Journal of the American Heart Association

ORIGINAL RESEARCH

Cause of Death After Surgical Aortic Valve Replacement: SWEDEHEART Observational Study

Natalie Glaser, MD, PhD; Michael Persson, MD; Anders Franco-Cereceda, MD, PhD; Ulrik Sartipy, MD, PhD

BACKGROUND: Prior studies showed that life expectancy in patients who underwent surgical aortic valve replacement (AVR) was lower than in the general population. Explanations for this shorter life expectancy are unknown. The aim of this nationwide, observational cohort study was to investigate the cause-specific death following surgical AVR.

METHODS AND RESULTS: We included 33 018 patients who underwent primary surgical AVR in Sweden between 1997 and 2018, with or without coronary artery bypass grafting. The SWEDEHEART (Swedish Web-System for Enhancement and Development of Evidence-Based Care in Heart Disease Evaluated According to Recommended Therapies) register and other national health-data registers were used to obtain and characterize the study cohort and to identify causes of death, categorized as cardiovascular mortality, cancer mortality, or other causes of death. The relative risks for cause-specific mortality in patients who underwent AVR compared with the general population are presented as standardized mortality ratios. During a mean follow-up period of 7.3 years (maximum 22.0 years), 14 237 (43%) patients died. The cumulative incidence of death from cardiovascular, cancer-related, or other causes was 23.5%, 8.3%, and 11.6%, respectively, at 10 years, and 42.8%, 12.8%, and 23.8%, respectively, at 20 years. Standardized mortality ratios for cardiovascular, cancer-related, and other causes of death were 1.79 (95% CI, 1.75–1.83), 1.00 (95% CI, 0.97–1.04), and 1.08 (95% CI, 1.05–1.12), respectively.

CONCLUSIONS: We found that life expectancy following AVR was lower than in the general population. Lower survival after AVR was explained by an increased relative risk of cardiovascular death. Future studies should focus on the role of earlier surgery in patients with asymptomatic aortic stenosis and on optimizing treatment and follow-up after AVR.

REGISTRATION: URL: https://www.clinicaltrials.gov; Unique identifier: NCT02276950.

Key Words: aortic valve replacement ■ cardiac surgery ■ cause of death ■ life expectancy

Prior studies showed that life expectancy in those who underwent surgical aortic valve replacement (AVR) was lower than in the general population, and loss in life expectancy was more pronounced in younger patients.[1] However, explanations for this shorter life expectancy are unknown. Some studies reported causes of death after transcatheter AVR,[2,3] although there is a paucity of literature on causes of death in contemporary surgical AVR populations, particularly with comparisons with the general population.

According to current guidelines, only symptomatic patients, or those with reduced left ventricular function secondary to their aortic valve disease, have a class I indication for surgery.[4,5] However, recent studies showed that asymptomatic patients may benefit from early surgery, and the optimal timing for AVR has been debated.[6–9] Severe valve disease results in gradual and irreversible myocardial damage.[10] Valve replacement before occurrence of symptoms and myocardial injury may improve long-term outcomes. To gain

Correspondence to: Natalie Glaser, MD, PhD, Department of Cardiology, Stockholm South General Hospital, Sjukhusbacken 10, SE-118 83 Stockholm, Sweden. E-mail: Natalie.Glaser@ki.se

Supplementary Material for this article is available at https://www.ahajournals.org/doi/suppl/10.1161/JAHA.121.022627

For Sources of Funding and Disclosures, see pages 9 and 10.

JAHA is available at: www.ahajournals.org/journal/jaha

CLINICAL PERSPECTIVE

What Is New?

- Life expectancy in patients who underwent surgical aortic valve replacement was lower than in the general population.
- Reduced life expectancy after aortic valve replacement was explained by an increased risk of cardiovascular death.
- Compared with the general population, the risk of death from cardiovascular causes was higher in younger age groups.

What Are the Clinical Implications?

- The increased relative risk of cardiovascular death can hypothetically be reduced by earlier surgery.
- Suboptimal postoperative follow-up is another potential explanation for the shorter life expectancy, which may result in delayed diagnosis of complications.
- Future research should focus on the role of earlier surgery in patients with aortic stenosis and on optimizing treatment and follow-up after aortic valve replacement.

Nonstandard Abbreviation and Acronym

AVR	aortic valve replacement

further insights into this hypothesis, it is necessary to determine if death from cardiovascular causes is a factor that contributes to shorter life expectancy following AVR. Therefore, we performed a population-based, nationwide, observational cohort study to investigate causes of death following surgical AVR. The relative risks for different causes of death after AVR were estimated by comparisons with cause-specific death rates from the general Swedish population.

METHODS

Study Design

This was an observational, register-based, nationwide, population-based cohort study. All data and supporting materials have been provided with the published article. The reporting follows the Strengthening the Reporting of Observational Studies in Epidemiology and the Reporting of Studies Conducted using Observational Routinely Collected Health Data guidelines for observational studies using routinely collected data.[11,12] This study complies with the Declaration of Helsinki. The Swedish Ethical Review Authority approved this study and the requirement for informed consent was waived (Dnr: 2020-04967).

Setting

We included all patients who underwent surgical AVR in Sweden between January 1, 1997 and December 31, 2018. Follow-up ended on December 31, 2018.

Data Sources

The study cohort and baseline characteristics were obtained from the SWEDEHEART (Swedish Web-System for Enhancement and Development of Evidence-Based Care in Heart Disease Evaluated According to Recommended Therapies) register.[13,14] The National Patient Register[15] and the longitudinal integration database for health insurance and labor market studies (maintained by Statistics Sweden)[16] were used to obtain additional baseline characteristics. Cause of death, vital status, and date of death were retrieved from the Swedish Cause of Death register.[17] The international version of the *International Classification of Diseases* (*ICD*) codes has been used for classification of causes of death since 1997. The Cause of Death register is updated annually and includes information from all death certificates issued in Sweden since 1961. Therefore, follow-up for the primary outcome was complete. Data from the national registers were able to be individually cross-linked because of the unique 12-digit personal identity number system used in Sweden.[18] The national registers used in this study have been described previously.[19]

Study Population and Exposure

We included all patients who underwent surgical AVR in Sweden between January 1, 1997 and December 31, 2018. Patients with concomitant coronary artery bypass grafting and those who underwent surgery of the ascending aorta and/or arrhythmia surgery were included, although patients who required concomitant procedures of other valves, prior cardiac surgery, or emergent surgery or had active endocarditis were excluded.

Outcome

The outcome of this study was cause-specific death retrieved from the Swedish Cause of Death register.[17] Cause of death was categorized as cardiovascular mortality, cancer mortality, or other causes of death according to the corresponding *ICD* codes (Table S1).

