Low systemic arterial compliance is associated with increased cardiovascular morbidity and mortality in aortic valve stenosis

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ABSTRACT
Objective Lower systemic arterial compliance (SAC) is associated with increased cardiovascular morbidity and mortality in hypertension, but this has not been assessed in a prospective study in aortic valve stenosis (AS).

Methods Data from 1641 patients (38% women) with initially asymptomatic mild-moderate AS enrolled in the Simvastatin and Ezetimibe in Aortic Stenosis study was used. Median follow-up was 4.3 years. SAC was assessed from Doppler stroke volume index to central pulse pressure ratio and considered low if ≤0.64 mL/m², corresponding to the lower tertile in the population. The association of SAC with outcome was assessed in Cox regression analysis and reported as HR and 95% CI.

Results Low SAC at baseline was characterised by older age, female sex, hypertension, obesity, presence of a small aortic root, lower mean aortic gradient and more severe AS by effective aortic valve area (all p<0.01). In Cox regression analysis adjusting for factors, low SAC was associated with higher HRs for cardiovascular death (HR 2.13 (95% CI 1.34 to 3.40) and all-cause mortality (HR 1.71 (95% CI 1.23 to 2.38)), both p=0.001. The results did not change when systolic or diastolic blood pressure, other measures of AS severity or presence of discordantly graded AS were included in subsequent models. Presence of low SAC did not improve mortality prediction in reclassification analysis.

Conclusions In patients with AS without diabetes and known cardiovascular disease, but a high prevalence of hypertension, low SAC was associated with higher cardiovascular and all-cause mortality independent of well-known prognosticators.

Trial registration number NCT00092677; Post-results.

INTRODUCTION
In asymptomatic aortic valve stenosis (AS) management is based on the assessment of prognostic risk markers.1 2 A number of clinical and echocardiographic factors have been demonstrated to influence prognosis in AS, including older age,3 the degree of aortic valve calcification,4 the AS severity,5 6 left ventricular (LV) ejection fraction7 and plasma levels of natriuretic peptides.7 8 Furthermore, in recent publications also concomitant hypertension,9 obesity,10 male sex,10 LV hypertrophy,11 presence of low flow12 or a small aortic root13 have been associated with higher cardiovascular morbidity and mortality in AS, independent of the AS severity.

Ageing and hypertension both lead to reduced systemic arterial compliance (SAC).14 Lower SAC has previously been associated with increased cardiovascular morbidity and mortality in patients with hypertension15 or diabetes16 as well as in general population.17 In AS, lower SAC has been associated with the presence of reduced LV systolic function,18 but the prognostic impact of reduced SAC has not been tested in a large, prospective study in AS. The present study tested the hypothesis that low SAC is associated with impaired outcome in asymptomatic patients with AS independently of stenosis severity, concomitant hypertension and older age.

METHODS
Patient population
The present analysis was prospectively planned within the Simvastatin and Ezetimibe in Aortic Stenosis study that enrolled 1873 patients with asymptomatic AS, defined as aortic valve thickening and peak aortic jet velocity ≥2.5 and ≤4.0 m/s. The design and main outcome of the SEAS study have previously been published.18 In short, subjects were randomised to double-blinded, placebo-controlled combined treatment with simvastatin 40 mg and ezetimibe 10 mg daily for a median of 4.3 years.18 Patients with established coronary, cerebral or peripheral vascular disease, diabetes mellitus, other significant valvular heart diseases, systolic heart failure, renal insufficiency, or patients with other indications or contraindications to lipid-lowering therapy were excluded from participation in the Simvastatin and Ezetimibe in Aortic Stenosis study.18 Informed consent was obtained from each patient and the study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in a priori approval by regional ethics committees in all participating countries.

