Prognosis and outcome determinants after heart failure diagnosis in patients who underwent aortic valvular intervention

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Abstract

Aims To study clinical phenotype, prognosis for all-cause and cardiovascular (CV) mortality and predictive factors in patients with incident heart failure (HF) after aortic valvular intervention (AVI) for aortic stenosis (AS).

Methods and results In this retrospective, observational study we included patients from the Swedish Heart Failure Registry (SwedeHF) recorded 2003–2016, with AS diagnosis and AVI before HF diagnosis. The AS diagnosis was established according to International Classification of Diseases 10th revision (ICD-10) codes, thus without information concerning clinical or echocardiographical data on the aortic valve disease. The patients were divided into two subgroups: left ventricular ejection fraction (LVEF) ≥ 50% (AS-HFpEF) and < 50% (AS-HFrEF). We individually matched three controls with HF from the SwedeHF without AS (control group) for each patient. Baseline characteristics, co-morbidities, survival status and outcomes were obtained by linking the SwedeHF with two other Swedish registries. We used Kaplan–Meier curves to present time to all-cause mortality, cumulative incidence function for time to CV mortality and Cox proportional hazards model to evaluate the relative difference between AS-HFrEF and AS-HFpEF and AS-HF and controls. The crude all-cause mortality was 49.0%, CV mortality 27.9% in AS-HF patients, respectively 44.7% and 26.6% in matched controls. The adjusted risk for all-cause mortality and CV mortality was similar in HF, regardless of LVEF vs. controls. No significant difference in factors predicting higher all-cause mortality was observed in AS-HFrEF vs. AS-HFpEF, except for diabetes (only in AS-HFrEF), with statistically significant interaction predicting death between the two groups.

Conclusions In this nationwide SwedeHF study, we characterized incident HF population after AVI. We found no significant differences in all-cause and CV mortality compared with general HF population. They had virtually the same predictors for mortality, regardless of LVEF.

Keywords Aortic stenosis; Aortic valvular intervention; Heart failure; Mortality; Determinants

Introduction

Although the prevention and treatment of coronary artery disease (CAD) as one of the main causes of heart failure (HF) have been greatly improved in the past decade,¹ the impact of valvular heart disease as a cause of HF remains poorly understood. Moreover, degenerative aortic stenosis (AS) increases with age,² and as the population life expectancy increases, AS and other valvular diseases will play a greater role in HF aetiology. In addition, more patients are treated with aortic valve intervention (AVI), including those previously considered at high risk, who are nowadays treated by transcatheter aortic valve implantation (TAVI).³ Accordingly, it is crucial to study incident HF in patients with AS who had undergone AVI.

The left ventricle (LV) responds to pressure overload imposed by the stenotic aortic valve, increasing wall thickness while the left atrium enlarges.⁴ Over time, the LV becomes
less compliant, worsening the diastolic function. Without AVI, dilation of the LV cavity occurs, leading to a worsened systolic function. Therefore, both HF with reduced ejection fraction (HFrEF) and HF with preserved ejection fraction (HFpEF) may occur in the natural course of AS, even after an AVI, as the adverse LV remodelling imposed by long-standing AS is not reversible after myocardial fibrosis appears. Several unanswered questions remain about whether this incident HF population after an AVI differs from the general HF population, their clinical phenotypes, prognosis and their underlying determinants.

This study investigates how clinical phenotypes, prognosis and its underlying factors differ in terms of all-cause and cardiovascular (CV) mortality in patients with incident HF after an AVI for AS in relation to HFrEF vs. HFpEF. A secondary aim is to compare this HF population with the general HF population. Two study hypotheses have been generated for this purpose: (1) For patients operated with either surgical aortic valve replacement (SAVR) or TAVI for AS in which AVI precedes HF diagnosis, those with HFrEF will have worse outcome (all-cause and CV mortality) than HFpEF patients; (2) patients operated with either SAVR or TAVI for AS in which AVI precedes HF diagnosis will have better outcome (all-cause and CV mortality) than individually matched HF patients without AS.

Methods

Study population

This study included patients from the Swedish Heart Failure Registry (SwedeHF) registered from 2003 to 2016 and who had available data on left ventricular ejection fraction (LVEF). The index visit in the SwedeHF for each patient was the baseline date. All patients were followed from this index visit until 31 December 2016.

Patients with incident HF were defined as those who had an AS diagnosis and had undergone an SAVR or TAVI before being diagnosed with HF. Patients with a coronary artery bypass graft (CABG) performed before AS or patients with prior HF before AS were excluded. The study cohort was divided into two subgroups: LVEF ≥ 50% (AS-HFpEF) and LVEF < 50% (AS-HFrEF). For each patient in these groups, we identified three patients from the SwedeHF with HF and without a history of preceding AS matched for sex, age at index visit in SwedeHF, age at HF diagnosis, year of HF diagnosis and LVEF (control group, non-AS-HF). Initially, we intended to differentiate between the patients with SAVR and those with TAVI, but the TAVI group was small, of only 23 patients, so this group was included in the AVI group containing both individuals with SAVR and TAVI.

