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Markers of Elevated Left Ventricular Filling Pressure are Associated with Increased Mortality in Non-Severe Aortic Stenosis

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Dr Strange has declares that he has received consulting fees from Edwards Life Sciences and has been invited speaker to international Medical Advisory Board for Edwards.

HIGHLIGHTS

1. Patients with non-severe aortic stenosis have elevated echocardiographic markers of left ventricular filling pressure.
2. Echocardiographic markers of increased left ventricular filling pressure are independently associated with increased mortality in patients with non-severe AS.
3. These markers may be useful to identify high-risk subgroups that may benefit from closer surveillance and potentially earlier intervention.

ABSTRACT

Background: Echocardiographic measures of elevated left ventricular filling pressures are associated with an adverse prognosis. The aim of this study was to determine the relationship between acute (ratio of early transmitral flow to mitral annular velocities; E/e') and chronic (indexed left atrial volume; LAVI) markers of left ventricular filling pressure (LVFP) and mortality in patients with non-severe aortic stenosis (AS), within the National Echo Database of Australia cohort. We hypothesised that they would reflect the early haemodynamic consequences of AS and be associated with increased mortality in this setting.

Methods: The first record for patients 18 years or over showing hemodynamically significant but non-severe (mild or moderate) AS (mean pressure gradient ≥ 10 to < 40 mmHg and $AVA > 1 \text{ cm}^2$) was analysed. Baseline demographics and echocardiographic variables were compared to patients without AS (mean pressure gradient < 10 mmHg). Mortality linkage data were available for all patients.

Results: Of 78,886 patients with aortic valve mean pressure gradient < 40 mmHg and $AVA > 1 \text{ cm}^2$, 13,768 (17%) were identified with non-severe AS (aortic valve mean pressure gradient 10-40 mmHg), of which 57% were male (mean age 73 ± 13.4 years) with a median follow-up of 3.4 years (interquartile range: 1.7-6.1 years). In unadjusted models, non-severe AS and a $LAVI > 34 \text{ ml/m}^2$ [Hazard Ratio (HR)=2.29 (95% CI 2.03-2.58)], an $E/e' > 14$ [HR=2.27 (95% CI 2.08-2.49)], a left ventricular ejection fraction (LVEF) $< 50\%$ [HR 2.82 (95% CI 2.50-3.19)], and a tricuspid regurgitation (TR) peak velocity $> 280 \text{ cm/s}$ [HR=2.54 (95% CI 2.30-2.80)] were associated with increased mortality hazard. The effect remained independent when combined in a multi-variable model.

Conclusions: Indices of elevated LVFP are independently associated with death in non-severe AS. Risk stratification models incorporating these variables may identify patients at risk of complications, warranting closer surveillance and possibly earlier intervention.

Keywords: Echocardiography, observational, aortic stenosis, left ventricular filling pressure, mortality.

ABBREVIATIONS

Aortic stenosis:	AS
National Echocardiography Database of Australia:	NEDA
Left ventricular filling pressure:	LVFP
Aortic valve replacement:	AVR
Ratio of early transmitral flow to mitral annular velocity:	E/e'
Indexed left atrial volume:	LAVI
Left atrial:	LA
National Death Index:	NDI
International Classification of Diseases:	ICD
Cardiovascular disease:	CVD
Aortic valve:	AV
Aortic valve area:	AVA
Tricuspid regurgitation:	TR
Left ventricular ejection fraction:	LVEF
Interquartile range:	IQR
Standard deviation:	SD
Confidence interval:	CI
Left ventricular:	LV
Hazard ratio:	HR

INTRODUCTION

Aortic stenosis (AS) is an increasingly prevalent condition, affecting 4-5% of those aged over sixty-five years, and associated with a high mortality.(1) Recent data from the National Echocardiography Database of Australia (NEDA) demonstrated poor long-term survival in patients with moderate AS, challenging traditional definitions of severity and timing of invasive intervention in this population.(2) While patients with moderate AS do not currently meet criteria for valve intervention, some studies suggest that a significant proportion will progress to severe stenosis within the current recommended window for echocardiographic follow-up.(3-4) Furthermore, there is mounting evidence that patients with chronically elevated left ventricular filling pressures (LVFP) may not re-model following aortic valve replacement (AVR).(5) Identifying patients in the pre-severe range at higher mortality risk, who may benefit from closer surveillance and potentially from earlier intervention, may therefore be important.

