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Incident Aortic Stenosis in 49,449 Men and 42,229 Women Investigated with Routine Echocardiography

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ABSTRACT

Objective: We addressed the paucity of data describing the characteristics and consequences of incident aortic stenosis (AS).

Methods: Adults undergoing echocardiography with a native aortic valve (AV) and no AS were studied. Subsequent age and sex-specific incidence of AS were derived from echocardiograms conducted a median of 2.8 years apart. Progressive AV dysfunction and individually linked mortality were examined per AS category.

Results: 49,449 men (53.9%, 60.9±15.8 years) and 42,229 women (61.6±16.9 years) with no initial evidence of AS were identified. Subsequently, 6,293 (6.9%) developed AS – comprising 5,170 (5.6%), 636 (0.7%), 339 (0.4%) and 148 (0.2%) cases of mild, moderate, severe low-gradient and severe high-gradient AS, respectively. Age-adjusted incidence of all grades of AS was 17.5 cases per 1,000 men/annum and 18.7 cases per 1000 women/annum: rising from ~5 to ~40 cases per 1000/annum in those aged <30 years versus >80 years. Median peak AV velocity increased by +0.57 (+0.36 to +0.80) m/s in mild AS compared to +2.75 (+2.40 to +3.19) m/s in severe high-gradient AS cases between first and last echocardiograms. During subsequent median 7.7 years follow-up, 24,577/91,678 cases (26.8%) died. Compared to no AS, the adjusted risk of all-cause mortality was 1.42-fold higher in mild AS, 1.92-fold higher in moderate AS, 1.95-fold higher in severe low-gradient AS and 2.27-fold higher in severe, high-gradient AS cases (all $p<0.001$).

Conclusions: New onset AS is a common finding among older patients followed-up with echocardiography. Any grade of AS is associated with higher mortality, reinforcing the need for proactive vigilance.

KEY QUESTIONS

What is known: Aortic Stenosis (AS) is a potentially deadly condition with clinical registry data suggesting the risk of developing this condition markedly increases with age. However, there is a surprisingly little data on the incidence of AS – even among high-risk clinical cohorts.

What this study adds: Within a large, representative cohort of adults routinely investigated with echocardiography, a significant portion (17.5 per 1,000 men and 18.7 per 1,000 women per annum) developed AS and subsequently experienced higher mortality.

Clinical Implications: With the development of lower-risk interventions for AS and greater recognition of the prognostic impact of all forms of AS, these data support more structured surveillance to detect progression to AS in higher-risk patients.

INTRODUCTION

Aortic Stenosis (AS) is a common form of valvular heart disease and a major cause of death among those aged >75 years.[1] However, there is a paucity of data describing its natural history.[1,2] Consequently, our understanding of the evolving burden of AS (particularly when its antecedents are at historical highs[3]) remains poor.[4] Durko and colleagues recently estimated that 3.5% of the European and North American population aged >75 years are living with severe AS[5]: with two-thirds symptomatic and therefore eligible, according to current clinical recommendations[6], for surgical or transthoracic aortic valve replacement (AVR).[7-9] However, there remains a paucity of data around the incidence of all grades of AS among those aged <75 years.[10] Recent findings from the National Echocardiography Database of Australia (NEDA)[11], underscore the need to address this deficit. Specifically, in a study of >300,000 men and women undergoing routine investigation of heart disease, 4% of cases had moderate-to-severe AS on their last echocardiogram. Critically, consistent with smaller cohort studies[12], the risk of mortality associated with moderate AS approached that of more severe forms of AS.[13]

STUDY AIMS

By analysing serial echocardiograms linked to mortality within the NEDA cohort[14], our primary aim was to describe the age and sex-specific incidence of all forms of AS within a representative cohort of cardiac patients. We further aimed to characterise the typical progression of aortic valve (AV) disease and determine the prognostic significance of incident AS during long-term follow-up.