Of the 1788 patients with baseline echocardiograms received at the core laboratory, SAC could be estimated from the provided images in 1641 patients (87.6%). Compared with the 232 excluded patients, 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 ≥30 kg/m².9 Hypertension was defined as treated hypertension or elevated clinic blood pressure at the baseline visit.9 Lower blood pressure
was defined as systolic blood pressure <130 mm Hg and higher blood pressure as systolic blood pressure ≥130 mm Hg.19

### Echocardiography

Baseline echocardiograms were obtained at 173 study centres in seven European countries (Norway, Sweden, Finland, Denmark, UK, Ireland and Germany) following a standardised protocol.8 All echocardiograms were sent for expert interpretation at the SEAS echocardiography core laboratory, and 94% of the echocardiograms were proofread by the same experienced reader (EG). The echocardiography protocol and methods have previously been published.8 Quantitative echocardiography and assessment of AS were performed following the joint European Association of Echocardiography and American Society of Echocardiography guidelines.20 21 The presence of a small aortic root was identified based on prognostically validated cut-off values LV mass/body surface area and low flow was identified as a stroke volume index ≤35 mL/m², as suggested by current guidelines.1 2 SAC was calculated as stroke volume index/central pulse pressure ratio.15 Low SAC was defined as the lowest tertile (≥0.64 mL/m²/mm Hg). Global LV load was assessed from valvuloarterial impedance as systolic arterial pressure + net mean aortic gradient/stroke volume index.24 A small aortic root was defined as inner aortic sinotubular junction diameter indexed for body height <1.4 cm/m in women and <1.5 cm/m in men.13 Inconsistently graded AS was defined as the presence of combined aortic valve area <1.0 cm² and mean aortic gradient <40 mm Hg.12 Four categories of severe AS (aortic valve area <1.0 cm²) were defined in the 450 patients referred for aortic valve replacement due to severe AS during the SEAS study conduct that had readable preoperative echocardiograms: low-flow, low-gradient AS (mean aortic gradient <40 mm Hg, stroke volume index ≤35 mL/m²), normal-flow, low-gradient AS (mean aortic gradient <40 mm Hg, stroke volume index ≤35 mL/m²), low-flow high gradient (mean aortic gradient ≥40 mm Hg, stroke volume index >35 mL/m²) and normal flow high gradient AS (mean aortic gradient ≥40 mm Hg, stroke volume index ≥35 mL/m²).12 The dimensionless index was calculated as velocity time integral LV outflow tract/velocity time integral aortic valve.25

### Study end-points

All study end-points were adjudicated by an independent committee.18 The present analysis targeted the end-points of cardiovascular death and all-cause mortality.

### Statistical analysis

Data management and analysis were performed using IBM SPSS V24.0 software. Data exploration found that all-cause mortality was significantly higher in the lower tertile of SAC (p<0.001 vs other groups), but comparable in the middle and upper tertiles (p=0.388). The study population was therefore grouped according to the presence of low SAC (lower tertile, SAC <0.64 mL/m²/mm Hg) versus normal SAC, the rest of the population. Continuous variables are presented as

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### Table 1  Clinical characteristics of the total study population and groups of patients with low and normal SAC