The SwedeHF is a quality registry covering nearly half of hospital-based patients in Sweden. The registry was established in 2003 and was formerly described. Briefly, the inclusion criterion is HF diagnosis based on a physician’s clinical judgement. The exclusion criterion is age < 18 years. It contains about 80 variables recorded either at hospital discharge or at a visit to an outpatient clinic. The Uppsala Clinical Research Centre in Uppsala, Sweden, manages the database. The protocol, registration form and annual reports are available at http://www.ucr.uu.se/rikssvikt. The collected data include information on demographic (age, sex), clinical measures (heart rate, blood pressure, New York Heart Association [NYHA] class) at the time of the inclusion, paraclinical measures (laboratory test, such as creatinine, potassium, haemoglobin or N-terminal pro-B-type natriuretic peptide [NT-proBNP] and X-ray and electrocardiography), data about co-morbidities and treatment in the cardiovascular sphere (medication and devices). Although echocardiography is not compulsory, most of the patients (90%) have a registered LVEF but no other echocardiographic parameters. Individual informed consent is not requested, but all patients are informed of their inclusion in national quality registries and the possibility of withdrawing. Using the Chronic Kidney Disease Epidemiology Collaboration algorithm, we calculated the estimated glomerular filtration rate (eGFR).

To obtain data on co-morbidities and surgical interventions the SwedeHF has been linked to the Swedish National Patient Registry (NPR) from 1997 and onwards using the personal identification number, a unique number assigned to all Swedish residents. All hospital discharge diagnoses are registered in the NPR, which has nationwide coverage since 1987. To identify participants and co-morbidities we used the International Classification of Diseases 10th revision (ICD-10) codes for AS-I.35.0 and HF-I.50. The ICD 10 codes used to identify co-morbidities are presented in Table S1. For surgical or endovascular procedures, we used the Swedish version of the classification of surgical procedures from the Nordic Medico-Statistical Committee (KKÅ). In this system, SAVR is coded FMD00, FMD10, FMD20, FMD30, FMD33, FMD40 or FMD96; percutaneous transluminal dilatation of AS is coded FMA00, FMA10, FMA20 or FMA 32; TAVI is coded FMD12; and CABG is coded FNA, FNB, FNC, FND or FNE.

Outcomes

All-cause and CV mortality were studied as outcomes and defined as the leading cause of death (ICD 10 codes I 00–I 99). We obtained data on the date and underlying cause of death for our patients and matched controls by linking the SwedeHF with the Swedish Cause of Death Registry, a registry containing information on the date and underlying causes of death occurring in the country or abroad for all Swedish residents.
The establishment of the registries and our study complied with the Declaration of Helsinki and were approved by the Ethical Committee of the University of Gothenburg, Sweden (DNR 2013/392-32).

Statistical analysis

Data are presented as the mean, standard deviation (SD), median, minimum and maximum for continuous variables and frequency or number and percentage for categorical variables. For the test between two groups (AS-HFpEF vs. AS-HFrEF), we used Fisher’s exact test for dichotomous variables, the Mantel–Haenszel chi-square trend test for ordered categorical variables, the chi-square test for non-ordered variables and the Mann–Whitney U test for continuous variables. Time-to-event is described by \( n \) (%), pooled event rate with 95% confidence intervals (CIs) and graphically presented by Kaplan–Meier curves for time to all-cause mortality and cumulative incidence function for time to CV mortality handling other reasons for death as competing risk events. The adjusted Cox proportional hazards model was used to evaluate the relative difference between AS-HFrEF and AS-HFpEF patients with AVI preceding HF diagnosis and between AS-HF and non-AS-HF patients. Age- and sex-adjusted analyses of these comparisons are described in Model 1. Model 2 additionally included all other predefined confounders: age at HF diagnosis, smoking, mean arterial pressure, haemoglobin, eGFR and co-morbidities (atrial fibrillation, stroke/transitory ischemic attack [TIA], renal disease, peripheral vascular disease). Model 3 also included factors known to be predictors in this cohort. These predictors included hypertension, diabetes and lung disease in analyses between AS-HF and non-AS-HF and years between AVI and HF diagnosis in the AS-HF group.

LVEF category and patient/control group interaction were analysed using the same methodology. Predictors for time to death (all-cause and CV) in AS-HFpEF and AS-HFrEF patients were identified using age- and sex-adjusted Cox regression. We investigated the interactions between the LVEF group and the predictors to identify variables that statistically significantly discriminate between the two LVEF groups (AS-HFpEF and AS-HFrEF).

The assumption of proportional hazard ratios (HRs) was tested by studying the variable-by-log (time) interaction and visually reviewing log (–log (survival)) vs. log (time) curves. Missing data were not imputed. Missing data for the covariates smoking (25%) and NYHA class (34%) were handled as own categories in the analyses in Models 2 and 3. All tests were two-sided. The interaction terms were considered statistically significant at \( P = 0.10 \).