METHODS

Study Design

NEDA is a large observational registry that captures routinely acquired echocardiographic data with individual linkage to mortality outcomes in Australia.[11] The study adheres to the REporting of studies

Conducted using Observational Routinely-collected health Data (RECORD) Statement.[15] With a heterogeneous population of ~25 million, Australia has equitable access to specialist cardiac management; 23 centres (Australia-wide) who provide such services participated. The study cohort were typically referred by a general practitioner or cardiologist to investigate or follow-up/manage pre-existing heart disease. NEDA is registered with the Australian New Zealand Clinical Trials Registry (ACTRN12617001387314) and approved by all relevant Human Research Ethics Committees.

Study Cohort

As described previously[14], during 29/05/1985 to 26/6/2019 NEDA captured 1,077,145 echocardiograms performed on 631,824 individuals – comprising 332,397 men (aged 60.1±18.7 years) and 299,517 women (aged 60.1±16.9 years). Excluding those aged <18 years, investigated pre-2000 and without AV profiling, 453,161 adults with a native AV were identified. Of these, 107,423 individuals (23.7%) had echocardiograms conducted at least 1 month apart at which time at least one AV haemodynamic parameter was available to categorise levels of AS according to current expert guidelines.[10] At the first echocardiogram (First Echo), 91,678 of these cases (85.3%) had normal AV function (the study cohort). Of the remainder, 10,478 (9.8%), 2,895 (2.7%), 1,185 (1.1%) and 1,187 (1.1%) were excluded due to evidence of mild, moderate, severe low-gradient and severe high-gradient AS, respectively. Among those 91,678 cases with no AS at baseline, initial to final AV profiling (Last Echo) comprised peak AV velocity (in 89,710 and 91,678 cases respectively), mean AV gradient (45,621 and 51,075 cases) and AV area (41,478 and 48,532 cases).

Study Variables

Study data comprise all echocardiographic measurement and report data, including basic demographic profiling (biological sex and date of birth) of individuals and date of investigation presenting to participating centres during the period 1/1/2000 to 21/5/2019. Left ventricular hypertrophy (LVH) and any form of valvular heart disease (VHD) was determined via American Society

of Echocardiography criteria.[16] Left heart disease (LHD) was defined as one or more of – left ventricular ejection fraction (LVEF) <55%; septal E:e' >12.0; indexed left atrial volume (LAVi) >34 ml/m^2; mitral valve mean gradient >5 mmHg; moderate-to-greater mitral or aortic regurgitation/stenosis and; AV area <1.0 cm^2 (the latter two being absent on the First Echo).[13,14] Primary AV haemodynamic parameters and then AV area (when documented) were used to categorise First and Last Echo as follows:

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

For categorisation purposes, an individual had to have at least one haemodynamic AV parameter (with peak AV velocity applied first) to determine the grade of AS.

Study Outcomes

Individual data-linkage to the well-validated Australia's National Death Index[17] starting from the Last Echo to a census date of 21/5/2019 was performed (total of 340,000 person-years follow-up). Listed causes of death were categorised according to ICD-10AM codes. A primary code of I00-I99 was categorised as a cardiovascular-related death.[18]

Statistical Analyses

Standard methods for describing/comparing grouped data, including means (± standard deviation), median (interquartile range, IQR) and proportions (with 95% confidence intervals [CI]) were performed. No data were imputed. Incidence rates (with 95% CI) were calculated from the number of de novo AS cases detected on Last Echo with adjustment for the duration between echocardiograms and the age and sex of the cohort. The overall age-adjusted rate of incidence of AS and per age-group are reported on a sex-specific basis as the number of newly detected cases per 1,000 subjects/annum (expressed as the number of cases per 1000 person-years follow-up). The rate of change in key AV parameters (mean AV gradient, peak AV velocity and AV area) were derived from the difference between measurements on First and Last Echo and divided by the number of months between each timepoint (expressed as unit of change per annum). The Kaplan Meier method followed by Cox-Proportional Hazard Models (entry method with proportional hazards confirmed by visual inspection) were used to derive adjusted hazard ratios (HR) for all-cause and cardiovascular-related mortality for each category of AS detected on Last Echo. Hazards were adjusted for age, sex, timing of the Last Echo (3-year epochs), LVEF at baseline, presence/absence of LHD, and observed changes in LVEF and peak AV velocity between First and Last Echo (complete data available for 72,703 [79.3%] of cases). All analyses were performed with SPSS v26.0 and statistical significance accepted at a 2-sided p-value of <0.05.