Statistical Analysis

Baseline characteristics are presented as mean and SD (continuous variables) and as number and percentage (categorical variables). The relative risks for all-cause

Table 1. Baseline Characteristics in 33 108 Patients Who Underwent Aortic Valve Replacement in Sweden Between 1997 and 2018 According to Cause of Death

	All patients n=33 108 (100%)	Alive n=18 781 (57%)	Cardiovascular death n=7778 (24%)	Cancer death n=2483 (8%)	Other death n=3976 (12%)
Age, y, mean (SD)	68.9 (12)	65.4 (12)	73.8 (8.3)	72.5 (8.1)	73.5 (8.8)
Female sex	12 141 (37)	6295 (34)	3302 (43)	852 (34)	1692 (43)
Civil status					
Not married or cohabiting	20 451 (62)	11 642 (62)	4733 (61)	1638 (66)	2438 (61)
Education					
<10 y	14 313 (44)	6587 (35)	4286 (56)	1275 (52)	2165 (56)
10–12 y	12 302 (38)	7808 (42)	2430 (32)	841 (34)	1223 (31)
>12 y	6008 (18)	4239 (23)	933 (12)	335 (14)	501 (13)
Region of birth					
Non-Nordic countries	1969 (6.0)	1340 (7.1)	324 (4.2)	110 (4.4)	195 (4.9)
Body mass index (kg/cm^2)					
<18.5	323 (1.1)	133 (0.8)	99 (1.5)	25 (1.2)	66 (1.9)
18.5–25	10 342 (35.2)	5629 (32.7)	2519 (38.3)	858 (39.5)	1336 (39.3)
>25	18 681 (63.7)	11 438 (66.5)	3960 (60.2)	1289 (59.3)	1994 (58.7)
Household disposable income					
Q1 (lowest)	8253 (25)	2823 (15)	3091 (40)	796 (32)	1543 (39)
Q2	8253 (25)	3987 (21)	2315 (30)	750 (30)	1201 (30)
Q3	8253 (25)	5347 (29)	1531 (20)	571 (23)	804 (20)
Q4 (highest)	8252 (25)	6622 (35)	839 (11)	366 (15)	425 (11)
Cardiac implantable electronic device	710 (2.2)	353 (1.9)	223 (2.9)	44 (1.8)	90 (2.3)
Diabetes	5934 (18)	3009 (16)	1547 (20)	405 (16)	973 (25)
Atrial fibrillation	5628 (17)	2551 (14)	1848 (24)	423 (17)	806 (20)
Hypertension	14 144 (43)	9153 (49)	2765 (36)	846 (34)	1380 (35)
Hyperlipidemia	5689 (17)	3856 (21)	1006 (13)	297 (12)	530 (13)
Stroke	3190 (9.7)	1606 (8.6)	938 (12)	234 (9.4)	412 (10)
Peripheral vascular disease	4819 (15)	3082 (16)	1015 (13)	279 (11)	443 (11)
Chronic pulmonary disease	2908 (8.8)	1462 (7.8)	743 (9.6)	243 (9.8)	460 (12)
Prior myocardial infarction	4721 (14)	2077 (11)	1551 (20)	404 (16)	689 (17)
Prior percutaneous coronary intervention	2575 (7.8)	1426 (7.6)	651 (8.4)	187 (7.5)	311 (7.8)
Prior major bleeding event	2211 (6.7)	1133 (6.0)	538 (6.9)	208 (8.4)	332 (8.4)
Alcohol dependency	723 (2.2)	414 (2.2)	150 (1.9)	56 (2.3)	103 (2.6)
Liver disease	375 (1.1)	182 (1.0)	100 (1.3)	24 (1.0)	69 (1.7)
Cancer	4122 (13)	2315 (12)	819 (11)	538 (22)	450 (11)
Estimated glomerular filtration rate (mL/min per 1.73 m^2)					
>60	22 057 (73)	14 873 (82)	3716 (56)	1457 (67)	2011 (58)
45–60	5565 (18)	2344 (13)	1844 (28)	506 (23)	871 (25)
30–44	2177 (7.2)	707 (3.9)	857 (13)	191 (8.7)	422 (12)
<30	553 (1.8)	138 (0.8)	229 (3.4)	31 (1.4)	155 (4.5)
Dialysis	264 (0.9)	134 (0.8)	64 (1.0)	8 (0.4)	58 (1.7)
Heart failure	6942 (21)	2840 (15)	2427 (31)	570 (23)	1105 (28)
Left ventricular ejection fraction (%)					
>50	18 350 (74)	13025 (77)	2695 (63)	1069 (70)	1561 (68)
30–49	5431 (22)	3243 (19)	1230 (29)	373 (25)	585 (26)
<30	1195 (4.8)	650 (3.8)	328 (7.7)	77 (5.1)	140 (6.1)
Biological valve prosthesis	22 179 (67)	11 947 (64)	5588 (72)	1735 (70)	2909 (73)

(*Continued*)

Table 1. Continued

	All patients n=33 108 (100%)	Alive n=18 781 (57%)	Cardiovascular death n=7778 (24%)	Cancer death n=2483 (8%)	Other death n=3976 (12%)
Isolated aortic valve replacement	17 243 (52)	10 595 (56)	3444 (44)	1207 (49)	1997 (50)
Concomitant coronary artery bypass grafting	11 808 (36)	5069 (27)	3862 (50)	1107 (45)	1770 (45)
Concomitant surgery of the ascending aorta	4807 (15)	3613 (19)	682 (8.8)	221 (8.9)	291 (7.3)
Year of surgery					
1997–2002	8205 (25)	1817 (9.7)	3641 (47)	992 (40)	1755 (44)
2003–2008	8610 (26)	3831 (20)	2558 (33)	877 (35)	1344 (34)
2009–2013	8261 (25)	5802 (31)	1224 (16)	504 (20)	731 (18)
2014–2018	7942 (24)	7331 (39)	355 (4.6)	110 (4.4)	146 (3.7)

Data are n (%) unless otherwise noted.

and cause-specific mortality in patients who underwent AVR compared with the general population are presented as standardized mortality ratios, and stratified according to sex and age at surgery. Standardized mortality ratios and corresponding 95% CIs were calculated as the ratio of the observed number of deaths in the study population to the expected number of deaths in an age-, sex-, and calendar-year matched Swedish population obtained from the publicly available statistical database provided by the Swedish National Board of Health and Welfare.[20] A standardized mortality ratio over 1.0 indicates that there were more deaths (excess deaths) in the study population than expected. The cause-specific cumulative incidences of cardiovascular, cancer-related, and other causes of death were obtained from flexible parametric survival models.[21] The competing risk of death from other causes was accounted for in the models. The follow-up time for each patient was counted from the date of AVR until the date of death or end of follow-up (December 31, 2018). All analyses were repeated excluding patients who died during the first 90 postoperative days. Data management and statistical analyses were performed using R programming language version 4.0.3 (R Foundation for Statistical Computing, Vienna, Austria) and Stata version 16.1 (Stata Corp LP, College Station, TX, USA) and included use of the *stpm2cr* command.[21]

RESULTS

We included 33 018 patients who underwent primary surgical AVR in Sweden between 1997 and 2018. The number of operations per year is shown in Figure S1 and the baseline characteristics according to vital status and cause of death are shown in Table 1. In the total study population, mean age was 68.9 years and 12 141 (37%) patients were women. Patients who died from cardiovascular causes had increased incidence of ischemic heart disease (prior myocardial infarction and prior coronary artery bypass grafting), atrial fibrillation, and stroke compared with patients who were alive or who died from cancer-related or other causes.

