician in the case of missing information. Follow-up was completed in 2703 patients. All clinical events, including deaths and indications for AVR, were adjudicated by 2 investigators (A.C., D.M., or C.B.) blinded to each other. A third investigator (A.C., D.M., or C.B.) joined the adjudication in case of disagreement according to prespecified definitions. A consensus was then reached. Cardiovascular causes of death included congestive heart failure (HF), sudden death, stroke, myocardial infarction, limb ischemia, and other cardiovascular death. Noncardiovascular causes of death included cancer, sepsis, kidney failure, respiratory failure, unintentional injury, and other noncardiovascular death. Deaths by an unknown cause were kept as a separate category. The definitions for adjudication of the causes of death were published previously.[14]

Statistical Analysis

Continuous variables were described as mean (SD) or as median with interquartile range. Categorical variables were presented as absolute numbers and percentages. Baseline characteristics were compared using analysis of variance for continuous variables and the χ^2 or the Fisher test for categorical variables. Mortality rates were analyzed by censoring data at time of AVR. All-cause mortality was estimated using the Kaplan-Meier method. For AVR and for the different modes of death, cumulative incidence functions are shown. For AVR, the competing variable was all-cause death. For each specific mode of death, the competing variable was death from any other cause. Cause-specific mortality rates were estimated using cumulative incidence functions. Subgroup analyses were performed in asymptomatic (New York Heart Association class I)

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Table 1. Baseline Characteristics

Characteristic	No. (%)				
		Aortic stenosis			
	All patients (N = 2703)	Mild (n = 1154)	Moderate (n = 1122)	Severe (n = 427)	*P* value
Age, mean (SD), y	76.0 (10.8)	75.4 (11.0)	76.6 (10.5)	76.2 (11.3)	.02
Women	1260 (46.6)	544 (47.1)	496 (44.2)	220 (51.5)	.03
Men	1443 (53.4)	610 (52.9)	626 (55.8)	207 (48.5)	.03
Diabetes	820 (30.3)	371 (32.2)	329 (29.3)	120 (28.1)	.19
History of hypertension	2063 (76.3)	923 (80.0)	835 (74.4)	305 (71.4)	<.001
Prior myocardial infarction	251 (9.3)	126 (10.9)	98 (8.7)	27 (6.3)	.01
Prior coronary bypass	126 (4.7)	55 (4.8)	54 (4.8)	17 (4.0)	.77
Prior percutaneous coronary intervention	351 (13.0)	175 (15.2)	135 (12.0)	41 (9.6)	.006
Atrial fibrillation	607 (22.5)	257 (22.3)	260 (23.2)	90 (21.1)	.66
Prior hospitalization for heart failure	269 (9.9)	107 (9.3)	111 (9.9)	51 (11.9)	.29
Prior stroke	231 (8.6)	96 (8.3)	100 (8.9)	35 (8.2)	.85
NYHA class at inclusion[a]					
1	1062 (39.6)	531 (46.2)	407 (36.5)	124 (29.7)	
2	1289 (48.1)	513 (44.7)	568 (50.9)	208 (49.9)	<.001
3-4	331 (12.3)	105 (9.1)	141 (12.6)	85 (20.4)	
Angina at inclusion	109 (4.0)	30 (2.6)	50 (4.5)	29 (6.8)	.001
Peak aortic jet velocity, mean (SD), m/s	3.28 (0.65)	2.72 (0.14)	3.40 (0.29)	4.46 (0.41)	<.001
Left ventricular ejection fraction, mean (SD), %[b]	63.8 (8.8)	63.7 (8.9)	63.6 (8.8)	64.9 (8.7)	.03
Bicuspid aortic valve[c]	262 (12.3)	99 (10.3)	101 (11.6)	62 (20.7)	<.001
β-Blocker	1206 (44.6)	561 (48.6)	495 (44.1)	150 (35.1)	<.001
ACE-I or ARB	1779 (65.8)	797 (69.1)	722 (64.4)	260 (60.9)	.004
Statin	1491 (55.2)	676 (58.6)	601 (53.6)	214 (50.1)	.004
Antiplatelet drug	1217 (45.0)	520 (45.1)	514 (45.8)	183 (42.9)	.58
Oral anticoagulant	583 (21.6)	263 (22.8)	236 (21.0)	84 (19.7)	.35

Abbreviations: ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin 2 receptor antagonist; NYHA, New York Heart Association.

