Causes of death and predictors of survival after aortic valve replacement in low flow vs. normal flow severe aortic stenosis with preserved ejection fraction

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Aims
Reduced stroke volume index (SVI) in patients with severe aortic stenosis (AS) and preserved ejection fraction (EF) is associated with adverse outcomes even after aortic valve replacement (AVR), although specific reasons for impaired survival in this group are unknown. We investigated predictors of post-AVR survival and specific cause of death in patients with AS according to SVI.

Methods and results
Among 1120 consecutive patients with severe AS (aortic valve area \(< 1.0 \text{ cm}^2\) and preserved EF (≥ 50%) using 2-D and Doppler echocardiography who had AVR, 61 (5%) patients had reduced SVI \([< 35 \text{ mL/m}^2\) (low flow, LF)] and 1059 (95%) had normal SVI \([\geq 35 \text{ mL/m}^2\) (normal flow, NF)]. Survival post-AVR was lower in patients with LF compared with NF [3-year survival in LF group 76% (95% CI 70–82) vs. 89% (95% CI 88–90%), \(P = 0.03\)] primarily due to higher cardiac mortality [3-year event rate 13% (95% CI 8–18%) in LF vs. 5% (95% CI 5–7%) in NF, \(P = 0.02\)]. Congestive heart failure (CHF) was the most common cause of cardiac death in the LF group (57% of post-AVR cardiac deaths) and was a more frequent cause of death in LF compared with NF (3-year risk 7 vs. 2%, \(P = 0.008\)). Multivariable predictors of post-AVR mortality included age, creatinine, haemoglobin, right ventricular systolic pressure, SVI, and cognitive impairment.

Conclusion
Reduced SVI is associated with higher cardiac mortality after AVR. CHF is the predominant cause of cardiac mortality after AVR in patients with LF, suggesting the presence of persistent myocardial impairment in this population.

Keywords
aortic stenosis • survival • valves • surgery • stroke volume • cause of death

Introduction
Calcific aortic stenosis (AS) is a serious health problem worldwide with an increasing prevalence related to the ageing population.1 Due to revolutionary advances in transcatheter aortic valve replacement (AVR), more treatment options are available for a population with advancing age and multiple co-morbidities, making treatment decisions complex.2 In patients with increasing age, the relative contribution of severe AS to mortality may be different than in a younger population due to the common occurrence of non-cardiac co-morbidities including cancer, stroke, infection, and dementia.

Recently, reduced stroke volume index (SVI) has been identified as a risk factor for poor prognosis in patients with severe AS with preserved ejection fraction (EF).3–7 Although AVR improves outcomes in this group of patients, survival after AVR also appears to be impaired.8 Although one reason for impaired survival in low-flow, low-gradient severe AS patients has been attributed to under-referral for AVR,5 mechanisms for higher mortality after AVR are unknown. Unique features of patients with reduced SVI and severe AS and preserved EF include increased concentric remodelling, impaired left ventricular filling, and increased arterial afterload, but whether these factors play a role in long-term mortality after AVR is unknown.

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Accordingly, the aim of this investigation was to determine the long-term survival, contribution of cardiac vs. non-cardiac mortality, and specific causes of death after AVR in patients with severe AS and preserved EF with reduced SVI compared with normal SVI.

**Methods**

**Patients**

The Mayo Clinic Institutional Review Board approved this study. Consecutive patients aged ≥ 18 years who underwent transthoracic echocardiography between 1 January 2006 and 31 December 2011 with the following criteria were enrolled: (i) AVA < 1.0 cm²; (ii) preserved left ventricular EF (≥ 50%); (iii) absence of prosthetic valves, complex congenital heart disease, supravalvular or subvalvular AS, hypertrophic cardiomyopathy, and other moderate or severe native valvular lesions; and (iv) AVR performed during the study period. These criteria led to a final study population of 1120 patients. The medical record was reviewed for symptoms, co-morbidities, and laboratory data. History of heart failure was defined as a clinical history of congestive heart failure (CHF) for symptoms, co-morbidities, and laboratory data. History of heart failure was defined as a clinical history of congestive heart failure (CHF) determined by a physician with evidence of pulmonary vascular congestion on chest radiograph that responded to diuretic therapy. Cognitive impairment was defined as a history of either cognitive impairment or dementia documented in the medical record.