Data for echocardiographic predictors of survival in AS are currently predominately limited to indices reflecting systolic function and stenosis severity.(6) However, diastolic parameters, reflecting acute and chronic elevation in LVFP, confer a worse prognosis in many conditions (7-12) and are frequently abnormal in patients with AS as a consequence of increased myocardial stiffness. An elevated ratio of early mitral inflow E-wave peak velocity to peak early relaxation mitral annular tissue Doppler velocity (E/e' ratio) remains the most robust echocardiographic surrogate of acutely elevated LVFP and is a reliable marker of LVFP in patients with AS.(13) Indexed left atrial volume (LAVI), which reflects medium to long-term LVFP, is also required to accurately diagnose and quantify diastolic dysfunction.(14-16) We anticipate that these parameters would reflect the haemodynamic consequences of AS and be useful predictors of outcome in this setting.

Our aim was to determine the relationship between markers of increased LVFP (measured primarily by LAVI and the mitral E/e' ratio) and mortality in non-severe (mild and moderate) AS using the extensive NEDA database. We hypothesised that these markers would be independently associated with mortality in this cohort.

METHODS

Study Setting and Design:

The NEDA dataset was first described in the original NEDA report (17) and more recently in an analysis of mortality in patients with moderate AS.(2) 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 centres throughout Australia. At the time of study census, a total of 12 centres had contributed >500,000 investigations (approximately 20 million measurements) from approximately 350,000 individuals undergoing echocardiography. 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 centre is collected (study period April 11, 2000 to June 13, 2017). Each database is remotely transferred into a central database using a “vendor-agnostic”, automated data extraction process that transfers every measurement for each echocardiogram obtained in an entire echocardiography database 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 converted to a single variable according to the NEDA Study Protocol. Additional text recognition software captures free text, clinical comments, and conclusions. 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 (NDI).(18) 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) coding. Subsequently, consistent with previous reports of this type (19), all ICD-10 (Australian Modification) chapter codes in the range of 100 to 199 were considered a cardiovascular disease (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 one echocardiographic investigation. We included the first echocardiogram per patient showing hemodynamically significant but non-severe AS; defined by aortic valve (AV) mean pressure gradient greater than or equal to 10mmHg and less than 40mmHg and aortic valve area (AVA) greater than 1cm^2 , where present. Where patients had more than one echocardiogram and with none of these indicating AS, the first echo was included. Patients with aortic valve replacements were identified through text extraction and excluded from the analysis. We identified separately a group without hemodynamically significant AS (AV mean pressure gradient $<10\text{mmHg}$, also with $\text{AVA} > 1\text{cm}^2$) as a comparator for baseline echocardiographic characteristics only.

Study Measures:

Echocardiographic markers reflecting elevated LVFP included; 1) Left atrial (LA) volume indexed to body surface area (ml/m^2) and 2) E/e' ratio (unitless). Important prognostic indicators reflecting both pulmonary hypertension, represented by maximum tricuspid regurgitation (TR) velocity (cm/s), and left heart disease, represented by left ventricular ejection fraction (LVEF), were incorporated in the analysis.(17)

LAVI and E/e' ratio was recorded from raw data and, where absent, populated from text comment fields. LVEF was measured using primarily the percentage chosen by the reporting physician, followed by the Simpson's biplane, four and two chamber values respectively and followed lastly by Teichholz method if none of the aforementioned variables were populated.

Echocardiographic variables were represented as continuous variables and also dichotomised using cut-off ranges identified by the American Society of Echocardiography 2016 Recommendations for the Evaluation of Diastolic Function, i.e. $\text{LAVI} > 34\text{ml}/\text{m}^2$, average $\text{E}/\text{e}' > 14$ and $\text{TR velocity} > 280\text{cm}/\text{s}$.(16) The normal cut off for LVEF was defined as 50% or higher.