In this study, the four confirmatory tests described in the study hypotheses have been interpreted after adjusting for multiple testing by applying the Bonferroni–Holm correction for multiple comparisons. If the minimum \( P \)-value were \( \leq 0.0125 \), the test was confirmed; if the next \( P \)-value in order were \( \leq 0.017 \), it was confirmed; if the next \( P \)-value in order were \( \leq 0.025 \), it was confirmed; and if the last \( P \)-value were \( \leq 0.05 \), it was confirmed. All other tests were done in an exploratory manner. SAS software version 9.4 (SAS Institute Inc., Cary, NC, USA) was used for data analysis.

Results

Clinical phenotype

In total, 76,506 patients were registered in the SwedeHF. Of these 76,506 patients, 549 (0.7%) remained after exclusion of those with an HF diagnosis before 2003 (34.7%) or index HF before 2003 (0.3%), without an AS diagnosis (61%), with CABG surgery before AS (0.1%), without registered LVEF \( \geq \) 65.4% and an AVI before a diagnosis of HF (2.7%) (Figure 1). Of these 549 patients, 341 (62%) had reduced LVEF, and 208 (38.0%) preserved LVEF.

Patients with AS-HFpEF were older at registration in the SwedeHF compared with patients with AS-HFrEF (77.4% vs. 65.4% \( \geq 75 \) years) and older when HF was diagnosed (40.0% vs. 37.2% \( \geq 80 \) years and 72.6% vs. 61.6% \( \geq 75 \) years). Half of the patients in the AS-HFpEF subgroup were women vs. only 28% in the AS-HFrEF group. AS-HFpEF patients had numerically higher systolic blood pressure, a significantly lower heart rate, a significantly lower haemoglobin value and a higher prevalence of atrial fibrillation as a co-morbidity. They also had a lower presence of left bundle branch block and peripheral arterial disease and underwent less often PCI. AS-HFpEF patients were treated more often with mineralocorticoid receptor antagonist (MRA) and diuretics, whereas significantly more AS-HFrEF patients had treatment with angiotensin-converting enzyme inhibitors (ACEI)/angiotensin receptor II blockers (ARBs) (Table 1).

The whole group of 549 patients with AS (irrespective of LVEF) was matched 1:3 with controls, resulting in 437 AS patients who could be matched with corresponding controls (\( n = 1311 \) controls). We found no significant difference between patients with AS and controls in smoking habits, weight, body mass index (BMI), systolic blood pressure, heart rate, NYHA class, device treatment, creatinine, NTproBNP, eGFR, presence of diabetes, lung disease, stroke/TIA, liver disease, renal disease, obstructive sleep apnoea (as co-morbidities) or treatment with beta blockers, MRA, digoxin, diuretics, aspirin, nitrates or PCI. Statistically significant differences were found between patients with AS and controls for diastolic blood pressure, mean arterial pressure and haemoglobin values (all lower in AS patients). Pacemaker rhythm and other rhythms (except sinus rhythm and atrial fibrillation at the index visit), atrial fibrillation as a
co-morbidity, peripheral arterial disease, treatment with statins and anticoagulation occurred more often in the AS patients (Table S2).

Outcomes

In the whole group of 549 patients, crude all-cause mortality was 50.3% with a median follow-up time of 2.53 years (inter-quartile range, IQR 0.98–4.87 years), with an event rate per 100 person-years of 16.0 (95%CI 14.2–18.1). Crude CV mortality was 30.2%, with an event rate per 100 person-years of 9.7 (95%CI 8.2–11.2).

All-cause mortality was 47.8% in the subgroup with AS-HFrEF, with a median follow-up time of 2.42 years (IQR 0.93–4.87) and an event rate per 100 person-years of 15.4 (95%CI 13.1–18.0). CV mortality was 29.6%, with an event rate per 100 person-years of 9.5 (95%CI 7.8–11.6). In the AS-HFpEF subgroup, all-cause mortality was 54.3%, with a median follow-up time of 2.70 years (IQR 1.1–4.86); the event rate per 100 person-years was 17.1 (95%CI 14.1–20.5). CV mortality was 31.3%, with an event rate per 100 person-years of 9.8 (95%CI 7.6–12.5).

All-cause mortality in AS-HF compared with matched controls was 49%, with an event rate per 100 person-years of 14.7 (95%CI 12.8–16.9) during a median follow-up of about 2.8 years. In the matched controls, all-cause mortality was 44.7%, with an event rate per 100 person-years of 13.0 (95%CI 12.0–14.1). CV mortality in AS-HF patients was 27.9%, with an event rate per 100 person-years of 8.4 (95%CI 7.0–10.0). CV mortality in the matched controls was 26.6%, and the event rate per 100 person-years was 7.7 (95%CI 6.9–8.6).

In the AS-HFrEF subgroup, all-cause mortality was 44.6% vs. 42.3% in the matched controls. CV mortality was 26.8% in the AS-HFrEF subgroup and 25.7% in the matched controls. All-cause mortality was 56.0% in the AS-HFpEF subgroup and 48.6% in the matched controls. Finally, CV mortality was 29.8% in the AS-HFpEF subgroup and 28.2% in the matched controls (Table 2).