Cause-Specific Risk of Death According to Follow-up Time, Sex, and Age

During a mean follow-up time of 7.3 years (maximum 22.0 years), and a total follow-up time of 242 068 patient-years, 14 237 (43%) patients who underwent AVR died. Among them, 7778 (24%), 2483 (8%), and 3976 (12%) patients died because of cardiovascular, cancer-related, and other causes, respectively, and 30-day all-cause mortality was 2.7%. The cumulative incidence of death from cardiovascular, cancer-related, and other causes was 23.5%, 8.3%, and 11.6%, respectively, at 10 years and 42.8%, 12.8%, and 23.8%, respectively, at 20 years. The crude probability of death at 5, 10, 15, and 20 years after surgery according to cause of death, stratified by sex and age groups is shown in Table 2 and Figure S2 and S3, and stratified by valve type and surgical procedure in Figure S4 and Table S2. The probability of death according to different causes of death is shown in Figure 1, and the probability of death according to different causes of death, stratified by sex and age groups is shown in Figure 2.

Relative Risk of Cause-Specific Death

Standardized mortality ratios for cardiovascular, cancer-related, and other causes of death were 1.79 (95% CI, 1.75–1.83), 1.00 (95% CI, 0.97–1.04), and 1.08 (95% CI, 1.05–1.12), respectively. In other words, the relative risks of cardiovascular and other causes of death were significantly higher in patients who underwent surgical AVR than in the general population. The relative risk of cardiovascular death was higher in younger patients. In patients aged 35 to 39 years, the standardized mortality ratio was 51.9 (95% CI, 27.9–96.4) compared with 1.27 (95% CI, 1.22–1.32)

Table 2. Crude Probability of Death at 5, 10, 15, and 20 Years After Surgery According to Cause of Death by Age Group and Sex in 33 108 Patients Who Underwent Aortic Valve Replacement in Sweden Between 1997 and 2018

	Cardiovascular death, % (95% CI)	Cancer death, % (95% CI)	Other death, % (95% CI)
5 y after surgery			
Total population	10.2% (9.9%–10.5%)	3.8% (3.6%–4.0%)	4.3% (4.1%–4.5%)
Sex			
Men	9.5% (9.1%–9.8%)	4.0% (3.8%–4.3%)	4.0% (3.8%–4.2%)
Women	11.4% (10.9%–11.9%)	3.4% (3.1%–3.7%)	4.8% (4.5%–5.1%)
Age groups, y			
<50	1.8% (1.4%–2.1%)	0.6% (0.4%–0.8%)	1.0% (0.8%–1.3%)
50–59	4.2% (3.8%–4.6%)	1.9% (1.6%–2.2%)	1.8% (1.5%–20.1%)
60–69	7.2% (6.8%–7.6%)	3.8% (3.5%–4.2%)	3.2% (2.9%–3.4%)
70–79	12.7% (12.2%–13.1%)	4.8% (4.4%–5.1%)	5.2% (4.8%–5.5%)
>80	15.8% (15.0%–16.5%)	3.8% (3.4%–4.1%)	5.3% (4.9%–5.7%)
10 y after surgery			
Total population	23.5% (23.0%–24.0%)	8.3% (7.9%–8.6%)	11.6% (11.2%–12.0%)
Sex			
Men	21.9% (21.3%–22.5%)	8.8% (8.3%–9.2%)	10.8% (10.4%–11.3%)
Women	26.0% (25.2%–26.8%)	7.4% (6.9%–7.9%)	12.9% (12.3%–13.5%)
Age groups, y			
<50	4.4% (3.6%–5.3%)	1.3% (0.8%–1.8%)	3.0% (2.3%–3.7%)
50–59	10.2% (9.3%–11.2%)	4.1% (3.5%–4.8%)	5.1% (4.4%–5.8%)
60–69	17.2% (16.4%–18.1%)	8.2% (7.6%–8.9%)	9.0% (8.4%–9.7%)
70–79	29.0% (28.2%–29.8%)	10.3% (9.7%–10.8%)	14.4% (13.8%–15.1%)
>80	35.4% (34.1%–36.7%)	8.2% (7.4%–8.9%)	14.8% (13.8%–15.7%)
15 y after surgery			
Total population	34.9% (34.3%–35.6%)	11.0% (10.6%–11.4%)	18.8% (18.2%–19.3%)
Sex			
Men	32.7% (31.9%–33.5%)	11.6% (11.1%–12.2%)	17.6% (16.9%–18.2%)
Women	38.4% (37.4%–39.4%)	9.9% (9.3%–10.5%)	20.7% (19.8%–21.6%)
Age groups, y			
<50	7.1% (5.8%–8.3%)	1.8% (1.1%–2.5%)	5.0% (3.9%–6.1%)
50–59	15.9% (14.5%–17.3%)	5.6% (4.7%–6.4%)	8.5% (7.4%–9.6%)
60–69	25.9% (24.7%–27.1%)	11.0% (10.1%–11.8%)	14.6% (13.6%–15.5%)
70–79	42.0% (41.0%–43.0%)	13.6% (12.9%–14.3%)	22.9% (22.1%–23.8%)
>80	49.5% (47.9%–51.0%)	10.7% (9.8%–11.7%)	23.1% (21.8%–24.4%)
20 y after surgery			
Total population	42.8% (41.9%–43.7%)	12.8% (12.2%–13.3%)	23.8% (23.0%–24.5%)
Sex			
Men	40.3% (39.3%–41.3%)	13.6% (12.9%–14.2%)	22.2% (21.4%–23.1%)
Women	46.7% (45.4%–47.9%)	11.5% (10.8%–12.3%)	26.1% (25.0%–27.2%)
Age groups, y			
<50	9.2% (7.5%–10.8%)	2.1% (1.3%–2.9%)	6.5% (5.0%–7.9%)
50–59	20.3% (18.6%–22.1%)	6.5% (5.4%–7.5%)	10.9% (9.5%–12.3%)
60–69	32.3% (30.8%–33.7%)	12.6% (11.6%–13.6%)	18.4% (17.2%–19.7%)
70–79	50.7% (49.6%–51.9%)	15.6% (14.8%–16.4%)	28.5% (27.5%–29.6%)
>80	56.3% (54.8%–57.9%)	12.0% (11.0%–13.0%)	27.2% (25.7%–28.6%)

in patients >85 years old. The risk of death because of cancer was similar between those who underwent AVR and the general population. The risk of death from other causes was slightly higher in those who underwent AVR compared with the general population. The observed and expected deaths and standardized