[a] Missing data in 21 patients.

[b] Missing data in 2 patients.

[c] Undetermined in 569 patients.

vs symptomatic (New York Heart Association class ≥II) patients. All-cause mortality rate was compared with expected mortality of persons of the same age and sex in the same geographical area. Control data were obtained from the Region Nord Pas-de-Calais live tables for 2016 provided by the French Institute of Statistics.[15] Hazard ratios (HRs) and 95% CIs were calculated using the Cox model. The proportional hazards assumption was tested visually by examining plots of −ln (−ln[survival time]) against the ln(time) and by including time-dependent interaction terms in the regression analysis. Collinearity was excluded by constructing a correlation matrix between variables included into the models. All statistical analyses were performed with Stata version 14.2 (StataCorp). Statistical significance was assumed at $P < .05$. Analysis took place between August and November 2020.

Results

Study Population

Among 2703 patients with follow-up, 233 patients (8.6%) were recruited from a public university hospital, 757 (28%) in non-university public hospitals, and 1713 (63.4%) by cardiologists in private practice. At inclusion, 1154 patients (42.7%) had mild AS, 1122 (41.5%) had moderate AS, and 427 (15.8%) had severe AS. Baseline characteristics are depicted in **Table 1.** Overall, this was an elderly population (mean [SD] age, 76.0 [10.8] years) with a relatively high prevalence of risk factors and underlying cardiovascular diseases (atrial fibrillation, coronary artery disease, and stroke). When compared according to AS severity, we did not observe clinically relevant differences regarding age, sex, cardiovascular risk factors, or underlying cardiovascular disease. Patients with severe AS had higher incidence of HF symptoms (New York Heart Association class ≥II) or angina. Left ventricular ejection fraction was similar between the 3 groups. Baseline characteristics according to type of cardiology practice are shown in eTable 1 in Supplement 1.

Follow-up and AVR Procedures

There were 448 deaths during the follow-up period (median [interquartile range], 2.1 [1.4-2.7] years). Follow-up TTE in the pre-AVR period was repeated in 1791 patients based on the decision of the treating cardiologist during routine outpatient visits. AS progression (defined as an increase in AS severity category during the follow-up period) was detected in 775 patients: 350 patients (45.2%) progressed from mild to moderate, 60 (7.7%) from mild to severe, and 365 (47.1%) from moderate to severe AS.

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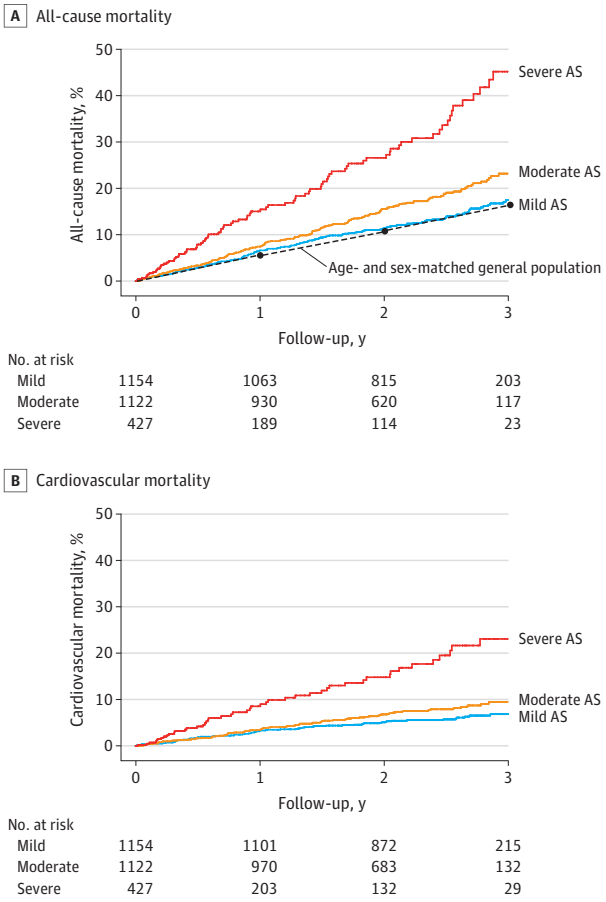
Figure 1. All-Cause and Cardiovascular Mortality



A, The expected mortality rate in an age- and sex-matched general population of the same geographical area is shown for comparison. Mild aortic stenosis (AS) serves as the reference; moderate AS: hazard ratio (HR), 1.45 (95% CI, 1.18-1.79); $P < .001$; severe AS: HR, 2.87 (95% CI, 2.21-3.73); $P < .001$. B, Mild AS serves as the reference; moderate AS: HR, 1.47 (95% CI, 1.07-2.02); $P = .02$; severe AS: HR, 3.66 (95% CI, 2.52-5.31); $P < .001$.