Statistical analysis:

No formal calculations of study power were performed given the large number of cases, fatal events, and patient-years of follow-up. Data were analysed using STATA version 15 (StataCorp, College Station, Texas, USA) and SPSS version 23.0 (SPSS Inc., Chicago, Illinois). Normally distributed continuous data are presented as means (standard deviation [SD]) and skewed data as median (IQR). Categorical data are expressed as frequencies and proportions (with 95% confidence intervals (CI) as appropriate). The “non-severe AS” and “no AS” groups were compared with respect to demographics and echocardiographic variables to establish baseline differences between the populations, particularly with respect to patterns of abnormal LVFP. Between-group comparisons were made using Student’s two sided t test or chi-square tests. The remainder of the analysis focussed on the non-severe AS cohort. The association between echocardiographic variables and all-cause mortality was initially investigated using Cox proportional hazard models. The proportional hazards assumption was assessed by visual examination of smoothed plots of Schoenfeld residuals versus time. Suspected violations were confirmed by testing interactions of all echocardiographic variables with time in a Cox regression model (time varying coefficient model). Univariate analysis was performed on dichotomised forms of the echocardiographic variables. All statistically significant variables were included in the multivariable time varying coefficient models, along with age and sex. Interactions between echocardiographic markers were tested. Only patients with all multivariate variables populated were included in the final multivariate analysis. Variations in the HRs over time were plotted for each variable, incorporating the effect of sex and age (fixed at the sample average) on the risk of death. A test of the Cox proportional hazards assumption for the included variables revealed non-proportionality for all variables except LAVI, indicating a time-varying effect. This was likely contributed to by the prolonged duration of follow-up. Kaplan Meier survival curves were used to demonstrate mortality differences between subgroups. Statistical significance was accepted as a two-sided p value of <0.05 .

RESULTS

There were 78,886 patients 18 years or older with aortic valve mean pressure gradient $<40\text{mmHg}$, $\text{AVA}>1\text{cm}^2$ and no history of AVR. Of these, there were 13,768 patients (17%) identified with AV mean gradient $\geq 10\text{--}40\text{mmHg}$; 57% were male with mean age 74 years and median follow up of 3.4 years [Q1-Q3 = 1.7-6.1, Interquartile range (IQR) = 4.4]. In total, 4,848 fatal events were recorded in the non-severe AS group (35% of the non-severe AS cohort). The final cohort included in the multivariate model comprised patients with populated data for all variables of interest and consisted of 3,777 patients.

Baseline demographic and echocardiographic characteristics of interest are summarized in Table 1. Patients in the non-severe AS cohort were older with a higher proportion of males, as compared to those without AS. Unadjusted baseline echocardiographic markers of LVFP were higher in the non-severe AS cohort, as compared to those with no AS; LAVI 38.4 ml/m^2 vs 32.4 ml/m^2 ($p<0.001$), $\text{E/e}'$ 13.2 vs 12.0 ($p<0.001$). There was a statistical but not clinically significant difference in LVEF between groups (62.5% in non-severe AS vs 60.0% in those with no AS, $p<0.001$). Furthermore, patients with non-severe AS demonstrated elevated pulmonary pressure, reflected by increased peak TR velocities (277cm/s vs 256 cm/s , $p<0.001$). Non-severe AS was associated with an unadjusted two-fold risk of death compared to no AS: median survival 8.7 years vs 14.8 years, respectively (HR 2.02, 95% CI 1.95–2.10, $p<0.001$). The excess mortality in the non-severe AS group largely reflected the older population. After adjusting for age and sex, the remaining risk of mortality in non-severe AS patients was 7% (HR 1.07, 95% CI 1.03–1.10, $p<0.001$). Adjusting for the absence of sinus rhythm had minimal effect on the observed hazard (HR = 1.06, 95% CI 1.02-1.10, $p = 0.002$).