| Variables                          | Total study population (n=1641) | Low SAC (n=545) | Normal SAC (n=1096) | P value |
|------------------------------------|---------------------------------|-----------------|---------------------|---------|
| Age (years)                        | 67±10                           | 72±8            | 65±10               | <0.001  |
| Women (%)                          | 38                              | 48              | 33                  | <0.001  |
| Systolic blood pressure (mm Hg)    | 145±20                          | 152±21          | 142±19              | <0.001  |
| Diastolic blood pressure (mm Hg)   | 82±10                           | 83±11           | 82±10               | 0.003   |
| Central pulse pressure (mm Hg)     | 59±10                           | 65±10           | 56±9                | <0.001  |
| Heart rate (beats/min)             | 66±12                           | 68±11           | 65±12               | <0.001  |
| Hypertension (%)                   | 83.8                            | 92.7            | 79.4                | <0.001  |
| Antihypertensive treatment (%)     | 56.7                            | 62.9            | 53.6                | <0.001  |
| ACE inhibitor (%)                  | 15.2                            | 16.0            | 14.9                | 0.562   |
| ARB (%)                            | 10.2                            | 13.0            | 8.8                 | 0.007   |
| Calcium antagonist (%)             | 17.0                            | 18.2            | 16.4                | 0.376   |
| Beta-blocker (%)                   | 27.6                            | 31.9            | 25.5                | 0.006   |
| Diuretics (%)                      | 23.5                            | 30.6            | 20.0                | <0.001  |
| Alpha-blocker (%)                  | 2.0                             | 2.9             | 1.5                 | 0.042   |
| Height (m)                         | 1.71±0.09                       | 1.69±0.09       | 1.71±0.09           | <0.001  |
| Weight (kg)                        | 78±15                           | 78±15           | 78±14               | 0.625   |
| Body surface area (cm²)            | 1.90±0.20                       | 1.88±0.20       | 1.90±0.20           | 0.025   |
| Obesity (%)                        | 20.5                            | 25.3            | 18.2                | <0.001  |

ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; SAC, systemic arterial compliance.
Table 2  Echocardiographic characteristics of the total study population and groups of patients with low and normal SAC

| Variables                    | Total study population (n=1641) | Low SAC (n=545) | Normal SAC (n=1096) | P value |
|------------------------------|---------------------------------|-----------------|---------------------|---------|
| Aortic root                  |                                 |                 |                     |         |
| Aortic annulus diameter (cm) | 2.19±0.27                       | 2.02±0.21       | 2.28±0.25           | <0.001  |
| Small aortic root (%)        | 17                              | 21              | 15                  | 0.010   |
| LV end-diastolic diameter (cm) | 5.04±0.63                       | 4.96±0.62       | 5.08±0.64           | <0.001  |
| LV end-systolic diameter (cm) | 3.19±0.56                       | 3.17±0.55       | 3.21±0.57           | 0.168   |
| Septal wall thickness (cm)   | 1.16±0.28                       | 1.15±0.28       | 1.16±0.28           | 0.497   |
| Posterior wall thickness (cm)| 0.89±0.19                       | 0.88±0.19       | 0.89±0.19           | 0.048   |
| LV mass index (g/m²)         | 45.8±14.7                       | 45.3±14.7       | 46.1±14.8           | 0.315   |
| LV hypertrophy (%)           | 33                              | 33              | 33                  | 0.915   |
| Ejection fraction (%)        | 66±7                            | 66±7            | 67±6                | 0.012   |
| Circumferential end-systolic stress (dyne/cm²) | 129±35                   | 138±37          | 125±34              | <0.001  |
| Stress corrected midwall shortening (%) | 97±20                        | 97±20           | 97±20               | 0.957   |
| Stroke volume index (mL/m²)  | 45±13                           | 34±6            | 50±12               | <0.001  |
| Low stroke volume index (<35mL/m²) (%) | 33                          | 87              | 17                  | <0.001  |
| SAC (mL/m²/mm Hg)            | 0.79±0.27                       | 0.53±0.08       | 0.93±0.24           | <0.001  |
| Valvuloarterial impedance (mm Hg/mL/m²) | 3.9±1.2                        | 5.2±1.0         | 3.3±0.7             | <0.001  |

AS, aortic valve stenosis; LV, left ventricular; SAC, systemic arterial compliance.

Table 3  Prevalences of different subtypes of severe AS in patients with low and normal SAC at the preoperative echocardiogram

| Pre-operative flow category at rest | Low SAC (n=153) | Normal SAC (n=297) |
|------------------------------------|-----------------|--------------------|
| Normal flow low gradient (%)       | 15.7            | 36.7               |
| Normal flow high gradient (%)      | 17.6            | 57.6               |
| Low flow low gradient (%)          | 31.4            | 2.0                |
| Low flow high gradient (%)         | 35.3            | 3.7                |

P<0.001 between low and normal SAC groups.
Valvular heart disease

RESULTS

Prevalence and covariables of low SAC

Patients with low SAC were older, shorter, included more women and subjects with hypertension and obesity (all p<0.05) (table 1).