Table 2. Adjusted HRs for All-Cause Mortality and for Cardiovascular Mortality[a]

Mortality	HR (95% CI)	*P* value
All-cause mortality		
Mild AS	1 [Reference]	NA
Moderate AS	1.44 (1.17-1.78)	.001
Severe AS	3.12 (2.39-4.06)	<.001
Cardiovascular mortality		
Mild AS	1 [Reference]	NA
Moderate AS	1.50 (1.08-2.07)	.01
Severe AS	4.01 (2.74-5.86)	<.001

Abbreviations: AS, aortic stenosis; HR, hazard ratio; NA, not applicable.

[a] Adjusted for age, sex, diabetes, history of hypertension, previous myocardial infarction, previous coronary bypass, previous percutaneous coronary intervention, atrial fibrillation, previous hospitalization for heart failure, prior stroke, left ventricular ejection, and type of cardiology practice.

During follow-up, 634 patients underwent AVR. The 2-year cumulative incidence of AVR was 3.4% (95% CI, 2.5-4.6) in patients with mild AS, 20.2% (95% CI, 17.9-22.7) in patients with moderate AS, and 54.6% (95% CI, 49.7-59.2) in patients with severe AS. The indications for AVR are summarized in eTable 2 in Supplement 1. There were 141 patients with peak aortic jet velocity 4 m/s or more at inclusion who met the criteria for AVR but did not undergo intervention during follow-up. The reasons for not performing AVR were patient refusal in 54 cases, contraindication for AVR (life expectancy <1 year, severe dementia or frailty unlikely to improve after AVR) in 49 individuals, death while waiting for AVR in 14 individuals, waiting for AVR at end of follow-up in 4 individuals, and cardiologist decision to maintain on close follow-up in 20 individuals.

Death Prior to AVR

The causes of death in patients who did not undergo AVR are detailed in eTable 3 in Supplement 1. A specific cause of death was adjudicated for 386 of 448 deaths (86.2%); in 62 individuals (13.8%), the cause of death was unknown. Cardiovascular deaths were most frequent (200 [44.7%]), with HF (101 [22.6%]) and sudden death (60 [13.4%]) predominating. There were 186 noncardiovascular deaths (41.5%), with cancer being the most frequent noncardiovascular cause (82 [18.3%]).

Death occurred in 163 of 1154 patients with mild AS (14.1%), 197 of 1122 patients with moderate AS (17.6%), and 88 of 427 patients with severe AS (20.6%). As shown in **Figure 1**A, all-cause mortality increased with increasing AS severity at inclusion. The 2-year cumulative risk of all-cause death was 11.6% (95% CI, 9.8-13.6) in patients with mild, 15.7% (95% CI, 13.6-18.2) with moderate, and 25.6% (95% CI, 20.5-31.6) with severe AS. Compared with patients with mild AS, the HR for all-cause mortality was 1.45 (95% CI, 1.18-1.79) in patients with moderate and 2.87 (95% CI, 2.21- 3.73) in patients with severe AS. As shown in Figure 1A, the observed mortality in patients with mild AS was indistinguishable from the expected mortality of the general population. Cumulative incidence of cardiovascular death is shown in Figure 1B. Compared with patients with mild AS, the HR for cardiovascular mortality was 1.47 (95% CI, 1.07-2.02) in patients with moderate AS and 3.66 (95% CI, 2.52-5.31) in patients with severe AS. Similar results were observed for all-cause and cardiovascular mortality when adjusted for baseline characteristics (**Table 2**). Outcome data according to type of cardiology practice are shown in eTable 1 in Supplement 1.

