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ORIGINAL INVESTIGATIONS

Poor Long-Term Survival in Patients With Moderate Aortic Stenosis

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ABSTRACT

BACKGROUND Historical data suggesting poor survival in patients with aortic stenosis (AS) who do not undergo treatment are largely confined to patients with severe AS.

OBJECTIVES This study sought to determine the prognostic impact of all levels of native valvular AS.

METHODS Severity of AS was characterized by convention and by statistical distribution in 122,809 male patients (mean age 61 ± 17 years) and 118,494 female patients (mean age 62 ± 19 years), with measured aortic valve (AV) mean gradient, peak velocity, and/or area. The relationship between AS severity and survival was then examined during median 1,208 days (interquartile range: 598 to 2,177 days) of follow-up. Patients with previous aortic valve intervention were excluded.

RESULTS Overall, 16,129 (6.7%), 3,315 (1.4%), and 6,383 (2.6%) patients had mild, moderate, and severe AS, respectively. On an adjusted basis (vs. no AS; 5-year mortality 19%), patients with mild to severe AS had an increasing risk of long-term mortality (adjusted hazard ratio: 1.44 to 2.09; $p < 0.001$ for all comparisons). The 5-year mortality was 56% and 67%, respectively, in those with moderate AS (mean gradient 20.0 to 39.0 mm Hg/peak velocity 3.0 to 3.9 m/s) and severe AS (≥40.0 mm Hg, ≥4.0 m/s, or AV area <1.0 cm^2 in low-flow, low-gradient severe AS). A markedly increased risk of death from all causes (5-year mortality >50%) and cardiovascular disease was evident from a mean AV gradient >20.0 mm Hg (moderate AS) after adjusting for age, sex, left ventricular systolic or diastolic dysfunction, and aortic regurgitation.

CONCLUSIONS These data confirm that when left untreated, severe AS is associated with poor long-term survival. Moreover, they also suggest poor survival rates in patients with moderate AS. (National Echocardiographic Database of Australia [NEDA]; ACTRN12617001387314) (J Am Coll Cardiol 2019;74:1851–63) © 2019 the American College of Cardiology Foundation. Published by Elsevier. All rights reserved.

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ABBREVIATIONS AND ACRONYMS

AR = aortic regurgitation

AS = aortic stenosis

AV = aortic valve

AVR = aortic valve replacement

CI = confidence interval

CVD = cardiovascular disease

HR = hazard ratio

LHD = left heart disease

LV = left ventricular

SVi = stroke volume index

As succinctly phrased by Eugene Braunwald 3 decades ago (1), the most important decision in the management of patients with aortic stenosis (AS), a condition that affects ~5% of a growing population of individuals 65 years of age or older (2), is when to refer them for a timely intervention. Regardless of the mode of intervention, it is well documented that when left untreated, severe AS is associated with poor survival (3). Historically, such intervention was usually surgical, with aortic valve (AV) replacement (AVR) (4). In recent years, transcatheter AVR has been successfully applied to patients with severe AS with high or prohibitive surgical risk (5-7). Moreover, 2 randomized trials have now reported the noninferiority (8) and superiority (9) of transcatheter AVR in respect to mortality and subsequent risk of stroke, respectively, when compared with the surgical repair of severe AS in low-risk patients. These new data add clarity to the risk-to-benefit ratios of actively managing the broad spectrum of patients with severe AS (from low to high surgical risk), but they also have potential implications for those patients with less severe forms of AS. Although there is both historical (10) and contemporary (11,12) evidence to suggest that mild to moderate forms of AS are not as benign as commonly assumed, particularly in the presence of concurrent systolic dysfunction (11), nearly all relevant studies have had limited numbers of patients and/or short-term follow-up. A study of the natural history of less severe or asymptomatic forms of AS confirmed that progression of AV disease is highly unpredictable; with 75% of patients either dead or requiring AVR within 5 years (13). However, as noted more recently, the natural history of AS remains poorly characterized overall (14). Moreover, newer research suggests that the incidence of AS will likely rise within populations with increased obesity rates (15). It was within this context that we sought to determine more definitively the prognostic impact of increasing severity of AS to inform the clinical management of affected individuals.

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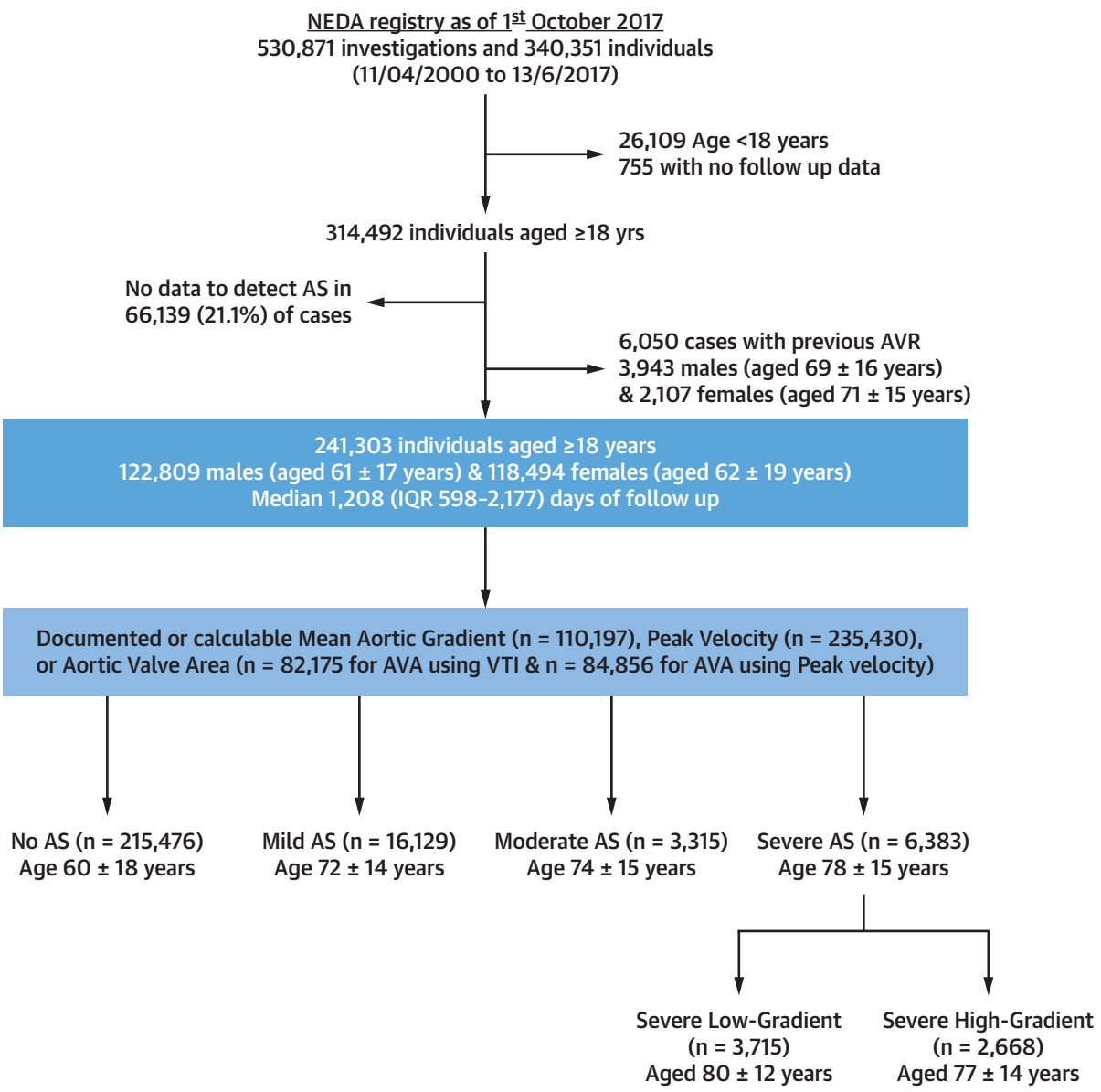
We applied the considerable resources of the National Echocardiographic Database of Australia (NEDA), with the capacity to individually link echocardiographic findings with long-term mortality, in a large, unselected patient group (16). We first hypothesized that a prospective analysis of short- and long-term survival outcomes (1- and 5-year actuarial survival), according to conventional thresholds for diagnosing the different stages of AS (17), would confirm a gradient of risk in respect to all-cause and cardiovascular disease (CVD)-related mortality. We further hypothesized that a more granular examination of survival outcomes according to the statistical distribution of AV parameters, accounting for factors such as concurrent left heart disease (LHD), would reveal a more precise threshold of increased mortality.