Amongst patients with non-severe AS, all echocardiographic parameters were associated with increased mortality in a univariable model (Table 2). The proportional hazards assumption was violated in either univariate or multivariable analysis for all echocardiographic variables, indicating varying hazard over time. For some parameters, the violation was minor and likely detected due to the power of the sample. However, the effect in LVEF $<50\%$ was more substantial and over time. When incorporated in a time-varying coefficients multivariable model and adjusted for age and sex, all variables remained independently associated with death over time. No significant interactions between echocardiographic markers were detected. Table 2 displays the HRs for each variable in the multivariable analysis at baseline as well as the change over time per year where relevant. For patients with LVEF $<50\%$, the risk of death was esti-

mated to be more than double the risk of death in those with LVEF $\geq$ 50% at the time of echocardiography (HR=2.38, 95%CI: 1.79-3.17, $p<0.001$) but this risk decreases by 13% per year over the follow up period (HR=0.87, 95%CI: 0.81-0.94, $p<0.001$). The change in mortality risk over time from the baseline echocardiogram is displayed in Figure 1 and was generated using estimates from the time varying coefficients multivariable model, assuming the average age of the sample. The pattern over time in males appears slightly different to females but this is due to the increased risk of mortality associated with being male (HR=1.36, 95%CI:1.21-1.53, $p<0.001$), not a variation in the change over time in the echocardiographic parameters between genders. LAVI demonstrated a stable risk of death over the follow-up period whilst the risk associated with elevated E/e' increased over time (E/e' >14 became significant by one year follow-up and conferred 5% increased risk per year thereafter). Conversely, the prognostic impact of LVEF $<50\%$ and TR peak velocity $<280\text{cm/s}$ decreased with time. The risk associated with elevated E/e' surpassed that of having a reduced LVEF after approximately four years follow-up.

Table 3 demonstrates the incremental effect on mortality with one or more markers of elevated LVFP and/or reduced LVEF, adjusted for age and sex. Patients who exhibited LAVI $>34\text{ml/m}^2$, E/E' >14 , TR velocity $>280\text{ms}$ and LVEF $<50\%$ had almost three-fold risk of mortality (HR 2.88, 95% CI 2.10-3.96, $p<0.0001$) compared to those with values below each of these thresholds. The unadjusted prognostic impact of markers of elevated LVFP in the presence of both normal and low LVEF is demonstrated in Kaplan Meier curves in Figure 2 (LAVI >34) and Figure 3 (E/E' >14).

DISCUSSION

The results from analysis of this large multi-centre echocardiography database support the hypothesis that markers of acute and chronic elevated LVFP, namely LAVI and E/e', are associated with increased all-cause mortality in the non-severe AS population independent of age, sex, LVEF and pulmonary hypertension.

We observed the presence of higher LVFP in patients with non-severe AS (AV mean gradient ≥ 10 to $<40\text{mmHg}$) compared to those without hemodynamically significant AS (AV mean gradient $<10\text{mmHg}$). We postulate two mechanisms for this. Firstly, it seems likely that this

reflects, at least in part, the haemodynamic consequences of AS, which results in early left ventricular remodelling and diastolic dysfunction. Secondly, elevated LVFP likely represents the final common pathway of multiple factors which increase myocardial stiffness and determine outcome, including blood pressure, atrial fibrillation and age. While this relationship is not specific to AS, it is clinically useful to know that patients with elevated LVFP are at increased risk within this group; particularly as we know that even if this abnormality is not exclusively, or even primarily, related to the AS it would be expected that AS will exacerbate it over time.

While the haemodynamic sequelae of elevated LVFP in patients with severe AS are widely appreciated, the significance in patients with non-severe AS has been previously under-recognised. Our findings are consistent with former studies in other settings which demonstrate the prognostic importance of elevated LVFP and markers of diastolic dysfunction. (7-12) Recent data from the NEDA cohort demonstrated an association between markers of diastolic dysfunction (including LAVI and septal E/e') and death in patients with AS using an artificial intelligence model. (20) A second publication showed that impaired valvular haemodynamics in the setting of AVR was associated with the same trajectory as in native AS. (21) Within the non-severe AS cohort, other studies outside the NEDA population have shown markers of myocardial dysfunction to be associated with poor outcomes. Levy-Neuman and colleagues demonstrated the relationship between peak and post exercise basal longitudinal strain and increased rate of future cardiovascular events in asymptomatic patients with moderate AS. (22) Other parameters including pressure recovery-adjusted aortic valve area and the ratio of aortic valve acceleration to ejection time have also been found to be useful in risk-stratifying patients with moderate to severe aortic stenosis. (23-24) There are, however, few previous data addressing the prognostic value of E/e', LAVI and other echocardiographic indices of elevated LVFP in the non-severe AS cohort over time. Biner and colleagues described E/e' as the single most predictive clinical and echo Doppler marker of overall prognosis amongst a small cohort (n=125) of patients with un-operated severe AS. (25) Rusinaru demonstrated an association between increased LA volume and mortality in patients with at least mild severity AS, although again in a small population. (26)