A further analysis was performed according to the symptomatic status at baseline. In asymptomatic patients, while there was evidence of increased mortality in patients with severe AS, the outcome of patients with moderate AS did not differ significantly from that of patients with mild AS (**Figure 2**A and B); compared with patients with mild AS, the HR in patients with moderate AS was 1.44 (95% CI, 0.95-2.19) for all-cause mortality and 0.99 (95% CI, 0.44-2.21) for cardiovascular mortality. By contrast, the patterns observed in symptomatic patients were similar to those observed in the overall study population (Figure 2C and D). In patients with mild AS, the presence of symptoms was associated with higher all-cause (HR, 2.49 [95% CI, 1.76-3.51]) and cardiovascular mortality (HR, 3.31 [95% CI, 1.87-5.88]) compared with asymptomatic patients.

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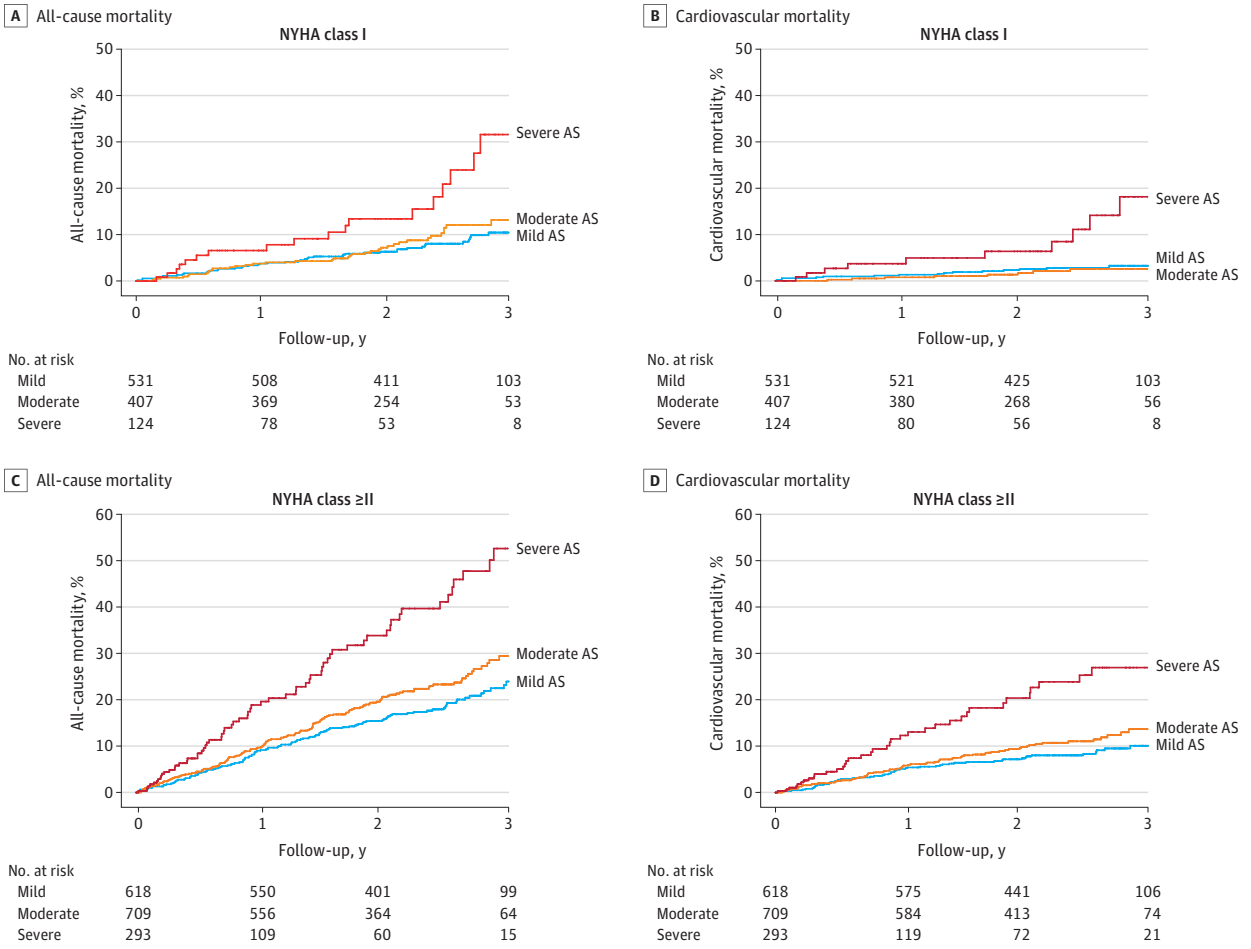
Figure 2. Mortality According to Baseline Symptomatic Status