METHODS

STUDY SETTING AND DESIGN. As described previously in our original report (16), as well as in a more recent analysis of the prognostic implications of pulmonary hypertension (18), NEDA is a very large observational registry that captures individual echocardiographic data (combined with basic demographic profiling) on a retrospective and prospective basis from participating centers throughout Australia. At the time of study census, a total of 12 centers had contributed >500,000 investigations (~20 million measurements) from ~350,000 individuals undergoing echocardiography. Individuals attending these centers are typically referred by a primary care physician to investigate potential heart disease or are being followed up as part of routine management of a heterogeneous range of CVD states. Given the nature of Australia's universal health care system, minimal referral bias applies to those patients being investigated. Moreover, NEDA collects echocardiographic data on every individual managed by participating centers. These data can then be individually linked to health outcomes (see later). NEDA is also registered with the publicly accessible Australian New Zealand Clinical Trials Registry (ACTRN12617001387314). Ethical approval has been obtained from all relevant Human Research Ethics Committees.

STUDY DATA. All echocardiographic measurement and report data contained in the echocardiographic database of a participating center is collected (study period April 11, 2000 to June 13, 2017). Each database is remotely transferred into a central database through a "vendor-agnostic" automated data extraction process. This process transfers every measurement for each echocardiogram performed into a standard NEDA data format. Precise definitions for each echocardiography variable are applied. Variables with the same name as the NEDA standard are automatically matched. Variables with different names are manually matched with the NEDA standard by the Principal Investigator. Duplicate measurements with different naming conventions are combined. Units are transformed to the single NEDA standard, and repeated measures for the same variable are

FIGURE 1 Study Flowchart



This flowchart shows the critical points of analyses performed in this study. AS = aortic stenosis; AVA = aortic valve area; IQR = interquartile range; NEDA = National Echocardiographic Database of Australia; VTI = velocity time integral.

converted to a single variable according to the NEDA Study Protocol. Additional text recognition software captures free text, clinical comments, and conclusions. These data were used to identify those individuals who had undergone an AVR (including the type of prosthesis inserted). A continuously updated NEDA Data Dictionary is maintained through a Master NEDA Database that forms the basis for all subsequent analyses.

To address the pre-specified hypotheses, individual NEDA data were linked to Australia's National Death Index (19). With enhanced probability matching, this linkage provided reliable data on the survival status and primary cause of death of individuals up to the study census date of October 20, 2017. If an individual had died, the listed causes of death were categorized according to International Classification of Diseases-10th Revision (ICD-10)

TABLE 1 Baseline Characteristics of Study Cohort (n = 241,303)