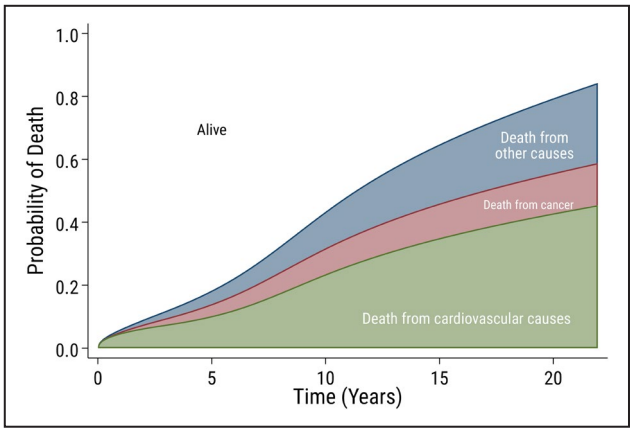


Figure 1. Crude probability of cause-specific death.
Crude probability of cause-specific death over time since surgery in 33 108 patients who underwent aortic valve replacement in Sweden between 1997 and 2018. The white area shows the probability of being alive.

mortality ratios according to cause of death, stratified by age group and sex are shown in Table 3, and stratified by valve type and surgical procedure is shown in Table S3. Standardized mortality ratios for cardiovascular deaths according to age group are shown in Figure 3. Men and women had similar relative risks for both all-cause mortality and cause-specific mortality (Table 3). However, in younger age groups, the relative risk of cardiovascular death was higher in women than in men (Table S4 and Figure S5). The relative risk of cardiovascular death was higher in patients with mechanical compared with biological valve prostheses and in patients with combined procedures compared with isolated AVR. However, the relative risks of cardiovascular death was significantly higher with both mechanical and biological valves and with isolated AVR and combined procedures compared with the general population. In a sensitivity analysis excluding all patients who died during the first 90 postoperative days, the standardized mortality ratio for all-cause, cardiovascular, cancer-related, and other causes of death was 1.25 (95% CI, 1.22–1.27), 1.56 (95% CI, 1.52–1.59), 1.00 (95% CI, 0.96–1.04), and 1.04 (95% CI, 1.01–1.08), respectively (Table S5).

DISCUSSION

This study confirmed our previous finding that life expectancy following AVR is lower than in the general population.[1] Lower survival after AVR was explained by an increased relative risk of cardiovascular death. Compared with the general population, the risk of death from cardiovascular causes was higher in younger age groups, particularly in women. The risks of death from cancer-related and other causes were similar to those in the general population.

McClure et al analyzed outcomes, including cause of death in 1701 consecutive patients aged <65 years who underwent surgical AVR between 1992 and 2011 and were followed-up for maximum 18 years.[22] They studied late outcomes in patients who received biological and mechanical valve prostheses and found that 27% of all deaths were cardiac related. The most common cardiac cause of death was cardiac arrest and/or myocardial infarction. However, the cause of death was unknown in 43% of cases, and as indicated by the authors, it was therefore likely the percentage of cardiac-related deaths was substantially higher than 27%. In the present study, the 15- and 20-year cumulative risk of cardiovascular death was 35% and 43%, respectively, and are likely consistent with the results reported by McClure et al[22] when considering the large proportion of unknown cause of death in their study and the older age in ours.

Another trial, performed by Hammermeister et al, which reported outcomes up to 16 years in 394 men who underwent AVR between 1977 and 1982, found that 58% of all deaths were either prosthesis or cardiac related.[23] These observations suggest the existence of even higher proportions of cardiovascular deaths than in our study, although the patients included in the study by Hammermeister et al underwent surgery up to 4 decades ago, partially with prostheses no longer on the market, which limits generalizability to contemporary patient populations.

Theut et al analyzed the cause of death in all 617 patients who underwent transcatheter AVR at Rigshospitalet, Denmark, between 2007 and 2014, and compared the results with an age- and sex-matched background population.[2] They found that cardiovascular deaths were more common in those who underwent transcatheter AVR compared with the general population during the first 90 postoperative days. After 90 days, an increased relative risk of death was present only in patients with low-flow aortic stenosis and in those with high preoperative risk. In the study by Theut et al, the mean age of the study population was 80 years, compared with 69 years in ours. The age difference may explain the discrepancy in results regarding cardiovascular deaths over the long term, because in contrast to younger patients, patients >80 years old have a life expectancy similar to that of the general population.[1] It is therefore plausible that older patients also have a relative risk of cardiovascular death similar to that of the general population.

Our study provides robust data on the causes of death following surgical AVR in a nationwide, contemporary cohort including over 33 000 patients with long-term follow-up. Furthermore, this study provides a reliable estimation of the relative risk of cause-specific death, which was possible because of the high quality of Swedish national registers.