A, Mild aortic stenosis (AS) serves as the reference; moderate AS: hazard ratio (HR), 1.44 (95% CI, 0.95-2.19); $P = .09$; severe AS: HR, 2.69 (1.55-4.67); $P < .001$. B, Mild AS serves as the reference; moderate AS: HR, 0.99 (95% CI, 0.44-2.21); $P = .98$; severe AS: HR, 4.50 (95% CI, 2.01-10.1); $P < .001$. C, Mild AS serves as the reference; moderate AS: HR, 1.33 (95% CI, 1.04-1.69); $P = .02$; severe AS: HR, 2.60 (95% CI, 1.92-3.52); $P < .001$. D, Mild AS serves as the reference; moderate AS: HR, 1.39 (95% CI, 0.98-1.99); $P = .06$; severe AS: HR, 3.15 (95% CI, 2.07-4.80); $P < .001$. NYHA indicates New York Heart Association.

A breakdown of the different causes of cardiovascular death according to AS severity is provided in **Figure 3** and eTable 4 in Supplement 1. In each group of patients, cardiovascular mortality was mainly associated with HF and sudden death with a progressive increase with increasing AS severity. In the asymptomatic group, cardiovascular mortality was very low in patients with mild or moderate AS. By contrast, there was an increase in cardiovascular mortality in patients with severe AS that was mostly associated with an increase in the risk of sudden death. In the symptomatic group, cardiovascular mortality was much higher, mainly associated with HF, with a progressive increase with increasing AS severity.

Among 163 patients with mild AS at baseline who died during follow-up, 31 (19.0%) had evidence of progression to moderate (n = 24) or severe (n = 7) AS. Among 197 patients with moderate AS at baseline who died during follow-up, 19 (9.6%) had evidence of progression to severe AS. Similarly, among 106 patients without symptoms at baseline who died during follow-up, 18 (17.0%) developed symptoms while 61 (57.5%) remained asymptomatic; information on changes in symptomatic status during follow-up was not available for 27 patients (25.5%).

To account for AS progression when assessing the association between AS severity and outcome, we performed an analysis in which AS severity category was modeled as a time-dependent variable. In the overall population, compared with patients with mild AS, there was an increased all-cause mortality for patients with moderate AS (HR, 1.54 [95% CI, 1.24-1.92]) and severe AS (HR, 2.65 [95% CI, 2.06-3.41]). Similarly, compared with patients with mild AS, there was an increased cardiovascular mortality for patients with moderate (HR, 1.49 [95% CI, 1.06-2.10]) and severe AS (HR, 3.46 [95% CI, 2.40-4.99]).

Discussion

The present study focuses on 2703 patients with a wide range of AS severity included in a prospective regionwide registry.

