

openheart Prognosis in asymptomatic patients with discordantly graded aortic valve stenosis based on pressure recovery adjusted valve area

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ABSTRACT

Objective We hypothesised that patients with asymptomatic aortic stenosis (AS) who remain with discordantly graded aortic valve stenosis (DGAS) after adjustment for pressure recovery in the aortic root represents a subgroup of patients with increased cardiovascular risk.

Methods Data from 1353 patients with asymptomatic mild–moderate AS and preserved left ventricular ejection fraction enrolled in the Simvastatin and Ezetimibe in AS study was used. DGAS was identified as combined pressure adjusted valve area (energy loss) <1.0 cm² and mean aortic gradient <40 mm Hg (DGAS_{EL}). Outcome was assessed in Cox regression analysis and reported as HR and 95% CI.

Results DGAS_{EL} was found in 196 (14.5%) patients at baseline, and was associated with older age, female sex, smaller aortic annulus diameter, lower heart rate, more extensive valve calcification and low flow (all p<0.05). In Cox regression analysis, DGAS_{EL} was associated with higher rate of heart failure (HF) hospitalisation (HR 3.31 (95% CI 1.54 to 7.09)), cardiovascular death (HR 2.63 (95% CI 1.34 to 5.17)) and all-cause mortality (HR 1.73 (95% CI 1.04 to 2.87)) independent of confounders including low flow and aortic valve calcification (all p<0.05).

Conclusions Patients with asymptomatic AS who remain with discordant grading after adjustment for pressure recovery have increased risk for HF and death.

Trial registration number NCT00092677.

INTRODUCTION

In asymptomatic patients with aortic valve stenosis (AS), discordantly graded aortic valve stenosis (DGAS) (ie, combined aortic valve area (AVA) <1.0 cm² and mean transvalvular gradient <40 mm Hg), is a heterogeneous and diagnostic challenging subgroup of AS.^{1–5} In clinical practice, DGAS is found in up to 30%–35% of patients with normal left ventricular (LV) ejection fraction.^{3 4 6} Both, current American College of Cardiology/American Heart Association (ACC/AHA)

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Aortic stenosis (AS) severity may be overestimated when pressure recovery in the aortic root is not taken into account, in particular in less severe AS. Adjusting for pressure recovery in the aortic root reduces the prevalence of discordantly graded AS (DGAS). This is performed by calculating energy loss rather than unadjusted aortic valve area.

WHAT THIS STUDY ADDS

⇒ The present study demonstrates that asymptomatic patients with normal left ventricular ejection fraction who remain with DGAS after adjustment for pressure recovery in the aortic root have increased risk for heart failure hospitalisation and death. Of note, this association was independent of well-known confounders of impaired prognosis, including hypertension, older age, sex, presence of low flow and more severe aortic valve calcification.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Identifying DGAS based on combined energy loss <1.0 cm² and mean aortic gradient <40 mm Hg may help identifying a high-risk subgroup within asymptomatic patients with DGAS and normal left ventricular ejection fraction. These patients have increased mortality and risk for heart failure hospitalisation and should be referred for further evaluation at a Heart Valve Center.

and European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS) guidelines on management of valvular heart disease emphasise the importance of multimodality imaging including the assessment of flow and aortic valve calcium score to distinguish between severe and moderate AS among patients that have DGAS.^{1 2}

The AS severity is often overestimated by Doppler echocardiography in patients with AS if pressure recovery in the aortic root is not taken into account, in particular in