Examining the cumulative incidence for all-cause or CV mortality, we found no difference between the HF patients with AS and an LVEF < 50% or ≥50% and the matched controls (Figure 2).

After adjusting for age at index visit and sex, there was no statistically significant difference in all-cause or CV mortality.
Table 1 Baseline characteristics of patients with incident HF after AVI, stratified by phenotype

| Variable                                      | Total (n = 549) | AS-HFrEF (n = 341) | AS-HFpEF (n = 208) | p-value |
|-----------------------------------------------|----------------|--------------------|--------------------|---------|
| **Age at HF index visit (years)**             | 77.2 (9.6)     | 76.5 (10.2)        | 78.3 (8.6)         | 0.094   |
|                                               | 79 (34; 96)    | 79 (34; 96)        | 79 (45; 94)        |         |
| **Age at HF index visit (years, categories)** |                |                    |                    |         |
| <60 years                                      | 31 (5.6%)      | 22 (6.5%)          | 9 (4.3%)           |         |
| 60–<70 years                                   | 64 (11.7%)     | 48 (14.1%)         | 16 (7.7%)          |         |
| 70–< 80 years                                  | 201 (36.6%)    | 116 (34.0%)        | 85 (40.9%)         |         |
| ≥80 years                                      | 253 (46.1%)    | 155 (45.5%)        | 98 (47.1%)         | 0.11    |
| ≥75 years                                      | 384 (69.9%)    | 223 (65.4%)        | 161 (77.4%)        | 0.0036  |
| **Age at HF diagnosis (years)**                | 76.0 (9.5)     | 75.2 (10.1)        | 77.2 (8.5)         | 0.068   |
|                                               | 78 (34; 95)    | 77 (34; 95)        | 78 (45; 94)        |         |
| **Sex**                                        |                |                    |                    |         |
| Men                                           | 350 (63.8%)    | 246 (72.1%)        | 104 (50.0%)        |         |
| Women                                          | 199 (36.2%)    | 95 (27.9%)         | 104 (50.0%)        | <.0001  |
| **Years from HF diagnosis to HF index visit**  | 1.21 (1.95)    | 1.29 (2.05)        | 1.07 (1.76)        | 0.32    |
|                                               | 0.12 (0; 11.2) | 0.13 (0; 11.2)     | 0.06 (0; 7.79)     |         |
| **Years from valve surgery to HF index visit**| 4.78 (4.31)    | 4.84 (4.51)        | 4.69 (3.96)        | 0.88    |
|                                               | 4.07 (0; 17.3) | 3.9 (0; 15.76)     | 4.13 (0; 17.73)    |         |
| **Years from valve surgery to HF diagnosis**   | 3.58 (3.89)    | 3.55 (4.14)        | 3.61 (3.45)        | 0.13    |
|                                               | 1.93 (0; 15.07)| 1.23 (0; 15.07)    | 2.68 (0; 13.06)    |         |
| **Smoking**                                    |                |                    |                    |         |
| Never                                          | 195 (47.4%)    | 118 (45.2%)        | 77 (51.3%)         |         |
| Former                                         | 192 (46.7%)    | 124 (47.5%)        | 68 (45.3%)         |         |
| Current                                        | 24 (5.8%)      | 19 (7.3%)          | 5 (3.3%)           | 0.10    |
| **BMI (kg/m²)**                                | 27.3 (5.0)     | 27.1 (4.6)         | 27.7 (5.6)         | 0.60    |
| **BMI ≥ 30 kg/m²**                             | 87 (26.9%)     | 52 (24.5%)         | 35 (31.5%)         | 0.23    |
| **Systolic blood pressure (mmHg)**             | 129.2 (21.2)   | 127.6 (20.9)       | 131.7 (21.4)       | 0.051   |
| **Diastolic blood pressure (mmHg)**            | 70.0 (12.0)    | 70.7 (11.9)        | 68.9 (12.2)        | 0.17    |
| **Heart rate (bpm)**                           | 74.1 (14.6)    | 75.3 (14.7)        | 72.0 (14.2)        | 0.018   |
| **Mean arterial pressure**                     | 89.8 (12.3)    | 89.7 (12.5)        | 89.9 (11.9)        | 0.98    |
| **NYHA**                                       |                |                    |                    |         |
| NYHA I                                         | 36 (10.0%)     | 20 (8.2%)          | 16 (13.7%)         |         |
| NYHA II                                        | 180 (50.0%)    | 123 (50.0%)        | 57 (48.7%)         |         |
| NYHA III                                       | 133 (36.9%)    | 91 (37.9%)         | 42 (35.9%)         |         |
| NYHA IV                                        | 11 (3.1%)      | 9 (3.7%)           | 2 (1.7%)           | 0.16    |
| **LVEF**                                       |                |                    |                    |         |
| <30%                                           | 71 (12.9%)     | 71 (20.8%)         | 0 (0.0%)           |         |
| 30–<40%                                        | 109 (19.9%)    | 109 (32.0%)        | 0 (0.0%)           |         |
| 40–<50%                                        | 161 (29.3%)    | 161 (47.2%)        | 0 (0.0%)           |         |
| ≥ 50%                                          | 208 (37.9%)    | 0 (0.0%)           | 208 (100.0%)       | <.0001  |
| **LBBB**                                       | 83 (18.6%)     | 69 (24.5%)         | 14 (5.9%)          | <.0001  |
| **Sinus rhythm**                               | 253 (46.6%)    | 154 (45.3%)        | 99 (48.8%)         | 0.49    |
| **Atrial fibrillation**                        | 198 (36.5%)    | 120 (35.3%)        | 78 (38.4%)         | 0.52    |
| Pacemaker/other rhythm                         | 92 (16.9%)     | 66 (19.4%)         | 26 (12.8%)         | 0.059   |
| **Device**                                     |                |                    |                    |         |
| None/PM                                        | 519 (96.5%)    | 317 (94.9%)        | 202 (99.0%)        |         |
| lCD without CRT                                | 9 (1.7%)       | 7 (2.1%)           | 2 (1.0%)           |         |
| CRT without ICD                                | 4 (0.7%)       | 4 (1.2%)           | 0 (0.0%)           |         |
| CRT with ICD                                   | 6 (1.1%)       | 6 (1.8%)           | 0 (0.0%)           | 0.064   |
| **Haemoglobin g/l**                            | 122.8 (16.4)   | 124.3 (16.6)       | 120.3 (15.7)       | 0.0042  |
| **Creatinine μmol/l**                          | 110.5 (51.8)   | 111.6 (55.1)       | 108.8 (46.1)       | 0.74    |
| **NT-proBNP pg/ml**                            | 98 (37; 673)   | 97 (37; 673)       | 98 (39; 389)       |         |
| **eGFR (ml/min/1.73 m², cat.) (CKD-EPI)**      | 4838 (7691)    | 5225 (7825)        | 4206 (7460)        | 0.17    |
| ≥60                                            | 247 (45.2%)    | 165 (48.5%)        | 82 (39.6%)         |         |
| 30–60                                          | 245 (44.8%)    | 143 (42.1%)        | 102 (49.3%)        |         |
| <30                                            | 55 (10.1%)     | 32 (9.4%)          | 23 (11.1%)         | 0.066   |
| **Hypertension**                               | 411 (74.9%)    | 247 (72.4%)        | 164 (78.8%)        | 0.11    |
| **Diabetes**                                   | 169 (30.8%)    | 108 (31.7%)        | 61 (29.3%)         | 0.63    |
For comparison between groups, Fisher’s exact test was used for non-ordered categorical variables, and the Mann–Whitney U test was used for ordered categorical variables. The chi-square test was used for ordered categorical variables.