	Male (n = 122,809)	Female (n = 118,494)	No AS (n = 215,476)	Mild AS (n = 16,129)	Moderate AS (n = 3,315)	Severe AS - high gradient (n = 2,668)	Severe AS - low gradient (n = 3,715)
Demographic profile							
Age, yrs	61 ± 17	62 ± 19	60 ± 18	72 ± 14	74 ± 15	77 ± 14	80 ± 12
Female	0	100	106,250 (49.3)	7,810 (48.4)	1,248 (37.6)	1,276 (47.8)	2,023 (54.4)
Anthropometrics							
Body mass index, m/kg^2	27.9 ± 11.3	27.4 ± 8.6	27.6 ± 10.2	28.5 ± 8.5	28.5 ± 6.2	26.7 ± 5.6	26.2 ± 5.5
Left ventricular dimensions and function							
LVDD, cm	4.9 ± 0.6	4.5 ± 0.5	4.7 ± 0.6	4.7 ± 0.7	4.7 ± 0.7	4.6 ± 0.7	4.6 ± 0.7
LVSD, cm	3.4 ± 0.9	2.9 ± 0.7	3.2 ± 0.9	3.1 ± 0.9	3.2 ± 0.9	3.1 ± 0.9	3.2 ± 1.0
LVEF, %	59.4 ± 11.6	63.4 ± 9.5	61.4 ± 10.5	62.6 ± 11.7	63.1 ± 12.0	60.7 ± 13.3	55.7 ± 15.4
Medial E:E′ ratio	9.9 ± 4.6	10.5 ± 5.0	9.8 ± 4.4	13.3 ± 5.8	14.5 ± 6.8	16.3 ± 8.4	16.7 ± 8.4
Medial mitral annular E′ velocity, m/s	8.3 ± 2.8	8.6 ± 3.1	8.6 ± 3.0	7.1 ± 2.4	6.8 ± 2.2	6.1 ± 2.1	6.1 ± 2.1
SVi, ml/m^2	39.2 ± 11.7	38.1 ± 11.3	38.1 ± 10.8	44.7 ± 13.4	49.8 ± 14.6	41.9 ± 13.9	29.0 ± 10.0
TR peak velocity, m/s	2.6 ± 0.5	2.6 ± 0.5	2.5 ± 0.5	2.8 ± 0.5	2.8 ± 0.5	3.0 ± 0.6	2.9 ± 0.6
Peak LVOT velocity, m/s	1.0 ± 0.2	1.1 ± 0.2	1.0 ± 0.2	1.2 ± 0.3	1.2 ± 0.4	1.0 ± 0.3	0.9 ± 0.2
Mean LVOT VTI	20.1 ± 5.3	21.9 ± 5.7	20.6 ± 5.2	24.5 ± 6.7	25.0 ± 7.3	22.6 ± 7.3	17.7 ± 5.8
Atrial measurements							
LA volume index, ml/m^2	32.6 ± 14.8	30.5 ± 13.7	30.6 ± 13.4	38.0 ± 17.4	40.0 ± 18.1	44.6 ± 18.5	45.3 ± 20.9
RA area, cm^2	19.1 ± 6.2	16.3 ± 5.6	17.5 ± 5.9	19.5 ± 6.8	20.1 ± 7.1	18.0 ± 5.9	21.5 ± 9.0
Aortic valve dimensions and function							
Peak aortic velocity, m/s	1.5 ± 0.6	1.5 ± 0.5	1.4 ± 0.3	2.4 ± 0.3	3.3 ± 0.3	4.6 ± 0.6	3.0 ± 0.7
Mean aortic gradient, mm Hg	4.4 (3.1–7.4)	4.7 (3.4–7.3)	4.3 ± 1.6	12.0 ± 3.1	24.3 ± 6.0	47.4 ± 17.2	21.2 ± 8.9
AV area (VTI), cm^2	2.5 ± 1.0	2.1 ± 0.8	2.6 ± 0.8	1.7 ± 0.5	1.4 ± 0.4	0.9 ± 0.5	0.8 ± 0.2
AV area (peak velocity), cm^2	2.8 ± 0.9	2.3 ± 0.7	2.7 ± 0.8	1.7 ± 0.6	1.3 ± 0.4	0.9 ± 0.7	0.8 ± 0.2
Aortic regurgitation	2,041 (4.5)	1,940 (4.3)	2,425 (3.1)	889 (11.7)	265 (15.2)	242 (15.1)	251 (11.4)
Left heart disease							
Any manifestation	39,518 (32.2)	33,373 (28.2)	60,762 (28.2)	6,987 (43.3)	1,488 (44.9)	1,551 (53.3)	2,452 (60.5)

Values are mean ± SD, %, n (%), or median (interquartile range). Data were available for 90,714 cases to calculate body mass index, 174,956 and 52,151 to calculate LVEF and SVi, respectively and 235,430, 110,197, and 84,856 to calculate peak AV velocity, mean AV gradient and AV area, respectively. Physician reported aortic regurgitation severity was present in 89,739 patients.

AV = aortic valve; LA = left atrial; LVDD = left ventricular diastolic diameter; LVEF = left ventricular ejection fraction; LVSD = left ventricular systolic diameter; LVOT = left ventricular outflow tract; RA = right atrial; SVi = stroke volume index; TR = tricuspid regurgitation; VTI = velocity time integral.

coding. Subsequently, consistent with previous reports of this type (18), all ICD-10AM chapter codes in the range of I00 to I99 were considered a CVD-related death.

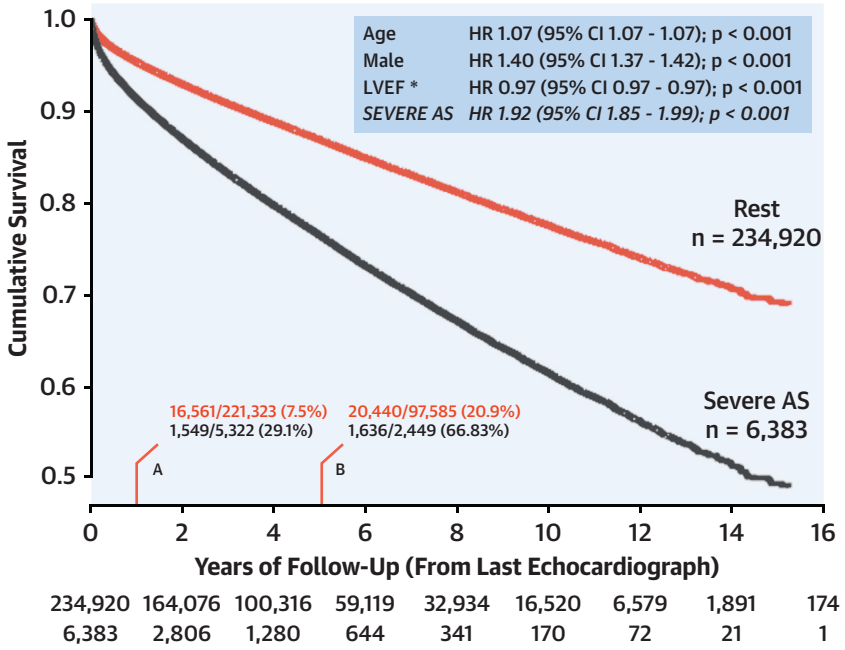
STUDY COHORT. NEDA data as of October 20, 2017 were used to identify the following: 1) men and women ≥18 years of age; and 2) at least 1 echocardiographic investigation. For study analyses, only data from the last recorded echocardiogram were used, and patients with documented AVR were excluded from the primary analyses. The overall NEDA cohort of 313,492 adults comprised 162,464 men (52%) and 151,028 women with a similar age profile: mean age 61 ± 17 years and 62 ± 19 years, respectively. After excluding 6,050 (2%) individuals with a documented history of AVR a total of 241,303 individuals (77% of the overall NEDA cohort ≥18 years old) with a (measured or calculable) mean AV gradient (mm Hg) in 110,197 cases (46%), peak AV velocity (m/s) in 235,430 cases (98%), and/or an AV area (cm^2) in 82,175 cases (34%) were considered for primary analyses (**Figure 1**).