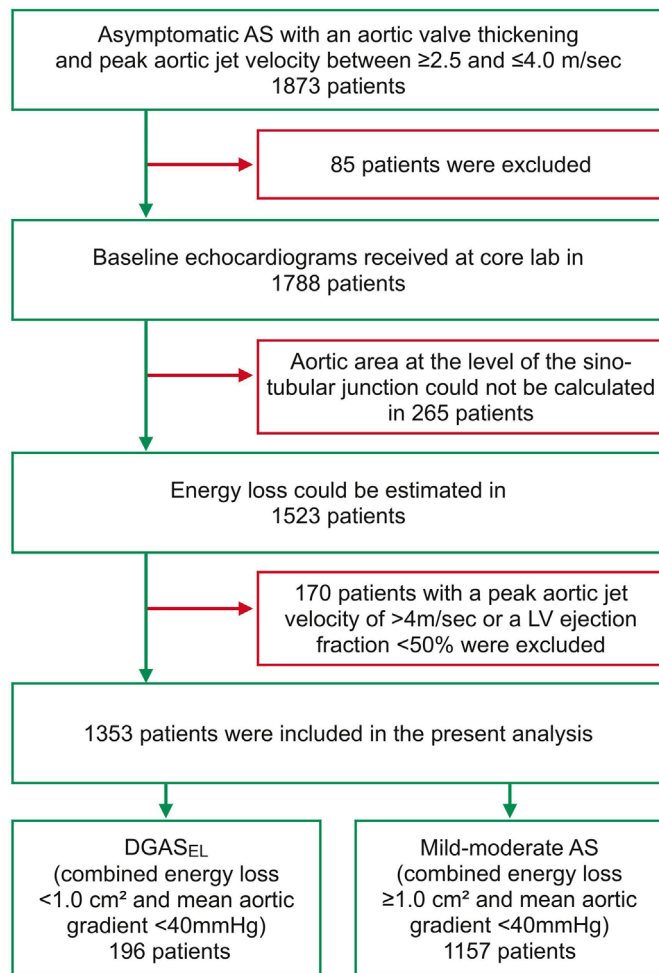


Figure 1 Study flow chart of the present study cohort. AS, aortic valve stenosis; LV, left ventricular; DGAS, discordantly graded aortic valve stenosis.

milder degree of AS and in patients with a small aortic root.^{7–9} The EACTS therefore recently recommended to take pressure recovery into account in the assessment of AS severity in these patients.¹⁰ Previous studies have demonstrated the prognostic value of pressure recovery adjusted valve area (energy loss (EL)) indexed for body surface area in AS.⁹ Use of EL index rather than AVA index reduced the prevalence of asymptomatic severe AS in the large Simvastatin Ezetimibe in Aortic Stenosis (SEAS) study⁸ as well as the phenomenon of DGAS in symptomatic patients, as recently demonstrated by Altes *et al.*¹¹

Recent publications have questioned the value of indexing AVA to body surface area.¹² It is also well demonstrated that both very small and very large body surface area in itself is associated with worse prognosis.^{13 14} Thus, current ACC/AHA and ESC/EACTS guidelines on management of valvular heart disease no longer recommend indexation of AVA by body surface area, mainly due to the increasing prevalence of obesity.^{1 2} The relevance for current clinical practice of previous studies on DGAS using indexed valve area may therefore be questioned. Among 790 patients with moderate AS, Pio *et al*

found higher mortality in DGAS based on unindexed AVA only in the group with reduced LV ejection fraction.¹⁵ However, pressure recovery adjustment was not included in their study. Thus, whether asymptomatic patients identified as having DGAS based on un-indexed $EL < 1.0 \text{ cm}^2$ and mean transvalvular gradient $< 40 \text{ mm Hg}$ ($DGAS_{EL}$) have increased risk for cardiovascular (CV) events and mortality is unknown. The present analysis aimed at documenting the prognosis of asymptomatic patients with normal LV ejection fraction who remain with DGAS after adjustment for pressure recovery in the aortic root ($DGAS_{EL}$) to those with concordantly graded non-severe AS.

METHODS

Patient population

The present work is a post-hoc analysis within the prospective SEAS study that enrolled 1873 patients with asymptomatic AS, defined as aortic valve thickening and peak aortic jet velocity between 2.5 and 4.0 m/s. The design and main outcome of the SEAS study have previously been published.¹⁶ In short, subjects were randomised to double-blinded, placebo-controlled treatment with combined simvastatin 40 mg and ezetimibe 10 mg daily for a median of 4.3 years.¹⁶ Patients with established coronary, cerebral or peripheral vascular disease, diabetes mellitus, other significant valvular heart disease, systolic heart failure (HF), renal insufficiency, or patients with any indication or contraindication to lipid-lowering therapy were excluded from participation in the SEAS study.¹⁶ For the present analysis, patients with SEAS with peak aortic jet velocity $< 4.0 \text{ m/s}$ and LV ejection fraction $\geq 50\%$ that had EL measured on the baseline echocardiogram were selected (figure 1).