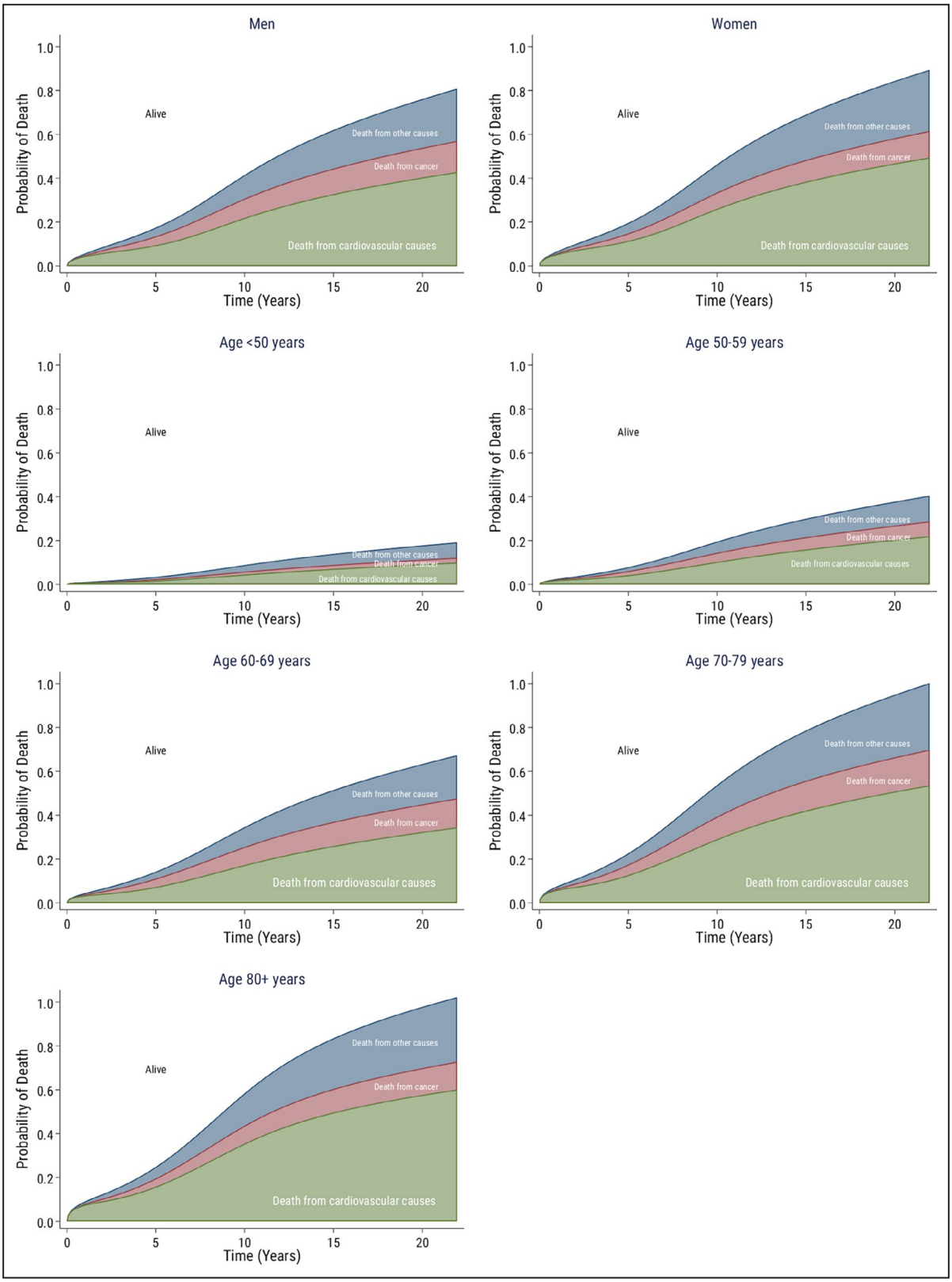


Figure 2. Crude probability of cause-specific death according to sex and age.
Crude probability of cause-specific death over time since surgery according to sex and age in 33 108 patients who underwent aortic valve replacement in Sweden between 1997 and 2018. The white area shows the probability of being alive.

Table 3. Observed and Expected Deaths and Standardized Mortality Ratios With 95% CIs for Different Causes of Deaths According to Sex and Age Groups in Patients Who Underwent Aortic Valve Replacement in Sweden Between 1997 and 2018

	All-cause mortality n=14 237 (100%)			Cardiovascular death n=7778 (%)			Cancer death n=2483 (%)			Other death n=3976 (%)		
	Observed	Expected	SMR (95% CI)	Observed	Expected	SMR (95% CI)	Observed	Expected	SMR (95% CI)	Observed	Expected	SMR (95% CI)
Total population	14 237	10 485.7	1.36 (1.34–1.38)	7778	4346.8	1.79 (1.75–1.83)	2483	2472.7	1.00 (0.97–1.04)	3976	3666.3	1.08 (1.05–1.12)
Sex												
Men	8391	6230.6	1.35 (1.32–1.38)	4476	2538.0	1.76 (1.71–1.82)	1631	1636.0	1.00 (0.95–1.05)	2284	2056.6	1.11 (1.07–1.16)
Women	5846	4255.1	1.37 (1.34–1.41)	3302	1808.8	1.83 (1.76–1.89)	852	836.7	1.02 (0.95–1.09)	1692	1609.7	1.05 (1.00–1.10)
Age groups, y												
20–24	0	0.25	…	0	0.01	…	0	0.02	…	0	0.22	…
25–29	3	0.54	5.59 (1.80–17.3)	1	0.03	32.58 (4.59–231)	0	0.05	…	2	0.46	4.39 (1.10–17.5)
30–34	8	0.90	8.88 (4.44–17.8)	3	0.06	46.69 (15.1–145)	0	0.12	…	5	0.71	7.01 (2.92–16.8)
35–39	20	1.7	11.66 (7.52–18.1)	10	0.2	51.88 (27.9–96.4)	2	0.3	5.82 (1.46–23.3)	8	1.2	6.79 (3.39–13.6)
40–44	23	3.9	5.90 (3.92–8.88)	13	0.7	19.52 (11.3–33.6)	2	0.9	2.11 (0.53–8.43)	8	2.3	3.50 (1.75–7.00)
45–49	54	9.4	5.73 (4.39–7.48)	28	2.1	13.50 (9.32–19.6)	7	2.6	2.66 (1.27–5.57)	19	4.7	4.03 (2.57–6.32)
50–54	89	24.1	3.69 (3.00–4.54)	52	6.0	8.61 (6.56–11.3)	10	7.9	1.27 (0.68–2.36)	27	10.2	2.64 (1.81–3.86)
55–59	215	64.7	3.32 (2.91–3.80)	128	18.0	7.11 (5.98–8.45)	37	24.3	1.52 (1.10–2.10)	50	22.4	2.23 (1.69–2.94)
60–64	428	169.2	2.53 (2.30–2.78)	228	49.5	4.60 (4.04–5.24)	96	68.8	1.40 (1.14–1.70)	104	50.9	2.05 (1.69–2.48)
65–69	837	389.7	2.15 (2.01–2.30)	452	119.6	3.78 (3.45–4.15)	187	161.0	1.16 (1.01–1.34)	198	109.9	1.81 (1.58–2.09)
70–74	1582	822.7	1.92 (1.83–2.02)	835	271.5	3.08 (2.87–3.29)	360	322.9	1.11 (1.01–1.24)	387	228.3	1.70 (1.53–1.87)
75–79	2499	1669.9	1.50 (1.44–1.56)	1404	617.0	2.28 (2.16–2.40)	525	550.0	0.95 (0.88–1.04)	570	503.0	1.13 (1.04–1.23)
80–84	3566	2743.8	1.30 (1.26–1.34)	1909	1127.3	1.69 (1.62–1.77)	685	687.2	1.00 (0.92–1.07)	972	929.3	1.05 (0.98–1.11)
85+	4913	4584.9	1.07 (1.04–1.10)	2715	2134.8	1.27 (1.22–1.32)	572	646.5	0.88 (0.82–0.96)	1626	1803.6	0.90 (0.86–0.95)

SMR indicates standardized mortality ratio.