Table 1 (continued)

| Variable                        | Total \((n = 549)\) | AS-HFrEF \((n = 341)\) | AS-HFpEF \((n = 208)\) | p-value |
|---------------------------------|---------------------|------------------------|------------------------|---------|
| Atrial fibrillation             | 380 (69.2%)         | 222 (65.1%)            | 158 (76.0%)            | 0.0093  |
| Lung disease/COPD               | 104 (18.9%)         | 66 (19.4%)             | 38 (18.3%)             | 0.84    |
| Stroke/TIA                      | 107 (19.5%)         | 74 (21.7%)             | 33 (15.9%)             | 0.12    |
| Liver disease                   | 14 (2.6%)           | 8 (2.3%)               | 6 (2.9%)               | 0.90    |
| Renal disease                   | 50 (9.1%)           | 26 (7.6%)              | 24 (11.5%)             | 0.17    |
| Peripheral vascular disease     | 95 (17.3%)          | 68 (19.9%)             | 27 (13.0%)             | 0.046   |
| Obstructive sleep apnoea        | 22 (4.0%)           | 15 (4.4%)              | 7 (3.4%)               | 0.72    |
| PCI                             | 90 (16.4%)          | 68 (19.9%)             | 22 (10.6%)             | 0.0049  |
| ACE/ARB                         | 427 (78.1%)         | 280 (82.6%)            | 147 (70.7%)            | 0.0017  |
| Beta blockers                   | 467 (85.7%)         | 296 (87.6%)            | 171 (82.6%)            | 0.14    |
| MRA                             | 139 (25.7%)         | 75 (22.5%)             | 64 (31.1%)             | 0.035   |
| Digoxin                         | 69 (12.6%)          | 44 (13.0%)             | 25 (12.1%)             | 0.87    |
| ARNI                            | 0 (0.0%)            | 0 (0.0%)               | 0 (0.0%)               | 1.00    |
| Statins                         | 322 (59.0%)         | 204 (60.2%)            | 118 (57.0%)            | 0.52    |
| Diuretics                       | 451 (82.4%)         | 268 (78.8%)            | 183 (88.4%)            | 0.0052  |
| Anticoagulant                   | 307 (56.2%)         | 200 (59.0%)            | 107 (51.7%)            | 0.11    |
| ASA                             | 231 (43.3%)         | 145 (43.9%)            | 86 (42.2%)             | 0.75    |
| Nitrates                        | 63 (11.6%)          | 35 (10.4%)             | 28 (13.6%)             | 0.33    |

For categorical variables, \(n\) (%) is presented.