The group with low SAC also had higher heart rate, blood pressure and global LV load, smaller aortic root dimension, lower stroke volume index and less use of antihypertensive treatment compared with those with normal SAC (all p<0.05) (table 2).

In multivariable linear regression analysis, lower SAC at baseline was independently associated with older age (ß=0.25), female sex (ß=0.08), hypertension (ß=0.15), obesity (ß=0.05), presence of a small aortic root (ß=0.16), lower mean aortic gradient (ß=0.37) and energy loss index (ß=0.65, all p<0.01) (multiple R²=0.53, p<0.001). Low SAC was not associated with a faster rate of progression of AS compared with normal SAC (0.15 m/s/year vs 0.14 m/s/year, p=0.419). The majority of patients presenting with low flow, low gradient or low flow, high gradient AS on the preoperative echocardiogram had low SAC at the baseline echocardiogram (table 3). In contrast, the majority of patients with normal SAC at baseline developed normal flow severe AS (table 3).

Association of low SAC with outcome

Survival was significantly lower in patients with low compared with normal SAC (p<0.001, figure 1, part A and B). In adjusted Cox regression analysis run with aortic valve replacement as a competing event, low SAC predicted a 2.1-fold increase in HR for cardiovascular death, and a 1.7-fold increase in HR for all-cause mortality after adjusting for confounders including mean aortic gradient, obesity, age, sex and presence of a small aortic root, antihypertensive treatment and randomised lipid-lowering study treatment (all p<0.05, model 1, table 4). Adding aortic valve area (model 2, table 4), dimensionless index (model 3, table 4) or inconsistently graded AS (model 4, table 4) in additional models did not change the results. In univariable Cox analyses, low SAC was associated with higher HRs for both cardiovascular and all-cause mortality in patients with systolic blood pressure ≥130 mm Hg (HR 2.22 (95% CI 1.42 to 3.48), p=0.001 and HR 1.71 (95% CI 1.38 to 2.64), p<0.001, respectively). As only 22 deaths in total, of these 9 cardiovascular deaths, occurred in patients with systolic blood pressure <130 mm Hg, multivariable analyses could not be performed in this subgroup. In a separate set of Cox models, estimated central pulse pressure was substituted by brachial pulse pressure in the calculation of SAC. Although low SAC estimated from brachial pulse pressure was associated with higher cardiovascular and all-cause mortality in univariable analyses (HR 1.54 (95% CI 1.01 to 2.33) and HR 1.59 (95% CI 1.17 to 2.14), respectively, both p<0.05), these associations became non-significant when adjusted for the same covariables as in the primary Cox model (HR 1.15 (95% CI 0.72 to 1.83), p=0.567 and HR 1.26 (95% CI 0.89 to 1.74), p=0.196, respectively).

In univariable receiver-operating characteristic analysis, baseline SAC, stroke volume index, central pulse pressure and valvuloarterial impedance, all predicted higher all-cause mortality during follow-up (all p<0.05, figure 2). In this analysis baseline SAC was a superior predictor of all-cause mortality compared with stroke volume index, and comparable to central pulse pressure and valvuloarterial impedence (figure 2). In reclassification analysis including low SAC in the Cox model one in table 4 did not consistently improve the predictive performance of the model. The net reclassification of all-cause mortality during a median event time of 1047 days improved by 13% (95% CI 4 to 24, p=0.040), while an integrated discrimination improvement did not change (estimate 0.4% (95% CI −0.1 to −1.6, p=0.136). In ROC curve analysis, the AUC for prediction of all-cause mortality was higher without than with low SAC included in the model (data not shown).