STUDY METHODS. Applying current diagnostic criteria (17), all individuals with intact native valves were initially categorized as follows (primarily according to mean AV gradient and peak AV velocity measurements given available data):

1. No evidence of AS (mean gradient <10 mm Hg and/or peak velocity <2.0 m/s and/or an AV area >1 cm^2)
2. Mild AS (mean gradient 10.0 to 19.9 mm Hg and/or peak velocity 2.0 to 2.9 m/s and/or an AV area >1 cm^2)
3. Moderate AS (mean gradient 20.0 to 39.9 mm Hg and/or peak velocity 3.0 to 3.9 m/s and/or an AV area >1 cm^2)
4. Severe AS, characterized as either high-gradient (mean gradient >40.0 mm Hg and/or peak velocity >4.0 m/s with or without an AV area ≤1 cm^2) or low-gradient (AV area ≤1 cm^2 in the absence of high-gradient AS)

These same AV parameters were also categorized according to their quintile distribution (data for men

FIGURE 2 Prognostic Impact of Severe AS During Long-Term Follow-Up



This figure compares the Kaplan-Meier survival curves of those individuals with severe aortic stenosis (AS) **(black)** versus the rest of the cohort **(red)** with actual 1-year and 5-year mortality also shown. The **inset** shows the results of a Cox proportional hazards model (separate model run in 174,956 cases to adjust further for left ventricular ejection fraction). AV = aortic valve; CI = confidence interval; CV = cardiovascular; HR = hazard ratio.

and women were combined given similar distributions). They were then examined in more granular detail (see the Statistical Analyses section). LHD was defined as 1 or more of the following: 1) left ventricular (LV) ejection fraction <55%; 2) mitral E:E′ >12.0; 3) left atrial volume index >34 ml/m^2; or 4) mitral valve mean gradient >5 mm Hg.

STUDY FOLLOW-UP. All individuals were followed up from the date of their last recorded echocardiogram to the point of death or being censored alive at the census point. The pattern of all-cause and cardiovascular-related mortality during >1 million person-years of follow-up (derived from 44,235 case-fatalities from a median 1,208 days [interquartile range: 598 to 2,177 days]) of follow-up were then examined according to conventional definitions of AS severity and then by the statistical distribution of AV parameters.

STATISTICAL ANALYSES. No formal calculations of study power were performed given the large number of cases, fatal events, and patient-years of follow-up. Unless otherwise specified, between-group comparisons were assessed by Student's *t*-tests, Mann-Whitney U test, chi-square test (with calculation of odd ratios and 95% confidence intervals [CIs]), and analysis of variance (with post hoc Dunnett's *t*-test) where appropriate. Actuarial 1- and 5-year survival rates (all-cause and CVD-related) were calculable in the 226,645 (94%) and 100,034 (42%) cases with complete follow-up at these time points. Consistent with study hypotheses, survival comparisons (including construction of Kaplan-Meier survival curves) first explored potential differences among conventional categories of increasing AS severity. Survival analyses then primarily focused on the statistical distribution of mean AV gradient and peak AV velocity. Multiple logistic regression (entry at a univariate p value of <0.05) models were used to derive adjusted odds ratios for mortality outcomes at fixed time points. Cox proportional hazard models (entry model at a univariate p value of <0.05, with proportional hazards confirmed by visual inspection of adjusted survival curves) were used to derive adjusted hazard ratios (HRs) for mortality outcomes during long-term follow-up. All adjusted analyses included age and sex. Where available and appropriate, models included AV area (as a continuous variable), aortic regurgitation (AR), LV ejection

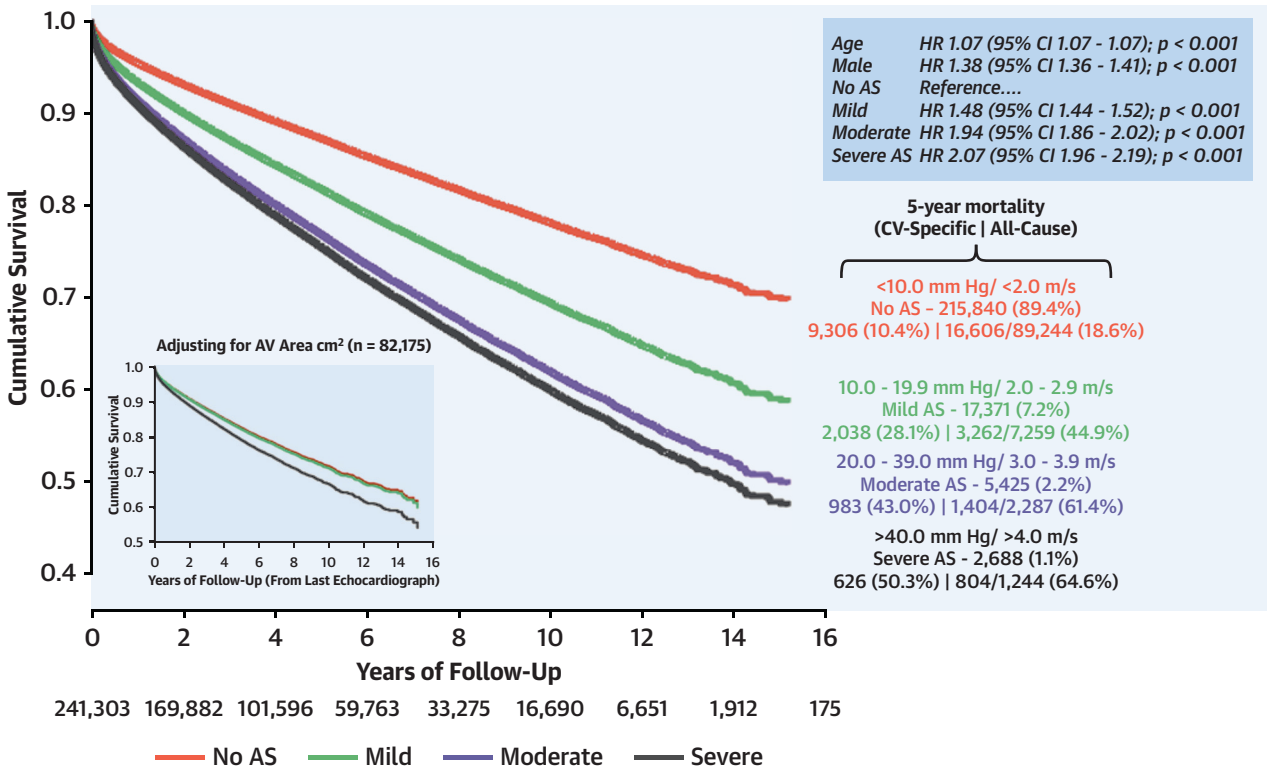
TABLE 2 Survival Profile and Adjusted Risk of Mortality According to Severity of AS