Although LAVI and E/e' are routinely measured in echocardiographic assessment of diastolic dysfunction, they remain under-represented in guidelines for echocardiogram-based risk stratifications of AS, which focus on stenosis severity and LVEF in guiding intervention. (1) We

therefore propose that the incorporation of LAVI and particularly E/e' in risk stratification models for patients with non-severe AS, in addition to traditional markers of stenosis severity and left ventricular function, may be useful in guiding future clinical decision making; though currently there are no data supporting valve replacement in non-severe AS. This is, however, an issue that is currently being explored in the Transcatheter Aortic Valve Replacement to UNLOAD the left ventricle in patients with advanced heart failure (TAVR UNLOAD) trial (NCT02661451) which is testing the hypothesis that transcatheter aortic valve replacement plus optimal medical therapy improves the outcome of patients with moderate AS and heart failure with reduced LVEF when compared to optimal medical therapy alone.

LIMITATIONS

There are a few limitations to this study. NEDA cohort typically comprises individuals being investigated for possible or pre-existing cardiovascular disease. NEDA does not (yet) capture important clinical details pivotal to outcomes relevant to AS and conditions such as coronary artery disease, hypertension and diabetes. We did identify patients with “non-sinus” rhythm by the presence of a documented E wave without a documented A wave. However, on an adjusted basis, the absence of sinus rhythm did not significantly influence the threshold for increased mortality and had had little impact on the model overall (data not shown). Furthermore, the echocardiographic variables contained within the NEDA database rely on the reports of individual laboratories and hence contain a significant proportion of missing values which may have introduced bias. Finally, these data were largely derived from specialist centers or clinics in Australia and care should be exercised when extrapolating these results to the rest of the world. Since this study, NEDA has continued to extend the number of contributing centers to improve applicability of these data to the entire population.

CONCLUSION

These data describe the prognostic implications of markers of LVFP in a very large cohort of adults over a prolonged period. Markers of raised LVFP were shown to be independently associated with mortality in this population. These easily measured and routinely available echocardiographic parameters might therefore be useful to identify high-risk subgroups that may benefit from closer surveillance and potentially earlier intervention. This, however, is an area requiring further prospective evaluation.

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FIGURE TITLES AND LEGENDS

Figure 1. Hazard Ratios over time derived from a time varying coefficient Cox regression model in males and females with non-severe AS, stratified by LAVI cut-off of 34ml/m², E/e' cut-off of 14, LVEF cut-off of 50% and TR peak velocity cut-off of 280cm/s. LAVI demonstrates non-proportionality with fixed risk over time, whilst hazard associated with E/e' increases over the follow-up period. LAVI = Left atrial volume indexed, E/e' = Ratio of early mitral inflow E-wave peak velocity to peak early relaxation mitral annular tissue Doppler velocity, LVEF = Left ventricular ejection fraction, TR = tricuspid regurgitation.

Figure 2. Kaplan Meier 10-year survival in patients with non-severe AS with and without reduced LVEF, as stratified by LAVI cut-off of 34ml/m². This graph compares survival curves of patients with different categories of LAVI and LVEF. Values per line represent the number and percentage deceased at 10-years as a proportion of the initial number per category. Abbreviations as per Figure 1.

Figure 3. Kaplan Meier 10-year survival in patients with non-severe AS with and without reduced LVEF as stratified by E/e' cut-off of 14. This graph compares survival curves of patients with different categories of E/e' and LVEF. Values per line represent the number and percentage deceased at 10-years as a proportion of the initial number per category. Abbreviations as per Figure 1.