RESULTS

Cohort Profile

The study cohort comprised 49,449 men (53.9% aged 60.9±15.8 years) and 42,229 women (61.6±16.9 years) with no evidence of AS on their First Echo. During a median of 2.8 (1.2 – 5.6) years follow-up, whilst 85,385 cases (93.1%) continued to demonstrate no evidence of AS, at total of 6,293 cases (6.9%, 95% CI 6.7 to 7.0%) comprising 3,203 men and 3,090 women, were found to have de novo

evidence of AS on their Last Echo. The distribution of these AS cases was as follows – mild AS (5,170 cases/5.6% 95% CI 5.5 to 5.8%), moderate AS (636 cases/0.69%, 95% CI 0.64 to 0.75%), severe low-gradient AS (339 cases/0.37%, 95% CI 0.33 to 0.41%) and severe high-gradient AS (148 cases/0.16%, 95% CI 0.14 to 0.19%) – **Table 1**. These cases were more likely to exhibit more baseline features of cardiac disease overall. Specifically, on the First Echo, subsequent AS cases had a higher mitral inflow E wave velocity and E/e' ratio, a lower septal e' velocity, a larger LAVi, and a higher left ventricular mass and tricuspid regurgitation velocity.

Rate of Incident Aortic Stenosis

The overall age-adjusted rate of incident AS was 17.5 men and 18.7 women per 1000 person-years follow-up. A steep age-gradient was evident in both sexes (see **Figure 1**). In men, the incidence of AS rose from 5.1 to 43 cases per 1000 person-years in those initially aged <30 years to >80 years. In women the equivalent incidence rates rose from 5.0 to 39 cases per 1000 person-years.

Progression to Aortic Stenosis

Table 2 compares the observed rate of change in AV parameters according to an individual's final AS category. Compared to the negligible changes observed in those who did not develop AS, the trajectory of change in those who developed AS was markedly different (see **Figure 2**). The greatest rate of change occurred in those who developed severe, high gradient AS (~5mmHg increase in mean AV gradient/annum); $p<0.001$ when compared to the mild AS group. Incident AS was associated with a parallel changes cardiac structure and function typically associated with AS: increased left ventricular mass index, diastolic dysfunction (E/A ratio, E wave velocity, e' velocity, E/e' ratio, and LAVi), and pulmonary hypertension (peak TR velocity). In addition, the degree of mitral and tricuspid regurgitation, and right ventricular dysfunction, all increased with the onset of significant (moderate or greater) AS.

Mortality

During median 7.7 years follow-up 24,577 individuals (26.8%) died from any cause. Overall, mortality rates were higher among those with progressively worse AS – from 25.8% all-cause mortality in those with no AS to 58.5% and 50.0% in those with severe AS low- and high-gradient, respectively. The adjusted risk of all-cause mortality ranged from 1.4 to 1.9-fold higher in those with mild- to severe, low-gradient AS compared to those with no AS. The equivalent risk for those subsequently presenting with severe, high-gradient AS was 2.3-fold higher ($p<0.001$ for all comparisons) – see **Figure 3**. Cardiovascular disease was identified as the primary cause of death in 7,471 cases (30.4% of all deaths). Compared to those with no AS (7.8% mortality), the adjusted HR for cardiovascular-related mortality in those who developed mild (11.9%) and moderate (13.4%) AS was 1.33 (95% CI 1.20, 1.47) and 1.99 (95% CI 1.55, 2.56), respectively. Those who developed severe, low-gradient AS had a similarly elevated risk to those with moderate AS (HR 1.83, 95% CI 1.40, 2.38). Despite a slightly lower absolute mortality rate compared to those with severe, low-gradient AS, those with severe, high-gradient AS had a slightly higher risk profile (HR 2.65, 95% CI 1.71, 4.13) compared to those with no AS. For all AS group comparisons (against the reference group of no AS) $p<0.001$.