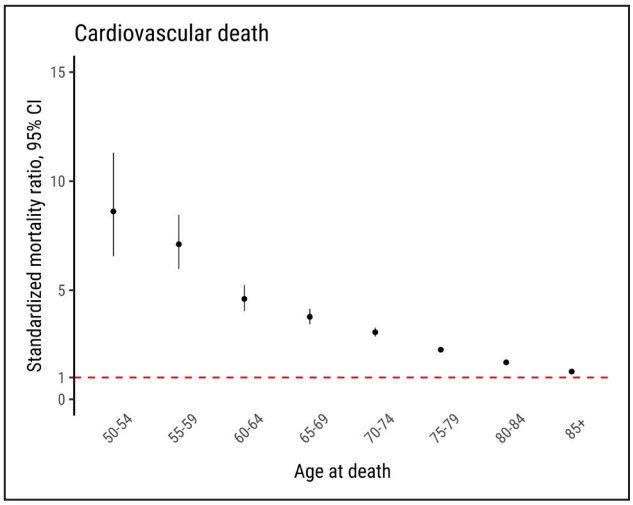


Figure 3. Relative risk for cardiovascular mortality.
Standardized mortality ratios with 95% CIs for cardiovascular cause of death according to age (in years) in patients who underwent aortic valve replacement in Sweden between 1997 and 2018. The red dashed line marks a standardized mortality ratio of 1, that is, no difference in the risk of cardiovascular mortality between the study population and the general population.

The risk of death from cardiovascular causes was almost twice as high after undergoing AVR compared with the reference population and explains the reduced life expectancy observed following AVR. Prosthetic aortic valves pose an inevitable risk of complications, both over the short and long term, although our results also raise questions concerning the optimal timing of surgery in patients with aortic valve disease.

It is possible that the patients in our study had already experienced irreversible myocardial damage before surgery.[24] In such cases, the increased relative risk of cardiovascular death can hypothetically be reduced by undergoing surgery earlier. Considering the higher relative risk of cardiovascular death in younger patients (especially in women), undergoing surgery earlier may be particularly important in this patient population. However, further research is needed to confirm this hypothesis and to analyze the reasons for the higher relative risk of cardiovascular death in younger women. Although this finding is highly interesting, it must be interpreted with caution owing to the limited number of events in women below 60 years.

Another potential explanation for shorter life expectancy and increased risk of cardiovascular death following AVR is therapeutic inertia; that is, failure to initiate or intensify therapy when treatment goals are not met.[25] Poor guideline implementation and failure to integrate new knowledge into clinical practice contribute to therapeutic inertia, although the problem is multifactorial and includes clinician, patient, health care system, and policy factors.[25] Within the context of AVR, suboptimal postoperative follow-up may include lack of structured follow-up with annual visits[5] and the fact that it may take longer than necessary before possible complications are diagnosed and treated. Optimizing follow-up after AVR remains an important area for future research.

Strengths and Limitations

We recognize that the quality of the cause of death register is dependent on the quality with which the physicians certify the cause of death. However, the limitations of the Swedish Cause of Death register have been well described, and the agreement between medical records and the death certificates for cardiovascular disease is almost 90%.[17] Notable strengths of our study include the nationwide and population-based design, long-term follow-up period, and large number of patients, which increase its generalizability. Additionally, because of the accuracy of Swedish health-data registries, data quality in this study was high and follow-up was complete. The cause-specific death rates in the study cohort were compared with an age-, sex-, and calendar-year matched general population. However, it remains possible that other patient characteristics differed between the study and general populations. Furthermore, although it is noteworthy that we examined mortality and causes of death, we did not examine other aspects of health following AVR, such as quality of life and the rate of reoperations and repeat hospitalizations.

CONCLUSIONS

We found that life expectancy in patients who underwent AVR was lower than in the general population. Lower survival after AVR was explained by an increased relative risk of cardiovascular death. Compared with the general population, the risk of death from cardiovascular causes was higher in younger age groups. Future studies should focus on the role of earlier surgery in patients with asymptomatic aortic stenosis and optimizing treatment and follow-up after AVR.

ARTICLE INFORMATION

Received July 7, 2021; accepted October 11, 2021.

Affiliations

Department of Cardiology, Stockholm South General Hospital, Stockholm, Sweden (N.G.); ; Department of Molecular Medicine and Surgery, Karolinska Institutet, Stockholm, Sweden (N.G., M.P., A.F., U.S.); and Department of Cardiothoracic Surgery, Karolinska University Hospital, Stockholm, Sweden (M.P., A.F., U.S.)..

Acknowledgments

We thank the SWEDEHEART steering committee for providing data for this study.

Sources of Funding

This work was supported by the Swedish Heart-Lung Foundation (grant number 20190570 to NG, and grant numbers 20160522, 20160525, and 20180400

to US); the Swedish Society of Medicine (grant number SLS-934749 to NG); a clinical postdoctoral appointment from Region Stockholm (grant number FoUI-955489 to NG), a regional ALF agreement between Stockholm County Council and the Karolinska Institutet (grant number FoUI-954783 to NG, and grant number 20180114 to US); Capio Research Foundation (grant number 2019-3239 to NG); Eva and Oscar Ahrén Research Foundation (to NG); the Seraphim Hospital Foundation (to NG); the Åke Wiberg Foundation (grant number M18-0016 to US); the Karolinska Institutet Foundations and Funds (grant number 2018-01784 to US); and a donation from Mr Fredrik Lundberg (to AFC).

Disclosures

None.