	1-Yr Mortality (n = 226,645)	5-Yr Mortality (n = 100,034)	All Fatal Events (n = 241,303)	Cardiovascular Mortality (n = 241,303)
	OR (95% CI)	OR (95% CI)	HR (95% CI)	HR (95% CI)
All cases	18,110 (8.0)	22,076 (22)	44,235 (18)	22,9637 (9.4)
No AS (n = 215,476)	13,407/202,442 (6.6) Reference	16,549/89,148 (19) Reference	33,914 (16) Reference	16,550 (7.7) Reference
Mild AS (n = 16,129)	2,309/15,152 (15) 1.48 (1.41 to 1.56)	2,913/6,748 (43) 1.63 (1.54 to 1.72)	5,524 (34) 1.44 (1.40 to 1.48)	2,960 (18) 1.52 (1.46 to 1.58)
Moderate AS (n = 3,315)	649/3,077 (21) 2.01 (1.83 to 2.20)	793/1,411 (56) 2.60 (2.31 to 2.92)	1,410 (43) 1.83 (1.74 to 1.93)	868 (26) 2.20 (2.06 to 2.36)
Severe AS (n = 6,383)	1,745/5,974 (29) 2.57 (2.42 to 2.74)	1,821/2,727 (67) 3.05 (2.79 to 3.33)	3,387 (53) 2.09 (2.02 to 2.17)	2,259 (35) 2.67 (2.55 to 2.79)

Values are n (%) or n/N (%), unless otherwise indicated. Among those cases with *no LHD* and full 5-year follow-up, 12,046 of 72,354 (17%) died. Adjusting for age and sex, relative to no AS, the risk of all-cause and cardiovascular mortality at 5 years in these cases was 1.86 (95% CI: 1.72 to 2.00) and 1.70 (95% CI: 1.55 to 1.85), 2.92 (95% CI: 2.50 to 3.42) and 2.84 (95% CI: 2.41 to 3.34), and 3.07 (95% CI: 2.70 to 3.50) and 3.34 (95% CI: 2.93 to 3.81), respectively, for mild, moderate, and severe AS; $p < 0.001$ for all comparisons. Among equivalent cases but with *concurrent LHD*, 10,030 of 27,680 (36%) died. The adjusted risk of all-cause and cardiovascular mortality at 5 years in these cases was 1.34 (95% CI: 1.23 to 1.46) and 1.22 (95% CI: 1.11 to 1.34), 2.17 (95% CI: 1.82 to 2.60) and 2.08 (95% CI: 1.75 to 2.48), and 2.76 (95% CI: 2.44 to 3.11) and 2.36 (95% CI: 2.11 to 2.63), respectively, for mild, moderate, and severe AS; $p < 0.001$ for all comparisons.

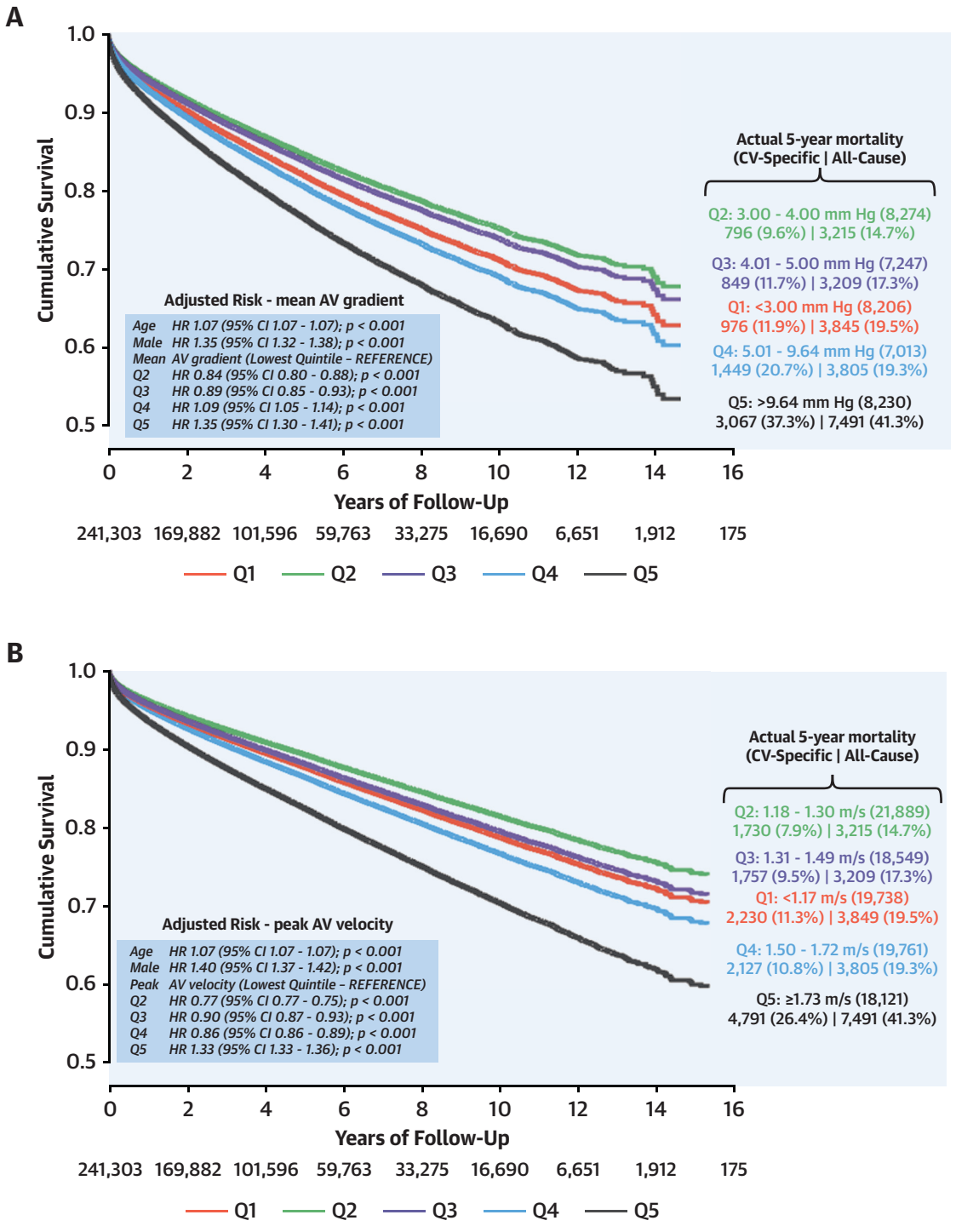
AS = aortic stenosis; CI = confidence interval; HR = hazard ratio; LHD = left heart disease; OR = odds ratio.