TABLE 1. Baseline characteristics of study cohort (n=78,886)

Characteristic	No AS (n=65,118)	Non-Severe AS (n=13,768)	P Value
Demographic Profile			
Male, %	50.8	57.2	<0.001
Age at echo, years (%)	60.8 (17.8)	73.7 (13.4)	<0.001
Anthropometrics			
Body Mass Index, kg/m ²	28.4 (6.8)	28.6 (6.5)	<0.001
Median time to death, years (CI)	14.8 (14.6-.)*	8.7 (8.5-8.9)	<0.001
Mean AV gradient, mmHg (SD)	4.4 (1.8)	16.0 (6.2)	<0.001
Echocardiographic characteristics			
LVEF (%)	60.0 ± 12.2 (n=41,542)	62.5 ± 11.4 (n=9,939)	<0.001
LAVI (ml/m²)	32.4 ± 15.3 (n=22,995)	38.4 ± 16.3 (n=7,968)	<0.001
E/e' (unitless)	12.0 ± 5.2 (n=22360)	13.2 ± 5.9 (n=6,560)	<0.001
TR peak velocity (cm/s)	255.9 ± 51.3 (n=33,266)	277.3 ± 49.2 (n=9,200)	<0.001

Values are mean ±SD, or median (interquartile range *upper bound of the CI does not drop below 0.5). Available data for echocardiographic characteristics are displayed in parentheses.

AS = aortic stenosis; CI = confidence interval, AV = aortic valve; LVEF = left ventricular

ejection fraction. LAVI = left atrial volume, indexed, E/e' = ratio of early transmitral flow (E) to mitral annular (e') velocity, HR = hazard ratio, TR = tricuspid regurgitation.

TABLE 2. Variables associated with increased all-cause mortality in non-severe AS (n = 13,768)						
Characteristic	Alive	Dead	Univariate (n as indicated)	P Value	Multivariate (n=3777)	P Value
Age at Echo			1.06 [#] (1.06-1.07)	<0.001	1.08 [#] (1.07-1.08)	<0.001
Male	4977/8920 (55.8%)	2903/4848 (59.9%)	1.11 [#] (1.05-1.18)	<0.001	1.36 [#] (1.21-1.53)	<0.001
LAVI >34ml/m ² (at baseline)	2265/5021 (45.1%)	1865/2947 (63.3%)	2.29 (2.03-2.58)	<0.001	1.18 [#] (1.05-1.34)	0.006
LAVI >34ml/m ² * time (variation per year)			0.96 (0.94-0.99)	0.002	N/A	
LVEF <50% (at baseline)	520/6361 (8.2%)	640/3578 (17.9%)	2.82 (2.50-3.19)	<0.001	2.38 (1.79-3.17)	<0.001
LVEF <50% * time (variation per year)			0.91 (0.88-0.94)	<0.001	0.87 (0.81-0.94)	<0.001
TR peak velocity >280cm/s (at baseline)	1796/5528 (32.5%)	1883/3672 (51.3%)	2.54 (2.31-2.80)	<0.001	1.65 (1.35-2.01)	<0.001
TR peak velocity >280cm/s * time (variation per year)			0.94 (0.92-0.96)	<0.001	0.96 (0.92-1.00)	0.042
E/e' >14 (at baseline)	1229/4597 (26.3%)	838/1963 (42.7%)	2.27 [#] (2.08-2.49)	<0.001	1.17 (0.96-1.43)	0.12
E/e' >14 * time (variation per year)			N/A		1.05 (1.01-1.09)	0.023

Values are expressed as a proportions and percentages of available records. Other abbreviations are as per Table 1. *multivariable HR is based on a final sample of 3777 patients in the proportional hazards model with time varying coefficients at baseline (time of echocardiogram),

adjusted for age, sex and all other echocardiographic variables tested. [#]Constant hazard across all follow-up years. Additional footnotes as per table 2.

TABLE 3. Mortality risk by cumulative echocardiographic markers of systolic and diastolic function in non-severe aortic stenosis

Number of Abnormal Echo Features*	Proportion, n (%)	Hazard Ratio (95% CI)	P Value
0	1270 (33.6)	Reference	
1	1264 (33.5)	1.29 (1.11-1.52)	<0.001
2	780 (20.7)	1.69 (1.43-2.00)	<0.001
3	396 (10.5)	2.67 (2.21-3.21)	<0.001
4	68 (1.8)	2.88 (2.10-3.96)	<0.001

Echo features* = LAVI>34ml/m², E/E>14, TR **peak velocity>280cm/s and LVEF<50%. Hazard ratio is age and sex-adjusted (95% CI) - abbreviations are as per Table 1.