Supplementary Material

Tables S1–S5
Figures S1–S5

REFERENCES

1. Glaser N, Persson M, Jackson V, Holzmann MJ, Franco-Cereceda A, Sartipy U. Loss in life expectancy after surgical aortic valve replacement: SWEDEHEART study. *J Am Coll Cardiol*. 2019;74:26–33. doi: 10.1016/j.jacc.2019.04.053
2. Theut M, Thygesen JB, De Backer O, Sondergaard L. Survival and cause of death after transcatheter aortic valve replacement as compared to an age- and sex-matched background population. *EuroIntervention*. 2017;13:e1058–e1066. doi: 10.4244/EIJ-D-17-00147
3. Amrane H, Deeb GM, Popma JJ, Yakubov SJ, Gleason TG, Van Mieghem NM, Reardon MJ, Group STCoDW. Causes of death in intermediate-risk patients: the randomized surgical replacement and transcatheter aortic valve implantation trial. *J Thorac Cardiovasc Surg*. 2019;158:718–728.e3. doi: 10.1016/j.jtcvs.2018.11.129
4. Otto CM, Nishimura RA, Bonow RO, Carabello BA, Erwin JP III, Gentile F, Jneid H, Krieger EV, Mack M, McLeod C, et al. 2020 ACC/AHA guideline for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association joint committee on clinical practice guidelines. *Circulation*. 2021;143:e72–e227. doi: 10.1161/CIR.0000000000000923
5. Baumgartner H, Falk V, Bax JJ, De Bonis M, Hamm C, Holm PJ, Iung B, Lancellotti P, Lansac E, Rodriguez Munoz D, et al. 2017 ESC/EACTS guidelines for the management of valvular heart disease. *Eur Heart J*. 2017;38:2739–2791. doi: 10.1093/eurheartj/ehx391
6. Kang DH, Park SJ, Lee SA, Lee S, Kim DH, Kim HK, Yun SC, Hong GR, Song JM, Chung CH, et al. Early surgery or conservative care for asymptomatic aortic stenosis. *N Engl J Med*. 2020;382:111–119. doi: 10.1056/NEJMoa1912846
7. Durko AP, Kappetein AP. Long-term survival after surgical aortic valve replacement: expectations and reality. *J Am Coll Cardiol*. 2019;74:34–35. doi: 10.1016/j.jacc.2019.05.008
8. Baumgartner H, Iung B, Otto CM. Timing of intervention in asymptomatic patients with valvular heart disease. *Eur Heart J*. 2020;41:4349–4356. doi: 10.1093/eurheartj/ehaa485
9. Crea F. Challenges in risk stratification of symptomatic and asymptomatic valvular heart disease: lessons from large observational studies. *Eur Heart J*. 2020;41:4289–4292. doi: 10.1093/eurheartj/ehaa951
10. Everett RJ, Tastet L, Clavel MA, Chin CWL, Capoulade R, Vassiliou VS, Kwiecinski J, Gomez M, van Beek EJR, White AC, et al. Progression of hypertrophy and myocardial fibrosis in aortic stenosis: a multicenter cardiac magnetic resonance study. *Circ Cardiovasc Imaging*. 2018;11:e007451. doi: 10.1161/CIRCIMAGING.117.007451
11. Benchimol EI, Smeeth L, Guttmann A, Harron K, Moher D, Petersen I, Sorensen HT, von Elm E, Langan SM, Committee RW. The reporting of studies conducted using observational routinely-collected health data (RECORD) statement. *PLoS Medicine*. 2015;12:e1001885. doi: 10.1371/journal.pmed.1001885
12. von Elm E, Altman DG, Egger M, Pocock SJ, Gotzsche PC, Vandenbroucke JP, Initiative S. The strengthening the reporting of observational studies in epidemiology (STROBE) statement: guidelines for reporting observational studies. *J Clin Epidemiol*. 2008;61:344–349. doi: 10.1016/j.jclinepi.2007.11.008
13. Jernberg T, Attebring MF, Hambraeus K, Ivert T, James S, Jeppsson A, Lagerqvist B, Lindahl B, Stenestrand U, Wallentin L. The Swedish Web-system for enhancement and development of evidence-based care in heart disease evaluated according to recommended therapies (SWEDEHEART). *Heart*. 2010;96:1617–1621. doi: 10.1136/hrt.2010.198804
14. Vikholm P, Ivert T, Nilsson J, Holmgren A, Freter W, Ternstrom L, Ghaidan H, Sartipy U, Olsson C, Granfeldt H, et al. Validity of the Swedish cardiac surgery registry. *Interact Cardiovasc Thorac Surg*. 2018;27:67–74. doi: 10.1093/icvts/ivy030
15. Ludvigsson JF, Andersson E, Ekbom A, Feychting M, Kim JL, Reuterwall C, Heurgren M, Olausson PO. External review and validation of the Swedish national inpatient register. *BMC Public Health*. 2011;11:450. doi: 10.1186/1471-2458-11-450
16. Ludvigsson JF, Svedberg P, Olen O, Bruze G, Neovius M. The longitudinal integrated database for health insurance and labour market studies (LISA) and its use in medical research. *Eur J Epidemiol*. 2019;34:423–437. doi: 10.1007/s10654-019-00511-8
17. Brooke HL, Talback M, Hornblad J, Johansson LA, Ludvigsson JF, Druid H, Feychting M, Ljung R. The Swedish cause of death register. *Eur J Epidemiol*. 2017;32:765–773. doi: 10.1007/s10654-017-0316-1
18. Ludvigsson JF, Otterblad-Olausson P, Pettersson BU, Ekbom A. The Swedish personal identity number: possibilities and pitfalls in healthcare and medical research. *Eur J Epidemiol*. 2009;24:659–667. doi: 10.1007/s10654-009-9350-y
19. Glaser N, Jackson V, Holzmann MJ, Franco-Cereceda A, Sartipy U. Aortic valve replacement with mechanical vs. biological prostheses in patients aged 50–69 years. *Eur Heart J*. 2016;37:2658–2667. doi: 10.1093/eurheartj/ehv580
20. The statistical database from the Swedish national board of health and welfare. https://www.socialstyrelsen.se/en/statistics-and-data/statistics/statistical-databases/ Last accessed 12 October 2021
21. Mozumder SI, Rutherford MJ, Lambert PC. Stpm2cr: a flexible parametric competing risks model using a direct likelihood approach for the cause-specific cumulative incidence function. *Stata J*. 2017;17:462–489. doi: 10.1177/1536867X1701700212
22. McClure RS, McGurk S, Cevasco M, Maloney A, Gosev I, Wiegerinck EM, Salvio G, Tokmaji G, Borstlap W, Nauta F, et al. Late outcomes comparison of nonelderly patients with stented bioprosthetic and mechanical valves in the aortic position: a propensity-matched analysis. *J Thorac Cardiovasc Surg*. 2014;148:1931–1939. doi: 10.1016/j.jtcvs.2013.12.042
23. Hammermeister K, Sethi GK, Henderson WG, Grover FL, Oprian C, Rahimtoola SH. Outcomes 15 years after valve replacement with a mechanical versus a bioprosthetic valve: final report of the veterans affairs randomized trial. *J Am Coll Cardiol*. 2000;36:1152–1158. doi: 10.1016/S0735-1097(00)00834-2
24. Tastet L, Tribouilloy C, Marechaux S, Vollema EM, Delgado V, Salaun E, Shen M, Capoulade R, Clavel MA, Arsenault M, et al. Staging cardiac damage in patients with asymptomatic aortic valve stenosis. *J Am Coll Cardiol*. 2019;74:550–563. doi: 10.1016/j.jacc.2019.04.065
25. Dixon DL, Sharma G, Sandesara PB, Yang E, Braun LT, Mensah GA, Sperling LS, Deedwania PC, Virani SS. Therapeutic inertia in cardiovascular disease prevention: time to move the bar. *J Am Coll Cardiol*. 2019;74:1728–1731. doi: 10.1016/j.jacc.2019.08.014

Supplemental Material

Table S1. Definitions of causes of death. Only the underlying cause of death was used.

	ICD-10 (1997-)
Cardiovascular death	I00-I99
Cancer death	C00-C99, D00-D48
Other death	Remaining

ICD = International Statistical Classification of Diseases and Related Health Problems

Table S2. Crude probability of death at 5, 10, 15, and 20 years after surgery according to cause of death by valve type and surgical procedure in 33108 patients who underwent aortic valve replacement in Sweden between 1997 and 2018.