DISCUSSION

Low SAC and outcome

This study is the first large, prospective study to demonstrate that the presence of low SAC is associated with increased cardiovascular and all-cause mortality in asymptomatic patients with AS free from diabetes and known cardiovascular and renal disease.

Figure 1  Kaplan-Meier plot of event-free survival from cardiovascular death (A) and all-cause mortality; (B) in groups of patients with low and normal SAC at baseline. SAC, systemic arterial compliance.
Table 4 Association of low SAC with outcomes in asymptomatic aortic stenosis in univariable and multivariable Cox analyses

| Event                        | Univariable analysis | Multivariable model 1 | Multivariable model 2 | Multivariable model 3 | Multivariable model 4 |
|------------------------------|----------------------|-----------------------|-----------------------|-----------------------|-----------------------|
|                              | HR (95% CI)          | P value               | HR (95% CI)          | P value               | HR (95% CI)          | P value               |
| Cardiovascular death (n=78)  | 2.49 (1.64 to 3.79)  | <0.001                | 2.13 (1.34 to 3.40)  | 0.001                 | 2.28 (1.28 to 4.06)  | 0.005                 |
| All-cause mortality (n=153)  | 2.00 (1.48 to 2.77)  | <0.001                | 1.71 (1.15 to 2.58)  | 0.001                 | 1.72 (1.14 to 2.58)  | 0.009                 |

All models were run with aortic valve replacement as a competing event and adjusted for randomised lipid-lowering study treatment, AS severity by mean aortic gradient, obesity, age, sex, presence of a small aortic root and antihypertensive treatment. Model 2 also adjusted for aortic valve area, model 3 also for dimensionless index and model 4 also for the presence of inconsistently graded AS.

SAC, systemic arterial compliance.

As demonstrated in the Cox models, low SAC at study baseline predicted higher HR of cardiovascular death and all-cause mortality independent of major prognosticators in asymptomatic AS including AS severity,1–3 age,3 sex,10 and presence of a small aortic root,13 and independent of aortic valve replacement and antihypertensive treatment. The associations of low SAC at study baseline with higher HR of cardiovascular death and all-cause mortality were also independent of dimensionless index and presence of inconsistently graded AS, adding to previous publications.1,2,6–7 The association of dimensionless index with outcome in the SEAS study has been previously published by Jander et al.25 The finding that the HRs associated with low SAC in the present population are much higher than those reported in a general population11 or even a hypertensive population15 underscores the importance of SAC for prognosis in AS. The prognostic value of SAC was also clearly demonstrated in the receiver-operating characteristic analysis where SAC was a better predictor of all-cause mortality than the stroke volume index, a parameter included in guideline recommendations for risk assessment in AS.1,2 The presence of low SAC did not improve mortality prediction beyond that provided by AS severity, sex, age, obesity, treated hypertension and presence of a small aortic root and antihypertensive treatment in combination. However, the independent association of low SAC with objective end-points like cardiovascular and all-cause mortality emphasises the importance of assessing both systemic arterial and valvular function in the evaluation of patients with AS.24 The finding that SAC was a better prognosticator when calculated from estimated central pulse pressure than from brachial pulse pressure is in line with several previous studies in different populations demonstrating that central aortic pulse pressure is a better predictor of target organ damage and future cardiovascular events compared with brachial peripheral pulse pressure.26–27

The results in the present study expand recent observations made in a post hoc analysis among patients with severe, symptomatic AS treated with transcatheter aortic valve replacement (TAVR) in the Placement of Aortic Transcatheter Valves I trial.19 In their study, low SAC was associated with higher cardiovascular and all-cause mortality. In particular, all-cause mortality was higher in patients with persistently combined low systolic blood pressure and high pulsatile load (low SAC or high pulse pressure) 30 days post-TAVR. These findings were explained by the known adverse effect of lower SAC on LV remodelling leading to output failure.15 It is well demonstrated that hypertension in patients with AS is associated with worse prognosis both preoperatively8 and postoperatively.28 Taken together, current knowledge on hypertension in AS suggests that treating hypertension in patients with AS should be recommended to prevent hypertension-associated cardiovascular events. However, there is a lack of data from prospective clinical trials to guide the choice of antihypertensive drugs and target blood pressure in patients with AS.