Within the 1353 eligible patients, we identified 196 patients with $DGAS_{EL}$ (combined $EL < 1.0 \text{ cm}^2$ and mean aortic gradient $< 40 \text{ mm Hg}$) and 1157 patients with concordantly graded mild-moderate AS (combined $EL \geq 1.0 \text{ cm}^2$ and mean aortic gradient $< 40 \text{ mm Hg}$). Compared with the 265 patients without EL measurements, the present study population did not differ in age, sex distribution or body mass index (all $p > 0.3$). Obesity was defined as body mass index $\geq 30 \text{ kg/m}^2$.¹⁴ Hypertension was defined as history of hypertension or use of antihypertensive treatment or elevated blood pressure at the baseline clinical visit.¹⁶

Echocardiography

Baseline echocardiograms were obtained at 173 study centres in 7 European countries (Norway, Sweden, Finland, Denmark, United Kingdom, Ireland and Germany) following a standardised protocol.⁸ All echocardiograms were sent for expert interpretation at the SEAS echocardiography core laboratory in Bergen, Norway, and 94% of the echocardiograms were proof read by the same experienced reader (EG). Quantitative echocardiography and assessment

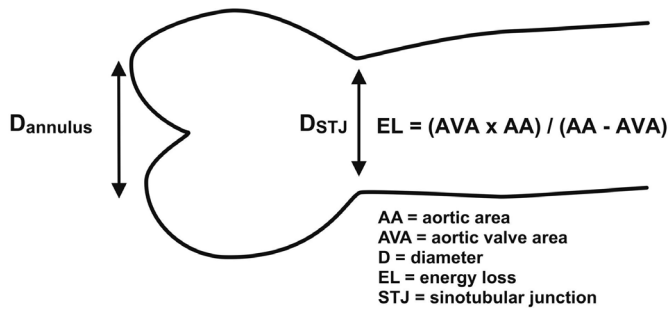


Figure 2 Schematic presentation of measurement of aortic diameter at the sinotubular junction and equation for calculation of pressure adjusted aortic valve area, the energy loss.

of AS was performed following the joint European Association of Cardiovascular Imaging and American Society of Echocardiography recommendations.^{10 17} Peak aortic jet velocity was measured from different windows by imaging and non-imaging transducers and the highest velocity was used for tracing of the time-velocity integral.¹⁰ The AVA was calculated by the continuity equation using velocity time integrals.¹⁰ Pressure recovery was estimated from inner aortic root diameter at the sinotubular junction level.⁹ EL was calculated by the validated equation as follows: $AVA \times Aa / (Aa - AVA)$, where Aa is the aortic area at the level of the sinotubular junction, that is, $Aa = \pi (\text{diameter at the sinotubular junction} / 2)^2$ (figure 2).⁹

LV hypertrophy was identified by the prognostically validated cut-off values in AS, LV mass/height^{2.7} $\geq 46.7 \text{ g/m}^{2.7}$ in women and $49.2 \text{ g/m}^{2.7}$ in men.¹⁸ Supine brachial systolic blood pressure measured at the end of the echocardiogram was used for calculation of haemodynamic variables. A small aortic root was considered present if inner aortic sinotubular

junction diameter indexed for body height $< 1.4 \text{ cm/m}$ in women and $< 1.5 \text{ cm/m}$ in men.¹⁹ Stroke volume (SV) was calculated by Doppler and indexed for body surface area (SVi). Low flow was identified as $SVi \leq 35 \text{ mL/m}^2$.^{1 2} Assessment of aortic valve calcification was performed by echocardiography following a validated score and grouped into none-mild and moderate-severe as previously described.²⁰

Study end-points

Pre-specified SEAS study end-points were adjudicated by an independent committee.¹⁶ The present analysis targeted HF hospitalisation, CV death and all-cause mortality.¹⁶