DISCUSSION

To our knowledge, this represents the largest single study reporting the age- and sex-specific rate and characteristics (including the rate of AV dysfunction) of incident AS linked to mortality within a clinical cohort (see **Figure 4**). Specifically, in this very large cardiac patient cohort, we found that around 7% developed AS over a median of 3 years. There was a similar natural history observed in men and women with typical age-dynamics evident in detected cases. Overall, for every 100 patients followed-up for one year, two new cases of AS were detected. As expected, there was a marked age-gradient in incidence rates with an 8-fold difference between the youngest (~5 cases/1000 person-years) and oldest age groups (~40 cases/1000 person-years). One in five of these cases had developed

a moderate-to-severe form of AS associated with an adjusted risk of subsequent mortality around 2-fold higher than those who remained free from AS. Although these more severe cases had a longer interval between their First and Last Echo, their rate of deterioration in AV haemodynamic parameters was higher compared to those who had mild AS.

Reports of this size and nature are few and far between. Although the NEDA cohort is not representative of the Australian population and we report those being re-investigated by echocardiogram, our findings are worth comparing to a recent report from the (population-cohort) Tromsø Study in Central Norway.[19] A random sample of 3,273 individuals of a similar age profile to the NEDA cohort were subject to serial echocardiography over a period of 14 years. Subsequently, 164 subjects developed any form of AS (as defined by a mean AV gradient >15 mmHg[19]) with a rate of change in mean AV gradient (3.2 mmHg per annum in a sub-set of 188 subjects) not dissimilar to our cohort. By contrast, the incidence of AS (4.9 cases per 1000 person-years[19]) was approximately one quarter of that observed in NEDA. This undoubtedly reflects the key difference between a random population cohort and a cohort specifically investigated for underlying heart disease. Surprisingly, even severe forms of AS were not associated with an increased risk of mortality in that population cohort.[19] This contrasts with our previous report[13], supported by a growing evidence-base that moderate AS is not as benign as previously thought.[20-22]

The broader impact of AS on mortality underscores the value of better understanding its natural history to prevent its progression to more severe stages. Unfortunately, the preventable antecedents of AS remain at historical highs.[23,24] Determining who, as outlined in **Figure 2**, are in the group that progress to developing AS is critical. Consequently, there is merit in creating more proactive alerts for milder forms of AS. As shown by a US study of 17,000 echocardiograms an AS alert system resulted in a substantive increase (from 73% to 97%) in AS cases referred to a cardiologist, cardiac surgeon, or structural heart clinic.[25] Artificial intelligence programs that detect a deadly phenotype of AS may

also improve detection rates when specialist review is absent.[26] The challenge thereafter will be to determine the most cost-effective management of milder forms of AS to prevent progression and associated risk of mortality. Currently, evidence-based/clinical guidelines are largely focussed on detecting and then actively managing more severe, symptomatic cases of AS.[10] Independent of the potential for progression to more severe AS, the concurrent presence of AV sclerosis contributing to mild obstruction/mildly elevated haemodynamic pressures and subsequently increased risk of mortality should be strongly considered in such cases.[27,28] Given the close link between AS and uncontrolled hypertension[1], these data also reinforce the need for primary care-based interventions to achieve tight blood pressure control in high-risk individuals (including those with mild AS).[29]

Limitations

Any interpretation of our findings requires consideration of the inherent limitations of NEDA's "big data" approach.[13 18] This includes a lack of granular clinical data to fully explain observed associations between specific echocardiographic findings and subsequent mortality and the role of evidence-based treatments in changing an individual's clinical trajectory. For example, the higher mortality observed in those with mild AS may well be explained by concurrent conditions that we are unable to account for. NEDA does not (yet) capture important clinical data on comorbidity, pharmacological and device-based therapies. Nor do we have data on hospital episodes. Thus, we are unable to exactly pinpoint the reasons why an individual would develop AS, nor exclude the possibility that concurrent cardiovascular disease (including coronary artery disease) explains the higher mortality rates associated with increasingly severe AS. However, matching outcome data (currently unpublished) from large European and North American AS cohorts that have considered such confounders, support the mortality associations presented in this and previous reports. [13] While we identified those who underwent AVR, we excluded these cases to report on the "natural history" of AS – noting the favourable survival outcomes when more normalised AV function/haemodynamics is restored.[30]