Low SAC and covariables

The phenotype associated with the presence of low SAC included older age, female sex, hypertension, obesity, and all known predictors of impaired outcome in AS.1,4–9,12–13 The presence of a small aortic root was another characteristic of low SAC. We recently demonstrated the presence of a smaller aortic root dimensions as a high-risk feature in AS.13 In the Campania Salute Network including 12,392 patients treated for hypertension without known cardiovascular disease and with normal LV ejection fraction, an association of reduced SAC with smaller aortic root dimension and higher carotid intima-media thickness was recently reported.29 Furthermore,
in the Multiethnic Study of Atherosclerosis including 4806 adults free of clinical cardiovascular disease, lower SAC was associated with a high-risk phenotype including advanced age, female sex and a presence of hypertension, similar to that identified in the present population. In a retrospective study by Briand et al, reduced SAC was associated with a higher prevalence of reduced LV ejection fraction and impaired diastolic relaxation in 208 patients with AS with at least moderate AS. However, 59% of patients in their study had coronary artery disease, including 28% with previous myocardial infarction. In contrast, known coronary artery disease was excluded per design in the present study, and LV systolic function measured by ejection fraction and stress-corrected midwall shortening did not differ according to the presence or absence of low SAC.

LIMITATIONS
The large, prospective SEAS study excluded patients with atherosclerotic disease or diabetes by design. Implementation of results in less selective groups of patients with AS should, therefore, be done with caution, and further studies of SAC and outcome in less selected patients with AS are needed. Furthermore, a more detailed assessment of myocardial function by global longitudinal strain was not performed in the large Simvastatin and Ezetimibe in Aortic Stenosis study that...
was conducted during the years 2002–2008, as a majority of the echocardiograms were stored on videotapes and therefore unsuitable for strain analysis. Due to the design of our study, particular advice on the management of low SAC cannot be provided. As demonstrated, the association of low SAC with increased mortality was independent of hypertension, blood pressure and antihypertensive or lipid-lowering treatment. However, the low SAC group were on average 72 years old at study baseline, many probably with longstanding, uncontrolled hypertension. Whether regular exercise or modern, targeted antihypertensive therapy may preserve normal SAC should be assessed in epidemiological studies of AS.

CONCLUSIONS
In patients with AS without diabetes and known cardiovascular disease, but a high prevalence of hypertension, low SAC was associated with higher cardiovascular death and all-cause mortality independent of well-known prognosticators.

Key messages

What is already known on this subject?
► Low systemic arterial compliance (SAC) is associated with increased cardiovascular morbidity and mortality in the general population as well as in patients with hypertension and diabetes. In aortic valve stenosis (AS), low SAC has been associated with increased mortality after transcatheter aortic valve replacement.

What might this study add?
► The present study demonstrates that lower SAC was associated with higher cardiovascular and all-cause mortality in patients with AS without diabetes or known cardiovascular disease. Of note, this association was independent of well-known confounders of impaired prognosis in AS, including hypertension, older age, female sex, obesity, presence of a small aortic root, and AS severity. Furthermore, low SAC was a better predictor of all-cause mortality than stroke volume index.

How might this impact on clinical practice?
► Low SAC in asymptomatic mild to moderate AS characterises a subgroup of patients with increased mortality. Furthermore, low SAC identifies patients that are prone to develop low flow severe AS subtypes during stenosis progression independent of the mean transvalvular gradient. The findings emphasise the importance of assessing hypertension and arterial function in addition to stenosis severity in evaluation of patients with AS.

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