FIGURE 3 Adjusted Long-Term Survival According to Severity of AS Derived From Mean AV Gradient and Peak AV Velocity Levels



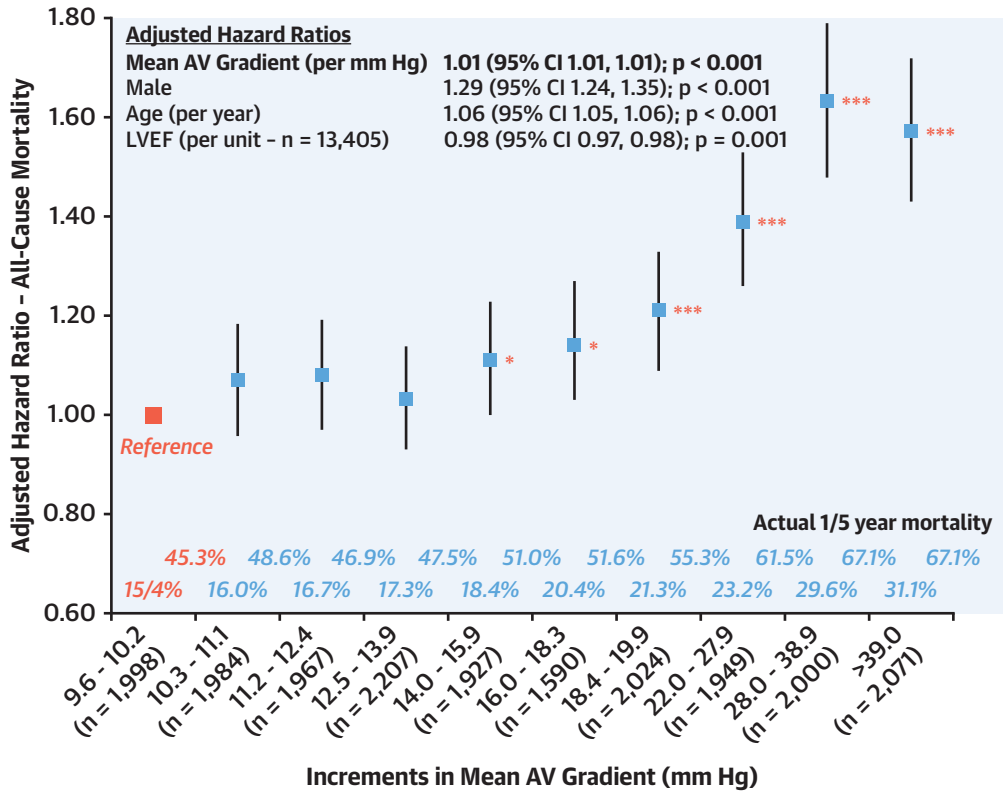
This graph compares the adjusted survival curves of individuals with increasing categories of aortic stenosis (AS). The **inset** shows those survival curves derived from the same model but with the aortic valve (AV) area added as a continuous variable (data were available in 82,175 individuals – adjusted hazard ratio (HR): 0.76; 95% confidence interval (CI): 0.74 to 0.77 per unit decrease; $p < 0.001$. An additional model with stroke volume index data added (available in 52,151 individuals – adjusted hazard ratio: 0.97; 95% confidence interval: 0.97 to 0.98 per unit decrease; $p < 0.001$) did not substantially change initial observations. CV = cardiovascular; Q = quintile.

FIGURE 4 Adjusted Long-Term Survival According to Quintile Distribution of Mean AV Gradients and Peak AV Velocity Levels



This graph compares the adjusted survival curves derived from the quintile distribution of **(A)** mean aortic valve (AV) gradient and **(B)** peak AV velocity among 110,197 and 235,430 individuals, respectively. Abbreviations as in Figure 3.

FIGURE 5 Adjusted Risk of All-Cause Mortality According to Decile Distribution Within the Upper Quintile of Mean AV Gradient (n = 19,722)



This graph summarizes the results of a granular analysis of the adjusted risk of all-cause mortality during long-term follow-up within the upper quintile of mean aortic valve (AV) gradient; the reference value is the lowest decile range (9.2 to 10.7 mm Hg). *p < 0.05. ***p < 0.001. CI = confidence interval; LVEF = left ventricular ejection fraction.

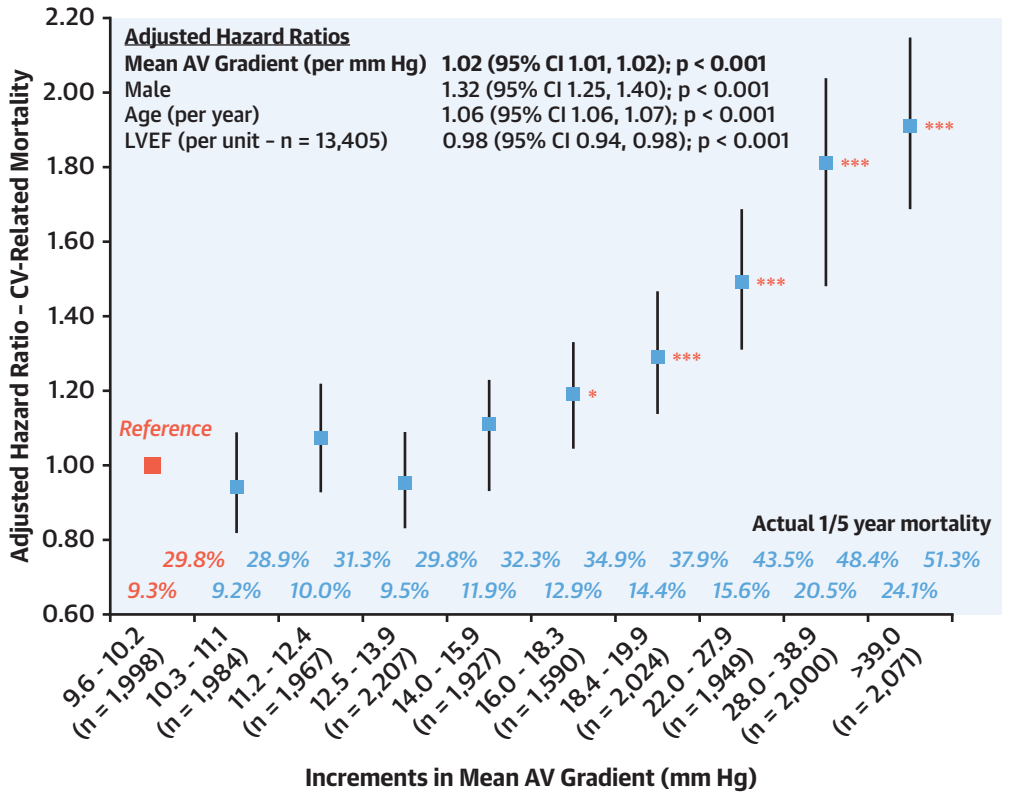
fraction, and stroke volume index (SVi). A priori, sensitivity analyses were performed in the presence or absence of concurrent LHD to determine whether these groups should be reported separately. All analyses were performed with SPSS software version 24.0 (IBM Corp., Armonk, New York), and statistical significance was accepted at a 2-sided p value of <0.05.