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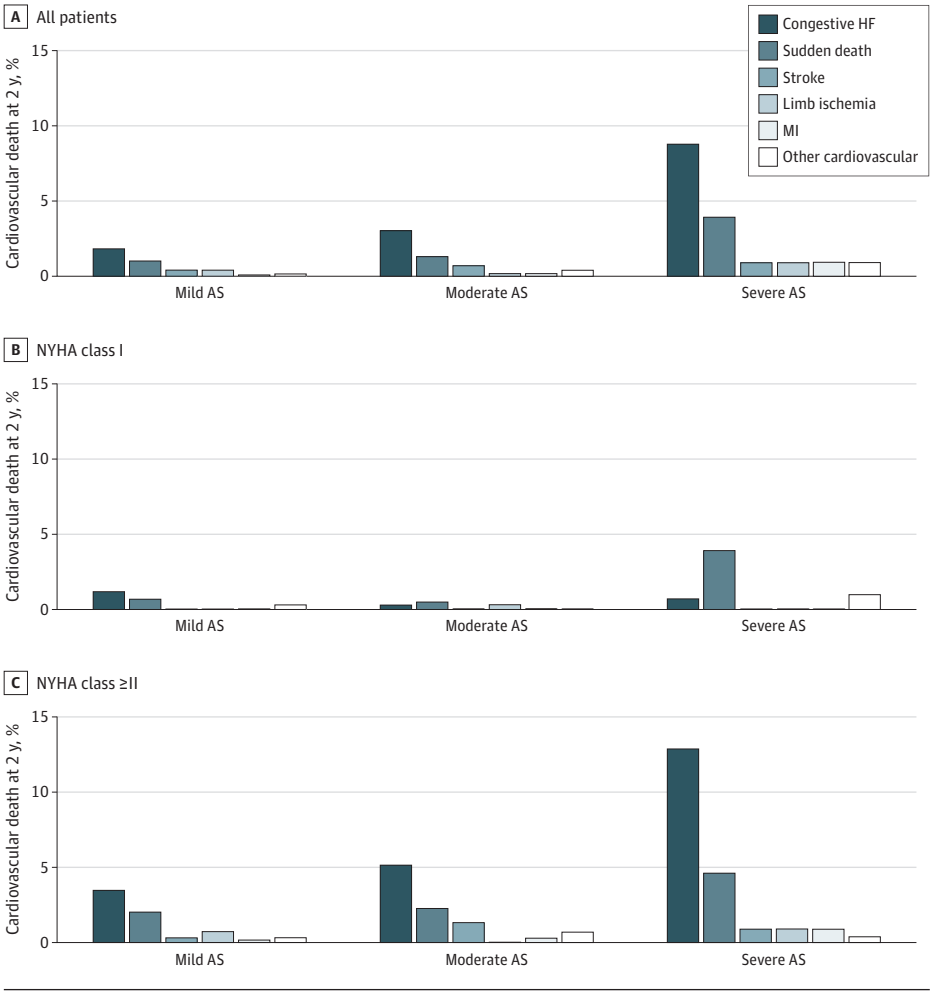
Figure 3. Causes of Cardiovascular Death in Aortic Stenosis (AS)



Comparison of patients with mild, moderate and severe AS. Data are 2-year cumulative incidences for each mode of death. HF indicates heart failure; MI, myocardial infarction; NYHA, New York Heart Association (NYHA).

The recruitment was performed by cardiologists regardless of their mode of practice. We chose to categorize patients with AS according to peak aortic jet velocity because the prognostic value of this parameter has been largely demonstrated in previous studies with various grades of AS severity.[2,16,17] The main results of our study can be summarized as follows. First, the spectrum of AS was mainly represented by mild and moderate AS, sharing the same clinical characteristics with a high prevalence of risk factors and underlying cardiovascular diseases. Second, despite a management in line with current guidelines,[18] all-cause mortality increased with increasing AS severity, primarily owing to differences in cardiovascular death associated with HF and sudden death. Third, although the observed mortality in patients with mild AS could not be distinguished from the expected mortality in the general population, patients with moderate AS displayed an increased risk of cardiovascular mortality without reaching that of severe AS; this observation remained valid after adjustment for baseline characteristics and also when the progression of AS was taken into account. Fourth, the increased mortality in moderate AS was only observed in symptomatic patients; by contrast, in asymptomatic patients, the cardiovascular mortality of patients with moderate AS was similar to that of patients with mild AS.

Although an increase in the prevalence of AS with age has been consistently reported in US and European studies throughout the past 30 years,[19,20] contemporary data concerning the distribution and the demographics of AS severity remains scarce. Moreover, no data regarding the modes of death of this growing population of patients is available to date and to our knowledge. The most recent and large study focusing on outcome of patients with AS was conducted in Australian tertiary centers by Strange et al.[9] The authors reported among 16 129 patients with AS recorded in the National Echocardiographic Database of Australia, linked to National Death Index, a relatively low proportion of moderate AS (mild AS, 62.5%; moderate AS, 13%; severe AS, 24.5%). The major finding of the study by Strange et al[9] was that the risk of death in moderate AS was as high as in severe AS. In the present study, avoiding the recruitment bias associated with the extremely specific populations referred to tertiary centers, we observed a much greater proportion of moderate AS (mild AS, 42.5%; moderate AS, 41.5%; severe AS, 16%). Regarding outcome, we observed a progressive increase in mortality with each higher

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grade of AS severity. However, while higher than in mild AS, the risk of death in moderate AS was much lower than in severe AS. In addition, when the analysis was restricted to asymptomatic patients, the mortality of patients with moderate AS was similar to that with mild AS. This discrepancy between our data and those of Strange et al[9] may be associated with the different modes of patient recruitment, ie, cardiologists from all types of clinical practice vs those practicing in tertiary centers. In a tertiary center referral practice, there might be a bias toward higher risk patients in the group with moderate AS.