For continuous variables mean (SD) or median (min; max)/p-value \(= \) is presented, as appropriate.

For comparison between groups, Fisher’s exact test (lowest one-sided p-value multiplied by 2) was used for dichotomous variables, and the Mantel–Haenszel chi-square test was used for ordered categorical variables.

The chi-square test was used for non-ordered categorical variables, and the Mann–Whitney \(U\) test was used for continuous variables.

Table 2  Event rate for all patients grouped by LVEF and their matched controls

| Endpoint       | Subgroup   | \(n\) events | Follow-up time (years) | Event rate per 100 person-years (95%CI) | Event rate per 100 person-years (95%CI) |
|----------------|------------|--------------|------------------------|----------------------------------------|----------------------------------------|
|                |            |              | Median (IQR)           |                                        |                                        |
| All-cause mortality | All patients | 214 (49.0%) | 2.80 (1.18–5.07)       | 14.7 (12.8–16.9)                      | 586 (44.7%)                           | 2.88 (1.02–5.45)                      | 13.0 (12.0–14.1)                      |
|                | LVEF < 50% | 120 (44.6%)  | 2.78 (1.16–5.20)       | 13.4 (11.1–16.1)                      | 341 (42.3%)                           | 2.87 (1.01–5.45)                      | 12.2 (11.0–13.6)                      |
|                | LVEF ≥ 50% | 94 (56.0%)   | 2.86 (1.23–5.03)       | 16.9 (13.6–20.6)                     | 245 (48.6%)                           | 2.88 (1.03–5.44)                      | 14.2 (12.5–16.1)                      |
|                | All patients | 122 (27.9%) | 2.80 (1.18–5.07)       | 8.4 (7.0–10.0)                       | 349 (26.6%)                           | 2.88 (1.02–5.45)                      | 7.7 (6.9–8.6)                         |
| CV mortality  | LVEF < 50% | 72 (26.8%)   | 2.78 (1.16–5.20)       | 8.1 (6.3–10.1)                       | 207 (25.7%)                           | 2.87 (1.01–5.45)                      | 7.4 (6.4–8.5)                         |
|                | LVEF ≥ 50% | 50 (29.8%)   | 2.86 (1.23–5.03)       | 9.0 (6.7–11.8)                       | 142 (28.2%)                           | 2.88 (1.03–5.44)                      | 8.2 (6.9–9.7)                         |

95%CI computed by using exact Poisson limits.

between AS-HFpEF and AS-HFrEF patients. Even after further adjustment for age at HF diagnosis, years between AVI and HF diagnosis, smoking, mean arterial pressure, haemoglobin, eGFR and co-morbidities (atrial fibrillation, stroke/TIA, renal disease, peripheral vascular disease, hypertension, diabetes and lung diseases), no significant differences were observed in mortality between these two groups. After adjusting for the same factors, excluding time between AVI and HF diagnosis, there were no significant differences between AS-HF and non-AS-HF (data not shown).

As shown in Table 3, there was no statistically significant difference in all-cause or CV mortality between AS-HFpEF or AS-HFrEF patients vs. their matched non-AS-HF controls. In the HFpEF subgroup, all respective model interactions between the group variable and log (time) were significant, indicating non-proportional hazards. Moreover, Figure 2 depicts a crossing of incidence curves along follow-up time.

Predictive factors

We investigated whether there were different underlying factors associated with all-cause mortality between the AS-HFpEF and AS-HFrEF subgroups. In both subgroups, age at index visit and HF diagnosis, both as a continuous variable and categorical variable (<75, ≥75 years), significantly correlated with higher all-cause mortality, as did duration between AVI and index HF visit. Atrial fibrillation was a predictive factor for worse survival in AS-HFrEF (HR 1.43; 95%CI 1.02–2.02), but not in AS-HFpEF (HR 1.00; 95%CI 0.62–1.60), with a non-significant \(P\) for interaction of 0.28. A similar pattern was observed for diabetes in AS-HFrEF (HR 1.67; 95%CI 1.21–2.31, \(P = 0.0019\)) and in AS-HFpEF (HR 1.05; 95%CI 0.67–1.63), but, in this case, the \(P\) for interaction was statistically significant (\(P\) for interaction 0.041) (Table S3).
Discussions

This nationwide SwedeHF registry study was the first to characterise an incident HF population after intervention (SAVR or TAVI) of the aortic valve. We found similar all-cause and CV mortality in the incident HF and general HF population, as well as a similar prognosis and a comparable risk profile (except for diabetes mellitus and atrial fibrillation) across the spectrum of HF phenotypes.