**2-Dimensional and Doppler echocardiography**

Echocardiographic methods for this study have previously been published. Briefly, comprehensive 2-D and Doppler echocardiographic studies were performed on commercially available ultrasound equipment (Acuson Sequoia, Siemens Medical, Mountain View, CA, USA; Vivid-7, GE Healthcare, Milwaukee, WI, USA, and IE33, Philips Healthcare, Andover, MA, USA) in accordance with the American Society of Echocardiography guidelines. Left ventricular outflow tract diameter was measured in the parasternal long-axis view in early systole from the point of aortic cusp insertion into the interventricular septum to the point of aortic cusp insertion into the interventricular fibrosa. Left ventricular outflow tract time velocity integral was measured using pulsed-wave Doppler by positioning the sample volume just below the region of flow convergence at ~5 mm apically from the aortic valve in the apical long-axis view and aligning it parallel with blood flow. Stroke volume was calculated using pulsed-wave Doppler as the product of left ventricular outflow tract area and left ventricular outflow tract velocity–time integral. For each study, a non-imaging probe was routinely used in multiple transducer positions to record the highest peak aortic jet velocity and mean gradient. For patients in sinus rhythm, 3 cardiac cycles were averaged; for atrial fibrillation, 10 cardiac cycles were averaged.

**Vital status and cause of death**

Vital status was determined through the Mayo Clinic registration office, surveillance telephone contact, the medical record, data obtained from the Rochester Epidemiology Project and the National Death Index Data Registry. Patients not known to be deceased were censored at time of last known follow-up. Specific cause of death was obtained by detailed physician review of the hospital medical record (M.F.E.), autopsy reports, or death certificate data either obtained from the Rochester Epidemiology Project or the National Death Index Data Registry. Causes of death considered to be cardiac included AS, cardiogenic shock, cardiomyopathy, CHF, coronary artery disease, myocardial infarction, cardiac interventional/surgical procedure related, or sudden cardiac death. Sudden cardiac death was defined as either a documented arrhythmogenic death or the out-of-hospital occurrence of an unexpected pulseless condition with the absence of a non-cardiac explanation. Non-cardiac causes of death were classified as cancer, stroke, dementia, infection, chronic lung disease, renal failure, or other.

**Statistical analysis**

Patients were stratified according to SVI (< 35 mL/m² or low flow (LF) vs. ≥ 35 mL/m² or normal flow (NF)). Data are reported as mean ± SD or number (percentage). Student’s t-tests were used to compare continuous variables and Pearson χ² or Fisher exact tests were used to compare categorical variables between individual groups. Kaplan–Meier methods and log-rank tests were used for temporal analysis of outcomes in each group. The end points of interest were cardiac and non-cardiac mortality. Cox proportional hazards regression was used to look for associations with outcomes of interest. To adjust for differences in baseline variables between groups, a multivariable model was constructed using stepwise selection for the outcome of post-AVR mortality. Candidate variables included into the multivariable model were selected based on univariable significance and included age, sex, obesity (defined as body mass index ≥ 30 kg/m²), SVF, EF, AVA, mean gradient, aortic peak velocity, systemic arterial compliance, right ventricular systolic pressure (RVSP), hypertension, coronary artery disease, diabetes mellitus, atrial fibrillation, history of heart failure, prior transient ischaemic attack or stroke, chronic obstructive pulmonary disease, prior coronary artery bypass grafting surgery, transcatheter AVR, serum creatinine, haemoglobin, and symptomatic status. Statistical analysis was performed using JMP version 9.0 and SAS version 9.3 (Cary, NC). An a priori level of significance was determined at P < 0.05.

**Results**

**Baseline characteristics**

The baseline clinical and echocardiographic characteristics have previously been published and are summarized in Table 1. Overall, 1057 patients underwent surgical AVR and 63 transcatheter AVR. Cardiac medication use was similar among groups, with the exception of diuretic use, which was more common in LF compared with NF group (95 vs. 86% on a diuretic, P = 0.04).

**Follow-up and cause of death ascertainment**

Mean follow-up duration of post-AVR was 2.2 ± 1.8 years (range 0–6.8 years). Post-AVR survival in the overall group was favourable (3-year estimate 86%; 95% CI 84.6–87.4), with low cardiac mortality (3-year mortality estimate 6%; 95% CI 5.1–6.9). Survival after transcatheter AVR was lower than surgical AVR (2-year survival 81 vs. 90%, P = 0.02).

During the study period, a total of 156 patients died; 14 (23%) of LF patients died and 142 (13%) of NF patients died (P = 0.05). The overall in-hospital mortality rate was 0.5% and was similar between LF (1 death, 1.6% in-hospital mortality rate) and NF (4 deaths, 0.4% in-hospital mortality rate) (P = 0.24) groups. Cause of death (Table 3) was determined by review of the hospital records in 92 (59%), autopsy in 5 (3%), by death certificate in 59 (38%), and was unable to be determined in 3 (2%).