Although the risk in patients with symptomatic[1] or asymptomatic[3,7,16,21] severe AS is well known, that of moderate AS has been less studied. Otto at al,[22] Rosenhek et al,[6] and Lancellotti et al[3] showed that mortality in patients with moderate AS was 1.5 to 2 times higher than that of age- and sex-matched populations. Our results in a more contemporary setting are consistent with these findings and suggest that moderate AS is not a benign condition; however, prognosis in moderate AS appears much less adverse than in severe AS, especially among patients who do not report symptoms, and the indications for replacing the valve (either by transcatheter or surgical AVR) in such patients remains uncertain. From a theoretical standpoint, the increased mortality of patients with moderate AS may be the result of 2 different scenarios: patients may die without progressing to severe AS or patients may progress to severe AS and die thereafter. Our observation of a persistent signal for higher mortality in the moderate group when AS severity was modeled as a time-dependent variable does not support the second hypothesis. However, we acknowledge that undetected progression may have occurred prior to a fatal event. Randomized studies are currently underway to investigate the potential benefit of early AVR in patients with moderate AS.[23]

Our data demonstrate that the principal causes of cardiovascular mortality, HF, and sudden death have a proportional graduation with increasing AS severity. The 2-year cumulative incidence of sudden death was high in patients with severe AS (4.5%), consistent with the data from the CURRENT AS Registry showing 5-year cumulative incidence of sudden death of 9.2% in symptomatic and 7.2% in asymptomatic patients with severe AS.[24] We observed that cardiovascular mortality in asymptomatic severe AS was primarily associated with sudden death while congestive HF was the main cardiovascular cause of death in symptomatic severe AS. It should be noted that the exact disease mechanism leading to sudden death in patients with AS is not well defined and may not always be associated with the valve per se.[25] Finally, although aortic valve calcification is a marker of atherosclerosis,[26] with associations between calcific AS and coronary heart disease,[27] our study also shows that the incidence of death from myocardial infarction is very low in this population.

Regarding progression of AS, we observed that more than one-third of patients with moderate AS progressed to severe AS in the study time frame of 2.1 years and thus faced the associated high risk for cardiac events. Our data were consistent with those published by Rosenhek et al,[6] who showed that almost half of patients with mild/moderate AS progressed to severe AS at 4-year follow-up. These data support the need for frequent reevaluations of patients with AS by echocardiographic grading as well as symptomatic assessment.

Limitations

The primary aim of our study was to provide data on outcomes of patients with AS cared for in a variety of clinical settings. As a consequence, indications for serial imaging or AVR were not standardized. A major limitation is the lack of a systematic TTE follow-up strategy, so that 912 patients (33.7%) did not have serial TTE data. A related issue is that undetected progression in AS severity prior to a fatal event is difficult to exclude. We acknowledge the possibility of misclassification of cause of death in some cases. We also recognize the imprecision in diagnosing severe low-gradient AS, which was an indication for AVR in many patients. TTEs were analyzed at individual sites without a central echocardiography core laboratory for standardized evaluation. Finally, our data reflect the practice in a regional area of France, and thus further investigation is warranted to determine whether these findings are generalizable and representative of practices in other parts of the world.

Conclusions

Our study brings new information regarding the cause of death in patients with different stages of AS severity. While patients with moderate AS had a slightly higher risk of death than patients with mild AS, this risk was much lower than that observed in those with severe AS. However, in the subgroup of patients who had no symptoms at entry into our database, moderate and mild AS were associated with similar risk of mortality.

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Author Contributions: Dr Bauters had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Concept and design: Coisne, Montaigne, Bauters.
Acquisition, analysis, or interpretation of data: All authors.
Drafting of the manuscript: Coisne, Montaigne, Richardson, Polge, Bauters.
Critical revision of the manuscript for important intellectual content: Coisne, Montaigne, Aghezzaf, Ridon, Mouton, Lancellotti, Bauters.
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