Statistical analysis

Data management and analysis was performed using IBM SPSS V.24.0 software and R studio V.1.4.1717. Patients were grouped into $DGAS_{EL}$ and concordantly graded mild-moderate AS. Continuous variables are presented as mean \pm SD and categorical variables as percentages. Groups were compared by Student's unpaired t-tests or analysis of variance with Scheffé's post-hoc test, as appropriate. Independent covariables of $DGAS_{EL}$ were identified in multivariable logistic regression analysis and are reported as OR and 95% CIs. Cumulative event rates calculated by Kaplan-Meier were compared between groups using log-rank test. The primary multivariable Cox model was adjusted for significant covariables from univariable analyses: hypertension, age, sex, heart rate, aortic valve replacement and for randomised study treatment, and reported as HR and 95% CI. In additional models, low SVi and aortic valve calcification score were added. Cumulative event rates calculated by Kaplan-Meier were compared between these groups

Table 1 Clinical characteristics of the groups of patients with $DGAS_{EL}$ and concordantly graded mild-moderate AS

Variables	$DGAS_{EL}$ (n=196)	Concordantly graded mild-moderate AS (n=1157)	P value
Age (years)	70 \pm 9	67 \pm 10	<0.001
Women (%)	58	35	<0.001
Systolic blood pressure (mm Hg)	147 \pm 21	148 \pm 20	0.540
Diastolic blood pressure (mm Hg)	83 \pm 10	83 \pm 10	0.899
Heart rate (beats/min)	66 \pm 10	66 \pm 12	0.606
Hypertension (%)	86	83	0.255
Antihypertensive treatment (%)	56	57	0.742
Height (m)	1.67 \pm 0.09	1.71 \pm 0.09	<0.001
Weight (kg)	74 \pm 15	79 \pm 14	<0.001
Body surface area (cm ²)	1.82 \pm 0.21	1.91 \pm 0.19	<0.001
Body mass index (kg/m ²)	26.4 \pm 4.3	26.9 \pm 4.1	0.122
Obesity (%)	21	19	0.611
Estimated GFR (mL/min)	87 \pm 17	85 \pm 17	0.190

AS, aortic valve stenosis; $DGAS_{EL}$, discordantly graded aortic stenosis based on EL and mean aortic gradient; EL, energy loss; GFR, glomerular filtration rate.

Table 2 Echocardiographic characteristics of the groups of patients with DGAS_{EL} and concordantly graded mild–moderate AS

Variables	DGAS _{EL} (n=196)	Concordantly graded mild-moderate AS (n=1157)	P value
Aortic root			
Annulus diameter (cm)	1.97±0.21	2.22±0.25	<0.001
Sinotubular junction diameter (cm)	2.70±0.43	2.83±0.44	<0.001
Area at sinotubular junction (cm ²)	5.87±1.85	6.41±1.99	<0.001
Small aortic root (%)	18	18	0.920
Left ventricle			
End-diastolic diameter (cm)	4.87±0.61	5.05±0.62	<0.001
End-systolic diameter (cm)	3.12±0.55	3.18±0.54	0.134
Septal wall thickness (cm)	1.14±0.28	1.16±0.27	0.361
Posterior wall thickness (cm)	0.87±0.18	0.89±0.18	0.133
Relative wall thickness	0.36±0.09	0.36±0.09	0.509
Mass index (g/m ^{2.7})	45±14	46±14	0.551
Hypertrophy (%)	35.3	35.3	0.986
Ejection fraction (%)	66±7	67±6	0.008
SVi (ml/m ²)	32±6	47±12	<0.001
Low SVi (≤35 mL/m ²) (%)	68.4	15.3	<0.001
Aortic valve stenosis			
Peak aortic jet velocity (m/s)	3.3±0.4	3.0±0.5	<0.001
Peak aortic gradient (mm Hg)	45±10	36±11	<0.001
Mean aortic gradient (mm Hg)	27±6	20±7	<0.001
AVA (cm ²)	0.73±0.11	1.39±0.43	<0.001
EL (cm ²)	0.84±0.13	1.90±0.88	<0.001
Moderate–severe aortic valve calcification (%)	87.4	60.6	<0.001

AS, aortic valve stenosis; AVA, aortic valve area; DGAS_{EL}, discordantly graded aortic stenosis based on EL and mean aortic gradient; EL, energy loss; LV, left ventricular; SVi, stroke vol index.

using log-rank test. The predictive performance of DGAS_{EL} for the outcome variable CV death was tested by the log likelihood ratio test comparing the multi-variable Cox model with and without DGAS_{EL} in the model. A p value<0.05 was regarded statistically significant in all analyses.