**Causes of death in overall group**

In the entire group, causes of death included cancer (n = 30), infection (n = 29), CHF (n = 23), chronic lung disease (n = 13), stroke

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**Table 1**

<table>
<thead>
<tr>
<th>Variable</th>
<th>LF (n = 495)</th>
<th>NF (n = 625)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>67 ± 11</td>
<td>67 ± 11</td>
<td>0.88</td>
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<tr>
<td>Sex (M:F)</td>
<td>327:168</td>
<td>441:84</td>
<td>0.32</td>
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<tr>
<td>Hypertension</td>
<td>235 (48%)</td>
<td>333 (53%)</td>
<td>0.06</td>
</tr>
<tr>
<td>Diabetes</td>
<td>133 (27%)</td>
<td>183 (29%)</td>
<td>0.01</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>19 (4%)</td>
<td>26 (4%)</td>
<td>0.57</td>
</tr>
<tr>
<td>Obesity</td>
<td>188 (38%)</td>
<td>273 (44%)</td>
<td>0.02</td>
</tr>
<tr>
<td>Mean gradient</td>
<td>16.9 ± 8.4</td>
<td>17.4 ± 7.9</td>
<td>0.08</td>
</tr>
<tr>
<td>Stroke volume</td>
<td>65.4 ± 15.9</td>
<td>69.5 ± 16.1</td>
<td>0.003</td>
</tr>
<tr>
<td>EF (per cent)</td>
<td>61 ± 16</td>
<td>60 ± 15</td>
<td>0.29</td>
</tr>
<tr>
<td>SVI (per cent)</td>
<td>45 ± 17</td>
<td>46 ± 16</td>
<td>0.23</td>
</tr>
<tr>
<td>AVA (cm²)</td>
<td>0.6 ± 0.3</td>
<td>0.7 ± 0.3</td>
<td>0.001</td>
</tr>
<tr>
<td>Mean gradient (cm²)</td>
<td>8.6 ± 4.3</td>
<td>8.9 ± 4.2</td>
<td>0.25</td>
</tr>
<tr>
<td>Mean of 3 cardiac cycles</td>
<td>6.2 ± 2.1</td>
<td>6.7 ± 2.2</td>
<td>0.01</td>
</tr>
<tr>
<td>Mean of 10 cardiac cycles</td>
<td>6.9 ± 2.3</td>
<td>7.2 ± 2.4</td>
<td>0.08</td>
</tr>
</tbody>
</table>

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**Table 2**

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(n = 7), trauma (n = 3), pulmonary embolism (n = 2), and dementia (n = 2) (Table 2).

**Cause of death by SVI groups post-AVR**
Cardiac causes of death were more frequent in the LF group compared with the NF group [7 (50%) vs. 51 (35%), P = 0.03]. Among specific causes of death, CHF was more common in the LF group after AVR than in the NF group [4 (29%) vs. 19 (13%), P = 0.03].

Survival post-AVR was lower in patients with LF compared with NF [3-year survival in LF group 76% (95% CI 70–82%) vs. 89% (95% CI 88–90%), P = 0.03] (Figure 1) primarily due to higher cardiac mortality with a 3-year event rate of 13% (95% CI 8–18%) in LF vs. 5% (95% CI 5–7%) in NF, P = 0.02 (Figure 2). Rates of non-cardiac death post-AVR were similar between groups, with a trend towards higher event rate in LF (Figure 3). CHF was the most common cause of cardiac death following AVR in the LF group (57% of post-AVR cardiac deaths) (Table 2). Risk of CHF-related death after AVR was higher in LF compared with NF (3-year risk of post-AVR heart failure-related death 7 vs. 2%, P = 0.008).

In patients with NF, non-cardiac causes were more common than cardiac causes of death. The most common specific causes of post-AVR death for NF patients in order of decreasing frequency were cancer, chronic lung disease, infection, CHF, other, dementia, renal failure, and stroke (Table 2).