Specific to this report, subjects were randomly selected from the cardiac patient population and retrospectively determined those with repeat echocardiograms at participating NEDA centres. Consequently, it was clinical imperatives that determined the timing of repeated echocardiograms. Therefore, the true age and sex-specific incidence of AS in the general cardiac patient population and broader general population is likely far lower. Moreover, given the often long-time between the Last Echo and censored follow-up/mortality, it's likely that many individuals with mild-to-moderate AS progressed to more severe forms. However, these systemic biases are a feature of nearly all other equivalent reports focussing on AS.

Conclusions

Among a very large cohort of adults investigated and then monitored for heart disease, around 7% developed any form of AS during a median of 2.8 years between repeated echocardiograms. Regardless of AS severity, mortality rates were elevated in these cases. At a time when the overall prevalence of AS is likely to rise in response to historically high levels of dyslipidaemia and/or obesity within our ageing populations[23,24], these unique data reinforce the need for greater efforts to develop evidence-based strategies to proactively prevent and detect early forms of AS. Without such a response, it is highly likely that a rising number of new AS cases will exert unsustainable demands for health care in addition to a high burden of premature mortality if left untreated.

Contributor Statement

GS and DP conceived and designed the National Echo Database of Australia Study. SS conceived this analysis and conducted study analyses with YKC, and all authors contributed to the interpretation of study data. SS wrote the first draft of the manuscript and all authors contributed to its revision. GS and DP are the guarantors of the overall veracity and accuracy of NEDA data presented in this manuscript.

Competing Interests

GS and DP are the Co-Principal Investigators and Directors of NEDA (a not-for-profit research entity). SS and YKC have received consultancy fees from NEDA. SS, DP, and GS have previously received consultancy/speaking fees from Edwards Lifesciences.

Patient & Public Involvement

No patients were specifically involved in the design and conduct of this observational study.

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Table 1 Characteristics of Study Cohort (N=91,678)

	MEN (n=49,449)	WOMEN (n=42,229)	No AS (n=85,385)	Mild AS (n=5,170)	Moderate AS (n=636)	Severe (HG) AS (n=148)	Severe (LG) AS (n=339)
Demographic Profile							
Age, years	60.9±15.7	61.6±16.9	60.6±16.4	68.3±13.3	67.9±12.6	68.9±12.8	74.6±10.7
Women, %	0%	100%	39,139 (46%)	2,538 (49%)	277 (44%)	73 (49%)	202 (60%)
Baseline Anthropometrics							
Body mass index, m/kg^2	28.5±5.7	28.3±6.7	28.4±6.3	29.5±6.7	29.5±6.0	29.0±6.4	27.2±6.0
Baseline Ventricular Dimensions and Function							
LVDD, cm	5.1±0.8	4.6±0.7	4.9±0.8	4.8±0.8	4.9±0.7	4.7±0.8	4.6±0.8
LVSD, cm	3.5±1.0	2.9±0.7	3.2±0.9	3.1±0.8	3.0±0.9	2.7±0.7	3.1±1.0
LVEF, %	56.1±15.3	62.5±12.8	58.9±14.6	61.7±13.5	65.8±14.5	66.2±13.8	59.3±15.3
E/e' ratio	11.0±5.3	11.4±5.5	11.1±5.3	12.7±6.0	12.1±5.0	11.3±3.5	15.0±7.2
E' velocity, cm/s	7.9±2.7	8.0±3.0	7.9±2.9	7.2±2.6	7.6±2.6	7.8±3.5	6.5±2.3
Stroke Volume Index mL/m^2	39.3±12.0	39.3±11.7	39.2±11.8	42.0±13.1	45.7±14.6	38.3±9.2	37.7±15.0
TR peak velocity, m/s	2.6±0.5	2.6±0.5	2.5±0.5	2.8±0.5	2.9±0.5	3.0±0.6	2.9±0.6
Baseline Atrial Dimensions							
LA volume index, ml/m^2	45.9±29.9	42.7±27.3	44.1±28.7	44.4±28.1	69.4±39.0	35.5±12.9	53.5±30.5
RA area, cm^2	22.9±7.8	19.9±6.8	21.5±7.5	22.7±7.7	25.1±6.9	21.4±5.2	21.1±7.8
Baseline Left Heart Disease							
Any manifestation, %	21,678 (44%)	15,959 (38%)	34,875 (41%)	2,230 (51%)	325 (51%)	54 (37%)	153 (45%)
Follow-up							
First to last echo, months	44.4±38.8	46.8±39.1	44.4±38.8	55.5±40.8	88.5±45.4	91.4±54.7	75.6±43.1
Last echo to census or death, months	112±90.1	113.9±88.9	114.6±90.2	91.3±76.7	78.3±71.8	76.3±73.4	53.1±50.1
Baseline Aortic Valve Profile							
Peak AV Velocity m/s	1.3±0.3	1.4±0.3	1.4±0.3	1.7±0.2	1.6±0.3	1.6±0.3	1.6±0.3
Mean AV Gradient mmHg	4.0±1.7	4.4±1.7	4.0±1.6	6.4±1.7	6.6±2.0	5.8±2.2	6.6±1.9
AV area cm^2	3.0±0.8	2.5±0.7	2.8±0.8	2.3±0.7	2.4±0.8	2.6±0.8	1.8±0.7
Final Aortic Valve Profile							
Peak AV Velocity m/s	1.4±0.4	1.5±0.4	1.4±0.3	2.3±0.2	3.2±0.3	4.4±0.5	2.8±0.6
Mean AV Gradient mmHg	4.8±4.0	5.2±4.2	4.1±1.7	13.1±2.6	24.0±5.0	44.9±10.1	20.2±7.7
AV area cm^2	2.9±0.9	2.4±0.7	2.8±0.8	1.9±0.6	1.4±0.4	1.0±0.8	0.8±0.2