The all-cause and cardiovascular mortality in AS-HF group were rather high, 49% and 30%, respectively. In literature, 5-year mortality rates of 56%,10 or even higher, of 66–66%11 were reported. Considering that our patients were old (77.2 ± 9.6) with a high prevalence of co-morbidities (such as atrial fibrillation in 69%, stroke/TIA in 20%, diabetes mellitus in 31% or severe renal insufficiency [eGFR < 30 mL/min/1.73 m2] in 10%), these survival results are plausible.

Given that life expectancy prolongs and the population ages, it is evident that an incident HF population after AVI is expected to increase. Aortic valve stenosis, the most common valvulopathy in the Western world,12 is more prevalent (2.4–5%) in people ≥75 years.13–14 Nevertheless, more patients are treated with AVI and even those considered to have a prohibitive surgical risk are offered TAVI. Therefore, after AVI, more patients survive and live longer, increasing the risk of HF development in their lifetime.

However, this HF population may differ from the general HF population because AS induces rather specific changes in LV structure and function. Therefore, at least theoretically, incident HF in patients with AS, despite AVI, may have a different prognosis than the general HF population.

This study found that both AS-HFrEF and AS-HFpEF patients have similar clinical phenotype compared with each other and to the general HF population. For instance, our AS-HFpEF patients are older, are more often women and have a higher prevalence of atrial fibrillation, lower haemoglobin levels or lower prevalence of atherosclerotic vascular disease and left bundle branch block, which is in line with previous findings.15–19

In addition, the risk for both all-cause and CV mortality was similar in AS-HFpEF and AS-HFrEF patients, a finding contrary to that of the general population. Patients with HFrEF regardless aetiology have been shown to have slightly better prognosis than patients with HFrEF.20,21 The process transforming AS to HF begins with the pressure overload imposed on the LV by the narrowed valve causing LV hypertrophy as a compensatory mechanism to maintain cardiac output, leading further to impaired blood flow reserve,22,23 cardiomyocyte apoptosis and replacement fibrosis, linking hypertrophy with HF.24,25 Hypertrophy affects diastolic function26 and, finally, systolic function.27 However, the finding that AS-HFrEF patients have the same prognosis as AS-HFpEF patients challenges this mechanism among patients who had undergone an AVI. One possible explanation is that in our cohort, all patients with AS have been treated with AVI, which may affect AS’s natural disease progression, either positively or negatively, through possible complications induced by a valve prosthesis (such as bleeding, valve thrombosis or infection and valve failure). Moreover, in this cohort, patients with prior CABG were excluded, resulting in a homogeneous study population despite the fact that LVEF was different. The finding that LVEF did not affect the prognosis may be important in evaluating these patients, as LVEF is an important marker in decision making regarding AS.

Of note, all-cause and CV mortality in this incident HF population after an AVI were similar to the general HF population without AS, suggesting that AVI altered the AS disease course. AVI thus improves the prognosis markedly and should not be delayed when indicated. This rationale is consistent with other studies showing that AVI improves survival in these patients compared with the general population,28,29 especially in the elderly.30,31

The longer period between an AVI and the HF diagnosis negatively affected survival in both the AS-HFrEF and AS-HFpEF patients, even after adjusting for age. Despite lacking data, we may assume that a possible explanation might...
Table 3  Adjusted Cox regression for time to all-cause and cardiovascular mortality for patients with AS-HFrEF or with AS-HFpEF vs. their matched controls, including interaction with AS-HFrEF/AS-HFpEF

| Outcome variable | Model | Value | AS-HFrEF | | | AS-HFpEF | | |
|------------------|-------|-------|---------|---|---|---------|---|---|
|                   |       |       | N  | n (%) events | HR (95% CI) | p-value | Proportional hazard assumption | P-value |       | N  | n (%) events | HR (95% CI) | p-value | Proportional hazard assumption | P-value | P-value for interaction |
| All-cause mortality | Model 1 | AS patients | 1076 | 120 (44.6%) | 1.10 (0.89–1.35) | 0.38 | 0.67 | | | 672 | 94 (56.0%) | 1.24 (0.98–1.57) | 0.077 | 0.010 | 0.46 |
|                   |       | Matched HF controls without AS | 341 | 42.3% | | | | | | | 245 | 48.6% | | | | |
|                   | Model 2 | AS patients | 1056 | 120 (45.1%) | 0.92 (0.74–1.15) | 0.48 | 0.92 | | | 661 | 93 (56.0%) | 1.12 (0.87–1.44) | 0.37 | 0.0070 | 0.53 |
|                   |       | Matched HF controls without AS | 337 | 42.7% | | | | | | | 241 | 48.7% | | | | |
|                   | Model 3 | AS patients | 1056 | 120 (45.1%) | 0.97 (0.78–1.20) | 0.76 | 0.75 | | | 661 | 93 (56.0%) | 1.12 (0.88–1.44) | 0.36 | 0.0055 | 0.69 |
|                   |       | Matched HF controls without AS | 337 | 42.7% | | | | | | | 241 | 48.7% | | | | |
| CV mortality      | Model 1 | AS patients | 1076 | 72 (26.8%) | 1.08 (0.83–1.42) | 0.56 | 0.46 | | | 672 | 50 (29.8%) | 1.15 (0.83–1.59) | 0.40 | 0.035 | 0.80 |
|                   |       | Matched HF controls without AS | 207 | 25.7% | | | | | | | 142 | 28.2% | | | | |
|                   | Model 2 | AS patients | 1056 | 72 (27.1%) | 0.95 (0.71–1.25) | 0.69 | 0.66 | | | 661 | 50 (30.1%) | 1.03 (0.74–1.44) | 0.85 | 0.034 | 0.93 |
|                   |       | Matched HF controls without AS | 204 | 25.8% | | | | | | | 141 | 28.5% | | | | |
|                   | Model 3 | AS patients | 1056 | 72 (27.1%) | 0.95 (0.72–1.26) | 0.74 | 0.59 | | | 661 | 50 (30.1%) | 1.01 (0.72–1.41) | 0.96 | 0.028 | 0.98 |
|                   |       | Matched HF controls without AS | 204 | 25.8% | | | | | | | 141 | 28.5% | | | | |