**Predictors of post-AVR mortality**
Overall univariate predictors of post-AVR mortality included age, aortic valve area, SVI, systemic arterial compliance, relative wall thickness, left atrial volume index, medial annulus e' velocity, RVSP, history of hypertension, prior coronary artery disease, diabetes mellitus, chronic obstructive pulmonary disease, atrial fibrillation, prior cerebrovascular event, cognitive impairment or dementia, prior history of heart failure, creatinine, haemoglobin, and transcatheter AVR. After multivariable analysis, overall independent predictors of post-AVR mortality included age, aortic valve area, SVI, systemic arterial compliance, relative wall thickness, left atrial volume index, medial annulus e' velocity, RVSP, history of hypertension, prior coronary artery disease, diabetes mellitus, chronic obstructive pulmonary disease, atrial fibrillation, prior cerebrovascular event, cognitive impairment or dementia, prior history of heart failure, creatinine, haemoglobin, and transcatheter AVR.
mortality were age, serum creatinine and haemoglobin, RVSP, SVI, and history of cognitive impairment (Table 3). For every 5 mL/m² reduction in SVI, there was a 1.3-fold increase in risk of post-AVR mortality.

Specific predictors of cardiac post-AVR mortality included age, EF, SVI, systemic arterial compliance, left atrial volume index, relative wall thickness, RVSP, chronic obstructive pulmonary disease, atrial fibrillation, prior cerebrovascular event, cognitive impairment, prior heart failure, creatinine, and haemoglobin. After multivariable analysis, independent predictors of cardiac post-AVR mortality were age, relative wall thickness, RVSP, atrial fibrillation, creatinine, and haemoglobin.

Specific predictors of non-cardiac post-AVR mortality included age, body mass index, aortic valve area, SVI, systemic arterial compliance, left atrial volume index, medial annulus e’ velocity, RVSP, prior coronary artery disease, chronic obstructive pulmonary disease, atrial fibrillation, prior cerebrovascular event, cognitive impairment, prior heart failure, creatinine, and haemoglobin. After multivariable analysis, independent predictors of non-cardiac post-AVR mortality were age, body mass index, serum creatinine and haemoglobin, RVSP, SVI, history of cognitive impairment, previous cerebrovascular event, prior coronary artery disease, and atrial fibrillation.

Discussion
This is the first study to investigate specific causes of death according to SVI in patients with severe AS and preserved EF after AVR. Major
increased arterial afterload may all predispose to heart failure, impaired diastolic filling, higher prevalence of atrial fibrillation, and smaller left ventricular cavity size due to concentric remodelling, multiple investigators, unique characteristics in LF patients including tivariable analysis, both SVI and RVSP remained significant predictors of mortality after AVR and is a predominant cause of death. After multivariable analysis, higher post-AVR CHF is also related to this mortality. Data from patients with LF may be a group that especially benefits from intensive heart failure and blood pressure management following AVR, including frequent encounters with cardiovascular care providers focused on the prevention and treatment of heart failure.

In patients with normal SVI, non-cardiac causes of death predominated, including cancer, infection, chronic lung disease, and others, both before and after AVR. Cardiac causes of death were still common, but, responsible for only one-third of deaths in patients with NF vs. one half of deaths in LF patients. Co-morbid conditions including advanced age, coronary artery disease, diabetes, and renal dysfunction were highly prevalent, reflecting an increasingly complex population of AS patients. This emphasizes the importance of using a comprehensive risk assessment approach to care of the patient with AS, including identification of major co-morbidities that may have a higher impact on longevity than the AS and selecting treatment strategies (surgical AVR, transcatheter AVR, medical therapy) that are best suited to each patient. The high rate of cancer-related deaths in the AS population after AVR represents an opportunity for future studies aimed at exploring this relationship to improve care in management and counseling of patients with AS and pre-existing cancer diagnosis in particular.

**Limitations**

The retrospective nature of this investigation is an inherent limitation, with potential patient group features, not accounted for in our study, which may have contributed to differences in outcomes. Death certificates may have a reduced accuracy for classifying cause of death with a recent study reporting a 58% accuracy. However, we used multiple methods for cause of death ascertainment, with the most common method being detailed review of existing complete medical records, including autopsies. Despite this, misclassification of cause of death may have occurred in some patients, particularly in cases of sudden cardiac death, as is well recognized in epidemiological studies. Given the time period of the study, frailty was not systematically assessed in this population. Despite a relatively low number of events occurring in LF patients, the observed mortality differences between LF and NF patients were evident and statistically significant. Our study is unique in that it provides insight into characteristics and clinical outcomes using a systematic AS severity assessment methodology that is consistently performed at our institution.

**Conclusions**

Reduced SVI in patients with severe AS is associated with higher cardiac mortality after AVR. CHF is the predominant cause of cardiac mortality after AVR in patients with LF, suggesting the presence of persistent myocardial impairment after AVR in this population. Co-morbidities including age, renal function, SVI, pulmonary hypertension, and cognitive impairment are the strongest predictors of survival following AVR in patients with AS.
Conflict of interest: None declared.

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Supplementary data are available at European Heart Journal – Cardiovascular Imaging online.

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