Legend: HG = high-gradient, LG = low-gradient (severe AS). Body mass index (67,707 cases), Left atrial (LA) volume index (27,287 cases), Left Ventricular Diastolic Diameter (LVDD – 65,284 cases), Left Ventricular Ejection Fraction (LVEF - 80,146 cases), Left Ventricular Systolic Diameter (LVSD = 55,950 cases), Left ventricular outflow tract (LVOT) peak velocity (34,146 cases), E/e' ratio (35,949 cases), e' velocity (40,243 cases), Right Atrial (RA) area (17,227 cases), Tricuspid Regurgitation (TR) peak velocity (53,169 cases). Left heart disease defined as any combination of – a) LVEF <55% (n=29,745), b) E/e' prime > 12.0 (n=30,365), c) LA volume index >34.0 ml/m^2 (n=32,972) OR d) Mitral valve mean gradient >5.0 mmHg (n=3,159).

Table 2 **Observed Change in Aortic Valve Profile (from first to last echocardiogram)**

	No AS (n=85,385)	Mild AS (n=5,170)	Moderate AS (n=636)	Severe HG AS (n=148)	Severe LG AS (n=339)
Absolute & Rate of Change in AV Profile (Median, IQR)					
Δ Peak AV Velocity, m/s *Rate per year (89,710 cases)*	+0.01 (-0.18 to +0.13) *0.02 (-0.05 to +0.06)*	+0.57 (+0.36 to +0.80) *+0.14 (+0.08 to +0.27)*	+1.54 (+1.28 to +1.82) *+0.21 (+0.15 to +0.34)*	+2.75 (+2.40 to +3.19) *+0.35 (+0.23 to +0.66)*	+1.11 (+0.68 to +1.17) *+0.19 (+0.12 to +0.29)*
Δ Mean AV Gradient, mmHg *Rate per year (35,556 cases)*	0.00 (-0.93 to +1.00) *0.00 (-0.31 to +0.37)*	+5.89 (-4.00 to +8.10) *+1.52 (+0.89 to +2.88)*	+16.9 (+13.6 to +21.2) *+2.61 (+1.91 to +3.81)*	+34.6 (+30.9 to +41.2) *+4.94 (+3.47 to +7.48)*	+11.8 (+7.86 to +19.3) *+2.37 (+1.52 to +4.07)*
Δ AV Area, cm^2 *Rate per year (32,416 cases)*	+0.03 (-0.48 to +0.43) *+0.01 (-0.18 to +0.17)*	-0.41 (-0.86 to +0.02) *-0.09 (-0.01 to +0.24)*	-0.98 (-1.45 to -0.59) *-0.13 (-0.08 to -0.25)*	-1.49 (-1.74 to -0.87) *-0.25 (-0.13 to -0.42)*	-0.96 (-1.38 to -0.57) *-0.17 (-0.10 to -0.26)*
Absolute Change cardiac function (Median, IQR)					
Δ TR Peak Velocity, m/s (42,547 cases)	+0.05 (-0.02 to +0.30)	+0.20 (-0.09 to +0.48)	+0.30 (+0.09 to +0.56)	+0.30 (-2.10 to +8.00)	+0.21 (-0.12 to +0.64)
Δ LA volume index, ml/m^2 (21,947 cases)	+3.00 (-4.00 to +12.0)	+5.0 (-3.0 to +14.0)	+18.0 (+6.00 to +34.00	+30.7 (+20.6 to +40.8)	+12.0 (+3.00 to +20.0)
Δ e' velocity, m/s (26,235 cases)	0.00 (-0.02 to +0.20)	0.00 (-0.13 to +0.15)	-3.82 (-3.11 to 0.00)	-	-
Δ E/e' ratio (26,235 cases)	+0.39 (-1.72 to +2.96)	+1.00 (-1.54 to +1.37)	+2.80 (0.00 to +5.88)	+3.00 (-1.10 to +7.25)	+3.48 (-0.59 to +6.11)