Patient and public involvement

Patients were not involved.

RESULTS

Prevalence and covariables of DGAS_{EL}

DGAS was found in 386 patients (28.5%) when diagnosed by AVA compared with in 196 patients (14.5%) at study baseline when identified by EL (DGAS_{EL}). The DGAS_{EL} group included more older women with smaller body size (table 1), lower LV ejection fraction and SVi, more extensive aortic valve calcification, and more severe AS by all

Table 3 Covariables of DGAS_{EL} in multivariable logistic regression analysis

Variables	OR	95% CI	P value
Patients age (years)	1.02	1.00 to 1.04	0.028
Female sex	2.56	1.65 to 3.97	<0.001
Aortic annulus diameter (cm)	0.05	0.02 to 0.15	<0.001
Low stroke volume index (≤35 mL/m ²)	11.35	7.28 to 17.69	<0.001
Moderate–severe aortic valve calcification	9.17	5.38 to 15.62	<0.001
Heart rate (beats/min)	0.98	0.96 to 1.00	0.018

DGAS_{EL}, discordantly graded aortic stenosis based on EL and mean aortic gradient; EL, energy loss.

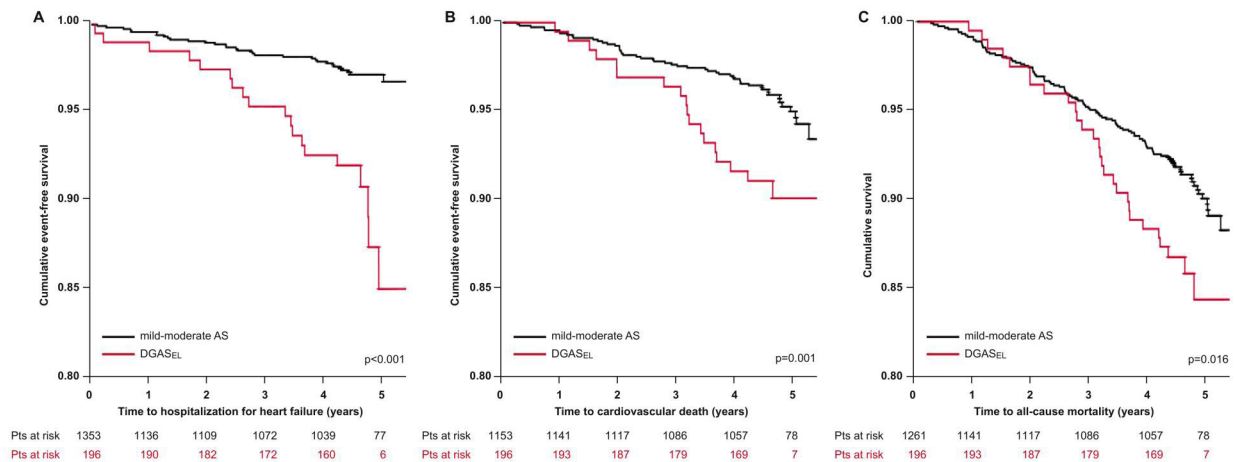


Figure 3 Kaplan-Meier plot of event-free survival from heart failure hospitalisation (A), cardiovascular death (B) and all-cause mortality (C) in groups of patients with DGAS_{EL} and concordantly graded mild–moderate aortic valve stenosis (AS). DGAS_{EL}, discordantly graded aortic valve stenosis.

conventional measures compared with the concordantly graded mild–moderate AS group (all $p < 0.05$), while the prevalence of small aortic root did not differ between groups (table 2).

Among patients with DGAS_{EL}, only 35 (18%) had a peak aortic jet velocity < 3.0 m/s, suggesting mild AS. In multivariable logistic regression analysis, the presence of DGAS_{EL} was associated with older age, female sex, smaller aortic annulus diameter, lower heart rate, more extensive valve calcification and presence of low flow (all $p < 0.05$, table 3).