RESULTS

COHORT PROFILE. Table 1 summarizes the broad demographic and echocardiographic characteristics of the study cohort according to evidence of no (89%), mild (6.7%; 95% CI: 6.6% to 6.8%), moderate (1.4%; 95% CI: 1.35% to 1.45%), or severe low- or high-gradient AS (2.6%; 95% CI: 2.5% to 2.8%). Overall, increasing severity of AS was correlated with advancing age and increasingly prevalent LHD (p < 0.001 for both comparisons). Men and women differed with respect to the proportions with severe AS characterized by high gradient (more men) and low gradient (more women, with a corollary reduction in those with moderate AS). The phenotypic response of the heart to AS was evident, with systolic function relatively well preserved, but signs of diastolic dysfunction and increased LV filling pressures appeared with increasing severity of AS. There was a corresponding increase in the indexed left atrial volume and peak tricuspid regurgitant velocity. SVi increased with the progression from no AS to mild and moderate AS. There was a decrease in SVi with high-gradient severe AS and a more marked decrease with low-gradient severe AS (p < 0.001 for all comparisons).

SURVIVAL ACCORDING TO SEVERITY OF AS. Overall, 44,235 (18%) individuals died during study follow-up. Compared with the rest of the cohort, on an adjusted basis (including concurrent LV dysfunction), patients with severe AS had a 1.9-fold increased

FIGURE 6 Adjusted Risk of Cardiovascular-Related Mortality According to Decile Distribution Within the Upper Quintile of Mean AV Gradient (n = 19,722)



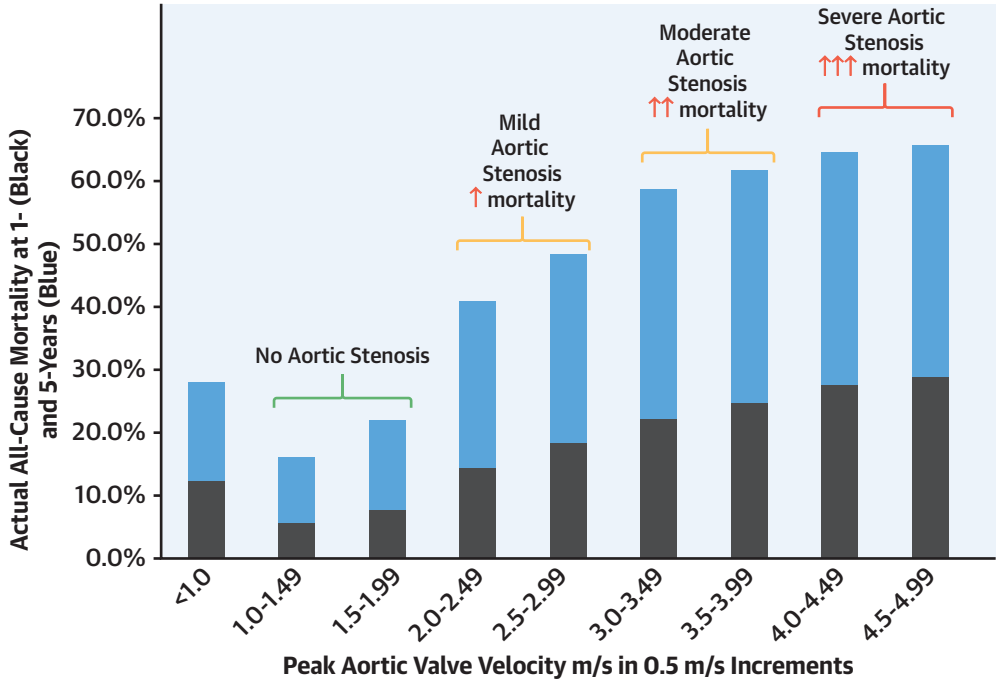
This graph summarizes the results of a granular analysis of the adjusted risk of cardiovascular (CV)-related mortality during long-term follow-up within the upper quintile of mean aortic valve (AV) gradient; the reference value is the lowest decile range (9.6 to 10.2 mm Hg). *p < 0.05. ***p < 0.001. Abbreviations as in Figure 5.

risk of all-cause mortality during long-term follow-up (Figure 2). As shown in Table 2 (1- and 5-year actuarial and overall survival rates), short- and long-term mortality was further delineated (p < 0.001 for all comparisons) according to increasing severity of AS; with the adjusted risk of 5-year mortality approaching that of severe AS (3.0-fold increased risk) in patients with moderate AS (2.6-fold increased risk). This trend was more pronounced in those without concurrent evidence of LHD at baseline. As further shown in Online Figures 1A and 1B, an examination of 1- and 5-year actual mortality according to increasing peak AV velocity (data available in 235,430 individuals), this trend of nearly equivalent 5-year mortality among patients with moderate to severe AS remained evident regardless of concurrent LHD. The same trends were evident in respect to mean AV gradient and AV area (data not shown).

As shown in Figure 3, compared with no AS, within the entire cohort, there was a gradient of adjusted mortality risk associated with conventional levels of mild AS (~1.5-fold increased risk) and then moderate to severe AS (~2.0-fold increased risk) on the basis of a combination of mean AV gradient and peak AV velocity. When adjusting for AV area as a continuous variable (available data in 82,175 cases) (Figure 3 insert), there was a clearer dichotomy of risk, with mild AS having a risk similar to that in patients with no AS (adjusted HR: 1.02; 95% CI: 0.98 to 1.07; p = 0.324) and moderate and severe AS also having a similar risk profile (adjusted HR: 1.19; 95% CI: 1.12 to 1.26; and adjusted HR: 1.22; 95% CI: 1.13 to 1.31, respectively, vs. no AS; p < 0.001 for both comparisons).

SURVIVAL ACCORDING TO DISTRIBUTION OF AV INDICES. An even more distinctive pattern of mortality was evident when age- and sex-adjusted survival curves were derived from the quintile distribution of mean AV gradient and peak AV velocity (Figures 4A and 4B). For both parameters there was a J-shaped pattern of increased risk associated

CENTRAL ILLUSTRATION **Moderate Native Valvular Aortic Stenosis and Long-Term Survival: 1- and 5-Year Mortality per Increment in Peak Aortic Valve Velocity**



Strange, G. et al. J Am Coll Cardiol. 2019;74(15):1851–63.