Δ Stroke Volume Index mL/m^2	+0.10 (-7.17 to +7.59)	+2.81 (-0.37 to +12.8)	+2.10 (0.00 to +10.2)	+4.27 (-7.26 to +9.47)	-4.05 (-12.9 to +2.12)
Δ LVEF, % (74,293 cases)	+0.03 (+0.06 to +1.20)	+0.26 (+0.11 to +0.64)	+1.00 (-5.63 to +9.00)	+0.39 (-9.20 to +7.00)	-3.4 (-14.0 to +5.00)

Legend: Data are presented as the mean change (95% CI's). Collectively, AS groups demonstrated different trajectories for all AV parameters and the additional seven parameters presented ($p<0.001$ for all comparisons). Within group comparisons also demonstrated highly statistically significant differences ($p<0.001$) relative to the no AS (reference) group excepting rate of change in AV area (Moderate AS group [p=0.193]) in addition to change in BMI (Moderate AS group [p=0.257] and Severe High-Gradient AS [p=0.083]), LVEF (Severe High-Gradient AS [p=1.00]), and E/e' ratio (Severe High-Gradient AS [p=0.133]).

Figure 1 Age and sex-specific incidence of all grades of AS

Legend: The horizontal bars show the sex-specific rate of de novo cases of AS detected on last Echo when adjusting for the time between first and last Echo (expressed as case per 1000 person-years follow-up) for each age group. The external figures show the actual number of de novo cases used to inform each rate calculation for men (blue) and women (purple) separately relative to the size of each age-group.

Figure 2 Proportional change in peak AV velocity from First to Last Echo

Legend: The two plots show the proportional change (expressed a ratio) in peak AV velocity according to the length of time between the First and Last Echo (in year) in which this difference was documented among 83,744 cases (blue/top graph) with no AS versus the 5,966 (red/bottom graph) cases who developed any grade of AS.

Figure 3 Adjusted risk of all-cause mortality

Legend: Risk estimates are derived from 72,703 adults with complete data in whom 18,631 (25.6%) all-cause deaths were observed – the adjusted HR (95% CI) for each AS group are shown in **black** for all-cause mortality and **red** for the equivalent HR (95% CI) for cardiovascular-related mortality. The insert box shows the HR (95% CI) for the other co-variates included in the Cox-Proportional Hazards Model.

Figure 4 Sex-specific rate and characteristics of incident AS linked to all-cause mortality

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