Association of DGAS_{EL} with outcome

During a median of 4.3 years follow-up, event-free survival from HF hospitalisation, CV death and overall survival were all significantly lower in patients with DGAS_{EL} compared with those with concordantly graded mild–moderate AS (all $p < 0.01$, figure 3). Overall, patients with DGAS_{EL} compared with those with concordantly graded mild–moderate AS experienced HF hospitalisation in 9.8% versus 2.8%, CV death in 9.8% versus 4.4% and all-cause mortality in 14.9% versus 9.4%, respectively (all $p < 0.01$).

In Cox regression analyses, DGAS_{EL} was associated with higher HR for HF hospitalisation, CV death and all-cause mortality both in univariable analyses (table 4) and after adjusting for confounders including hypertension, age,

sex, heart rate, aortic valve replacement and randomised study treatment (table 4, model 1). In additional models, the associations of DGAS_{EL} with higher HR for HF hospitalisation, CV death and all-cause mortality remained significant after adjustment for the presence of low flow (table 4, model 2), and the severity of aortic valve calcification (all $p < 0.05$) (table 4, model 3).

In the log likelihood ratio test, comparing the Cox analysis model 3 with and without including DGAS_{EL} among the covariables, adding the variable DGAS_{EL} to the Cox analysis model 3 improved the prognostic yield of the model for all 3 endpoints (Akaike’s information criterion and log likelihood value) with a p value of 0.003 for the endpoint HF hospitalisation, a p value of 0.003 for the endpoint CV death and a p value of 0.037 for the endpoint all-cause mortality.

DISCUSSION

The present post-hoc analysis within the large prospective SEAS study documents that patients with asymptomatic AS who remain with DGAS despite adjustment for pressure recovery in the aortic root (DGAS_{EL}) represent a subgroup with a less favourable prognosis. In fact, patients with DGAS_{EL} had a 3.3-fold increased risk for HF hospitalisation, a 2.6-fold increased risk for CV death and a 1.7-fold increased risk for all-cause mortality over

Table 4 Association of DGAS_{EL} with outcome in univariable and multivariable Cox analyses

Event	Univariable analysis		Multivariable analysis Model 1		Multivariable analysis Model 2		Multivariable analysis Model 3	
	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value
Heart failure hospitalisation (n=51)	3.77 (2.13 to 6.65)	0.001	2.98 (1.62 to 5.47)	<0.001	3.84 (1.87 to 7.86)	<0.001	3.31 (1.54 to 7.09)	0.002
Cardiovascular death (n=70)	2.31 (1.36 to 3.91)	0.002	2.60 (1.49 to 4.56)	0.001	2.74 (1.44 to 5.21)	0.002	2.63 (1.34 to 5.17)	0.005
All-cause mortality (n=138)	1.65 (1.09 to 2.48)	0.017	2.00 (1.30 to 3.08)	0.022	1.92 (1.18 to 3.12)	0.009	1.73 (1.04 to 2.87)	0.035

Model 1 adjusted for: hypertension, age, sex, heart rate, randomised study treatment, aortic valve replacement

Model 2 adjusted for: hypertension, age, sex, heart rate, randomised study treatment, aortic valve replacement, low flow

Model 3 adjusted for: hypertension, age, sex, heart rate, randomised study treatment, aortic valve replacement, low flow, degree of aortic valve calcification
DGAS_{EL}, discordantly graded aortic stenosis based on EL and mean aortic gradient; EL, energy loss.

a median follow-up of 4.3 years. These associations were independent of clinical prognostic characteristics in asymptomatic AS, including age,²¹ sex,²² hypertension,²³ presence of low flow,^{24 25} and the severity of aortic valve calcification.^{20 26 27}

Few studies have focused on DGAS in asymptomatic patients. In contrast to the results in the SEAS study by Jander *et al* finding comparable prognosis in patients with DGAS_{AVA} and those with moderate AS,³ Pio *et al* demonstrated in a register study of 790 patients that DGAS_{AVA} in moderate AS was associated with higher all-cause mortality during a median of 4.9 years follow-up, in patients with LV ejection fraction <50%.¹⁵ However, in the study by Pio *et al* a higher prevalence of comorbidities was found in patients with DGAS_{AVA}, and the majority had coronary artery disease.