This graph provides a color-coded comparison of 1- and 5-year mortality according to the conventional classification of severity of aortic stenosis according to peak aortic valve velocity values as recommended by the American College of Cardiology/American Heart Association (4) and European Society of Cardiology (16).

with the lowest and highest quintile levels compared with those in the middle quintile groups. On closer examination, there was a marked J-shaped distribution of risk of mortality (highest among those with very low values) within the lowest quintile group of mean AV gradients (Online Figure 2) on an adjusted basis. Within the upper quintile of mean AV gradient there was an apparent "pivot point" of increased risk (adjusted) of mortality over the longer term around 18 to 20 mm Hg (with an equivalent observation seen in peak AV velocity around a level of 2.4 m/s). This was statistically confirmed at a statistical level of $p < 0.001$ at a mean AV gradient of 20.0 mm Hg (**Figure 5**). The same phenomenon was evident when examining CVD-related mortality (**Figure 6**) and across the age spectrum (Online Figures 3A and 3B). Adjusting for the SVi or the presence of AR did not change the threshold at which mortality increased. Further, this observation remained unchanged when using the Dimensionless Index as a substitute for AV area (where severe and moderate AS was defined as <0.25 and 0.25 to 0.30, respectively).

DISCUSSION

In this large analysis of survival across the full spectrum of native valve AS severity, we found high rates of mortality associated with both moderate and severe AS during long-term follow-up (**Central Illustration**). Although lacking clinical granularity, the size and scope of identified patients with AS and their linked mortality data are substantially greater than in previous observational studies used to inform current clinical practice (4). According to contemporary guidelines for classifying affected individuals (17), we identified mild, moderate, or severe AS in a combined total of 25,827 individuals and then performed a robust series of survival analyses. As expected, there was a clear delineation in the survival profile of those with and without severe AS (2.8% of the cohort). Those with severe AS were 2- to 3-fold more likely to experience all-cause or CVD-related mortality in the short to longer term. After adjusting for age, sex, and other potential confounders (including concurrent LHD or LV dysfunction), individuals with moderate AS had a

high risk of dying in the longer term that was similar to the risk in patients presenting with severe AS at baseline. Subsequently, by applying more granular analyses of AV parameters, we found a threshold of increased risk of longer-term all-cause and CVD-related mortality around a mean AV gradient of 20.0 mm Hg and an equivalent peak AV velocity of 3.0 m/s. This was evident when plotting actuarial and adjusted survival rates. Patients with evidence of LHD at baseline (including LV dysfunction) displayed the same survival trends; albeit with higher mortality rates overall. In absolute terms, therefore, beyond an immediately identifiable high-risk group with severe AS, an additional 5% of individuals with less severe AS were found to be at increased risk of mortality on the basis of their last recorded transaortic velocity profile.

These data provide a clear signal about the likely survival outcome for those individuals presenting with a mean AV gradient >20.0 mm Hg or peak AV velocity >3.0 m/s. These findings remained unchanged when accounting for the confounding effects of age, the presence of absence of LV dysfunction or low-flow states as measured by SVi (20), or AR (7). Without being able to attribute causality, there are 2 plausible explanations. First, patients with an AV gradient in the moderate range may indeed die while they are still in that stage of the disease trajectory of AS (and possibly as a result of comorbid disease that would not necessarily require proactive management of the AS itself; see later). Second, a significant portion of patients determined to have moderate AS at baseline may have reached a tipping point of disease progression that inevitably led them rapidly to develop severe AS and a high risk of death.

Regardless of the mechanism, the high mortality rates in those patients determined to have moderate AS have important clinical implications. The foundation of clinical management of moderate AS, as largely advocated by current guidelines (4,17) is the so-called watchful wait approach (21). Whether these data support the application of AVR before progression to severe AS is open to debate; particularly when considering the possibility that the observed excess mortality in patients with moderate AS may be being partially driven by comorbidity (12). Although some patients may progress from moderate to severe AS relatively quickly and may require AVR (12–14), cardiac structural changes occurring in parallel with this trajectory may also affect mortality risk; these changes may not be fully reversed by AVR if AVR is performed after the AS has become severe and symptomatic (14). However, consistent with our overall finding that the adjusted mortality risk associated with moderate and severe AS appeared to merge over time, there is preliminary evidence to support a discussion and further investigations around the risk-to-benefit ratio of management strategies in patients with either asymptomatic severe AS or moderate AS (22–24). In this respect, the results of the ongoing AVATAR (Aortic Valve Replacement Versus Conservative Treatment in Asymptomatic Severe Aortic Stenosis) randomized trial (with appropriate testing to unmask symptoms and/or coronary artery disease requiring revascularization) will be important in clarifying these early, positive signals (25).

STUDY LIMITATIONS. We considered that AR could be a potential confounder of the mortality gradient observed. However, on an adjusted basis, cardiologist-reported AR severity did not influence the threshold for increased mortality. As recently noted, there is often inconsistent grading of AR during echocardiography reporting (26). As such, we also considered the potential influence of volume loading, such as would occur with hemodynamically significant AR. However, after adjusting for the SVi, the transaortic gradient remained a predictor of mortality at the same mean gradient, above 20.0 mm Hg. It is important to re-emphasize that the NEDA cohort typically comprises individuals being investigated for possible or pre-existing cardiovascular disease. Moreover, beyond the capacity to consider conclusions or clinical notes linked to each echocardiogram, NEDA does not (yet) capture important clinical details pivotal to outcomes relevant to AS and conditions such as coronary artery disease. Moreover, we have yet to analyze outcomes that are based on the findings of multiple echocardiographic investigations. We are unable to comment on the clinical reviews that may have occurred from the time of the last echocardiogram to the time of death or census and therefore are unable to determine the adherence to guidelines or symptom progression from our study. We plan to address these limitations in future studies using NEDA data. Last, these data were largely derived from specialist centers or clinics in Australia. When extrapolating our results to the rest of the world some caution should be applied. Alternatively, it is also important to note that the NEDA cohort is representative of Australia's diverse and multiethnic population with ready access to high-level health care. Moreover, study results were highly consistent across all contributing centers.

CONCLUSIONS

This work represents a large study of AS and long-term survival. Independent of the clinical approach to management of AS, severe AS itself was associated

with very high mortality. However, more modest levels of AS (i.e., mean AV gradient of 20.9 to 39.9 mm Hg or a peak AV velocity of 3.0 to 3.9 m/s) are also associated with similarly high rates of mortality. As such, we confirm previous suggestions that moderate AS is not a benign condition (10–12). In an evolving clinical environment where newer interventions are being considered for treating severe AS to improve typically poor outcomes (7–9,14), these data are relevant to a contemporary re-evaluation of Braunwald's (1) original principles for effectively managing AS. In particular, a re-evaluation of the prognostic impact of moderate AS and the potential value of more timely interventions to reduce a high risk of mortality in the medium to longer term are warranted.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Even moderate ASs (mean gradient 20.0 to 39.0 mm Hg or peak systolic flow velocity 3.0 to 3.9 m/s) may be associated with reduced long-term survival.

TRANSLATIONAL OUTLOOK: Future studies should examine the mechanisms responsible for increased mortality in patients with moderate AS and develop therapeutic interventions to prolong survival.

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APPENDIX For supplemental figures, please see the online version of this paper.