Model 1: adjusting for age at index and sex.
Model 2: model 1 with the addition of adjusting for age at HF diagnosis, smoking, mean arterial pressure, haemoglobin, eGFR categories, AF, stroke/TIA, renal disease and peripheral vascular disease.
Model 3: model 2, with the addition of adjusting for hypertension, diabetes and lung disease.
be a delay in diagnosing HF after AVI, as some of these patients might be considered as ‘cured’ and not followed after AVI. Another possibility is that more and more patients receive biological valves, and these valves have a higher predisposition to deteriorating compared with mechanical valves, directly proportional to time.

The AS-HFpEF and AS-HFrEF patients had roughly similar prognostic factors influencing the prognosis negatively. Diabetes mellitus was significantly different in predicting worse survival in the AS-HFrEF patients, but not in the patients with HFpEF. One explanation may be that patients with diabetes and HFrEF usually have a dismal prognosis caused by the associated CAD. Diabetes increases the risk of developing HF and may lead to diabetes cardiomyopathy, with myocardial fibrosis as an important driver of outcome. Diabetes also leads to LV hypertrophy, microangiopathy and extracellular volume expansion. Some of these changes are similar to those induced by AS. In patients with LVEF < 50% they seem to strengthen each other, leading to worse survival.

**Limitations**

This study was designed to focus on only the incident HF population after an AVI. Thus, the study results are not generalizable to all patients with HF caused by valvular disease. Furthermore, patients with severe AS who refused intervention or were considered an unacceptable risk even for a TAVI were not included in our study. Moreover, we cannot be sure that AS was the only aetiology of HF in our patient cohort. CAD is an important HF aetiology. However, it is difficult to draw any conclusions concerning CAD as HF aetiology in our study, due to 3 reasons: (1) The sample size of either AS-HFrEF or AS-HFpEF is too small to make further analysis; (2) because CABG was pre-specified as one of exclusions, it makes studying CAD as HF aetiology difficult; and (3) as no difference in PCI between AS-HF and matched HF without AS, the possible impact of CAD on HF outcome cannot be properly investigated in our study.

The nature of registry studies is that diagnosis is based solely on ICD codes, with limited potential for validation. Furthermore, the registries that we used in this study did not contain data concerning clinical status (symptoms, NYHA class), laboratory analyses, ECG, echocardiographic data from the time point for SAVR/TAVI or, if the surgery was urgent or not, information required to calculate STS score or EUROSCORE II. Therefore, we could not include these scores in our analyses and could not specify if the patients were symptomatic or in what NYHA class they were at the time of the AVI.

In addition, a major limitation of this study is the lack of echocardiographic data concerning validation of AS diagnosis, its severity or aetiology or consequences of AS on the LV morphology or function. Moreover, the data about the extension of CAD in these patients were lacking. Therefore, we could not include all these parameters in our analyses. Another limitation is that the group of patients who underwent TAVI was too small to be characterized and analysed separately.

**Conclusion**

In this nationwide SwedeHF registry study, we characterized an incident HF population after AVI. Our findings show similar all-cause and CV mortality between the incident HF and general HF population of other aetiologies. We also observed that patients in this incident HF population have virtually the same risk profile across the spectrum of HF phenotypes.

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**Conflict of interest**

Silvana Kontogeorgos, Erik Thunström, Aldina Pivodic, Ulf Dahlström and Michael Fu declare that they have no conflict of interest related to the present work. Dr Dahlström reports grants from AstraZeneca, Pfizer, Vifor, Boehringer Ingelheim, Boston Scientific and Roche Diagnostics and consultancies/honorariums from AstraZeneca, Amgen and Novartis outside the present work.

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**Supporting information**

Additional supporting information may be found online in the Supporting Information section at the end of the article.

**Table S1.** The ICD 10 codes used to identify comorbidities.
Table S2. Baseline characteristics of patients with incident HF after AVI and their matched controls.

Table S3. Age- and sex- adjusted Cox proportional hazards models for predictive factors analyses of all-cause mortality for AS-HFrEF and AS-HFpEF patients and interaction effect of the predictive factors with respective group.

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