In a series of 379 patients with DGAS, Altes *et al* reported that using EL index instead of AVA index for diagnosis of DGAS reclassified 39% of patients from inconsistently graded severe AS to consistently graded moderate AS.¹¹ Patients reclassified to moderate AS by EL index had a 50% lower risk of combined cardiac death or aortic valve replacement over 34 months follow-up.¹¹ Compared with the present study, Altes *et al* included symptomatic patients, and patients with a number of comorbidities, including history of atrial fibrillation in 40%, chronic renal failure in 32%, and diabetes mellitus in 36% of patients.¹¹

Of note, the association of DGAS_{EL} with higher CV morbidity and mortality in our study was independent of presence of low flow.²¹ Previous studies have particularly identified low flow as a predictor of poor prognosis irrespective of clinical management in patients with symptomatic AS.^{4 28 29} However, in asymptomatic patients with DGAS_{AVA}, the prognostic importance of low flow has varied in previous studies.^{3 24} In a small study by Lancellotti *et al* of 150 patients with asymptomatic severe AS defined by AVA <1 cm², DGAS_{AVA} with low flow was present in 7% and associated with a 5-fold reduced cardiac event-free survival as compared with those with normal flow.²⁴ In contrast, in moderate AS, Pio *et al* found that reduced LV ejection fraction rather than low flow was a prognostic marker in patients with DGAS_{AVA}.³

The present study adds to these previous reports by demonstrating that patients with DGAS_{EL} free from known diabetes and CV disease have impaired prognosis independent of presence of low flow. Of note, 31.6% of patients with DGAS_{EL} in our study, had normal flow, which by current ACC/AHA and ESC/EACTS guidelines on management of AS would be considered as non-severe AS.^{1 2}

The assessment of valve calcification has gained increasing importance in the setting of DGAS in symptomatic patients.^{1 2} The present findings demonstrate that DGAS_{EL} in asymptomatic patients predicted worse outcome also independent of the degree of aortic valve calcification assessed by echocardiography. Although current guidelines recommend cardiac CT for the

assessment of aortic valve calcium score in DGAS patients with low flow to resolve the degree of severity,^{1 2} several studies have validated the simpler aortic valve calcification score by echocardiography used in the present study.^{20 26 27} In 176 asymptomatic patients with mild to moderate AS, Rosenhek *et al* identified moderate-severe valve calcification as a strong predictor of combined death and aortic valve replacement.²⁰ Thomassen *et al* confirmed these findings in the large SEAS study.²⁷ Furthermore, moderate-severe aortic valve calcification was associated with lower aortic compliance and more severe AS in both sexes.²⁷ The present study adds to these studies by demonstrating that asymptomatic patients who remain with DGAS after adjustment for pressure recovery in the aortic root have an increased risk for hospitalisation for HF, CV death and all-cause mortality independent of the severity of aortic valve calcification. Taken together, our findings suggest that asymptomatic patients with DGAS_{EL} should be referred to a Heart Valve Center for further evaluation to establish the true AS severity and individualised treatment strategy.⁵

Study limitations

The present results are based on a post-hoc analysis within the SEAS study. This study excluded patients with symptoms, atherosclerotic CV disease or diabetes by design. The implementation of our results in less selective groups of patients with AS should therefore be done with caution. The severity of aortic valve calcification was not confirmed by cardiac CT. However, the echocardiographic aortic valve calcification score used in the SEAS study has been prognostically validated also in other AS populations.^{20 26}

CONCLUSION

In asymptomatic patients free from diabetes and known CV disease participating in the SEAS study, patients who remained with DGAS after adjustment for pressure recovery had increased risk for HF hospitalisation and mortality independent of known prognosticators including presence of low flow and degree of aortic valve calcification. These patients represent a high-risk subgroup within the challenging group of asymptomatic DGAS. The optimal management of patients with DGAS_{EL} should be tested in further prospective studies.

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Patient consent for publication Not applicable.

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Data availability statement All data relevant to the study are included in the article or uploaded as supplementary information. Data are available on reasonable request. All data relevant to the study are included in the article.

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