	Cardiovascular death, % (95% CI)	Cancer death, % (95% CI)	Other death, % (95% CI)
5 years after surgery			
Valve type			
Bioprosthesis	11.8% (11.4%-12.2%)	4.2% (4.0%-4.5%)	5.1% (4.8%-5.3%)
Mechanical	6.9% (6.6%-7.2%)	2.9% (2.7%-3.2%)	2.7% (2.5%-2.9%)
Procedure			
Isolated AVR	8.6% (8.2%-8.9%)	3.6% (3.3%-3.8%)	4.2% (4.0%-4.4%)
Combined	12.0% (11.5%-12.4%)	4.0% (3.8%-4.3%)	4.4% (4.1%-4.6%)
10 years after surgery			
Valve type			
Bioprosthesis	27.6% (26.9%-28.2%)	9.3% (8.9%-9.8%)	14.1% (13.6%-14.6%)
Mechanical	16.7% (16.1%-17.4%)	6.5% (6.0%-7.0%)	7.7% (7.2%-8.2%)
Procedure			
Isolated AVR	20.0% (19.4%-20.6%)	7.8% (7.4%-8.3%)	11.4% (10.9%-11.9%)
Combined	27.2% (26.5%-27.9%)	8.7% (8.2%-9.2%)	11.8% (11.3%-12.3%)
15 years after surgery			
Valve type			
Bioprosthesis	41.1% (40.3%-41.9%)	12.5% (11.9%-13.0%)	23.1% (22.3%-23.8%)
Mechanical	26.0% (25.1%-26.9%)	8.8% (8.2%-9.4%)	12.9% (12.2%-13.7%)

Procedure			
Isolated AVR	30.1% (29.3%-31.0%)	10.4% (9.8%-10.9%)	18.5% (17.7%-19.2%)
Combined	40.0% (39.0%-40.9%)	11.6% (11.0%-12.2%)	19.1% (18.3%-19.9%)
20 years after surgery			
Valve type			
Bioprosthesis	50.2% (49.2%-51.2%)	14.6% (13.9%-15.3%)	29.1% (28.1%-30.0%)
Mechanical	32.8% (31.6%-33.9%)	10.3% (9.6%-11.0%)	16.6% (15.7%-17.6%)
Procedure			
Isolated AVR	37.3% (36.2%-38.4%)	12.1% (11.4%-12.8%)	23.3% (22.4%-24.3%)
Combined	48.5% (47.3%-49.6%)	13.5% (12.7%-14.2%)	24.1% (23.1%-25.1%)

CI = confidence interval

Table S3. Observed and expected deaths and standardized mortality ratios with 95% confidence intervals for different causes of deaths according to valve type and surgical procedure in 33108 patients who underwent aortic valve replacement in Sweden between 1997 and 2018.

	All-Cause mortality n = 14 237 (100%)			Cardiovascular death n = 7778 (%)			Cancer death n = 2483 (%)			Other death n = 3976 (%)		
	Observed	Expected	SMR (95% CI)	Observed	Expected	SMR (95% CI)	Observed	Expected	SMR (95% CI)	Observed	Expected	SMR (95% CI)
Valve type												
Bioprosthesis	10232	8205.4	1.25 (1.22-1.27)	5588	3471.3	1.61 (1.57-1.65)	1735	1815.6	0.96 (0.91-1.00)	2909	2918.5	1.00 (0.96-1.03)
Mechanical	4005	2280.3	1.76 (1.70-1.81)	2190	875.5	2.50 (2.40-2.61)	748	657.1	1.14 (1.06-1.22)	1067	747.8	1.43 (1.34-1.52)
Procedure												
Isolated AVR	6648	5253.6	1.27 (1.24-1.30)	3444	2155.9	1.60 (1.55-1.65)	1207	1231.9	0.98 (0.93-1.04)	1997	1865.8	1.07 (1.02-1.12)
Combined	7589	5232.1	1.45 (1.42-1.48)	4334	2190.9	1.98 (1.92-2.04)	1276	1240.7	1.03 (0.97-1.09)	1979	1800.5	1.10 (1.05-1.15)

SMR = standardized mortality ratio, CI = confidence interval.

Table S4. Observed and expected deaths and standardized mortality ratios with 95% confidence intervals for cardiovascular cause of deaths according to sex and age groups in patients who underwent aortic valve replacement in Sweden between 1997 and 2018.

	Men n = 20967 (63%)			Women n = 12141 (37%)		
Age groups	Observed	Expected	SMR (95% CI)	Observed	Expected	SMR (95% CI)
20-24	0	0.01	-	0	0.00	-
25-29	1	0.03	37.4 (5.3-266)	0	0.00	-
30-34	1	0.06	17.7 (2.5-126)	2	0.01	258 (64.4-1030)
35-39	9	0.17	52.4 (27.3-101)	1	0.02	47.5 (6.7-337)
40-44	13	0.61	21.4 (12.4-36.8)	0	0.06	-
45-49	21	1.88	11.2 (7.3-17.1)	7	0.19	36.6 (17.5-76.9)
50-54	40	5.51	7.3 (5.3-9.9)	12	0.53	22.6 (12.8-39.8)
55-59	101	16.25	6.2 (5.1-7.6)	27	1.76	15.4 (10.5-22.4)
60-64	170	43.72	3.9 (3.3-4.5)	58	5.79	10.0 (7.7-12.9)
65-69	324	102.09	3.2 (2.8-3.5)	128	17.47	7.3 (6.2-8.7)
70-74	583	217.07	2.7 (2.5-2.9)	252	54.43	4.6 (4.1-5.2)
75-79	908	437.20	2.1 (1.9-2.2)	496	179.80	2.8 (2.5-3.0)
80-84	1069	690.64	1.5 (1.5-1.6)	840	436.62	1.9 (1.8-2.1)
85+	1236	1022.74	1.2 (1.1-1.3)	1479	1112.10	1.3 (1.3-1.4)

SMR = standardized mortality ratio, CI = confidence interval

Table S5. **Observed and expected deaths and standardized mortality ratios with 95% confidence intervals for different causes of deaths according to sex and age groups in patients who underwent aortic valve replacement in Sweden between 1997 and 2018. Patients who died within 90 days of surgery were excluded.**

	All-Cause mortality n=13060 (100%)			Cardiovascular death n=6764 (52%)			Cancer death n=2464 (19%)			Other death n=3829 (29%)		
	Observed	Expected	SMR (95% CI)	Observed	Expected	SMR (95% CI)	Observed	Expected	SMR (95%CI)	Observed	Expected	SMR (95%CI)
Total population	13060	10481.6	1.25 (1.22-1.27)	6764	4345.1	1.56 (1.52-1.59)	2467	2471.5	1.00 (0.96-1.04)	3829	3665.0	1.04 (1.01-1.08)
Sex												
Men	7715	6227.9	1.24 (1.21-1.27)	3892	2536.9	1.53 (1.49-1.58)	1625	1635.2	0.99 (0.95-1.04)	2198	2055.8	1.07 (1.03-1.11)
Women	5345	4253.8	1.26 (1.22-1.29)	2872	1808.2	1.59 (1.53-1.65)	842	836.3	1.01 (0.94-1.08)	1631	1609.2	1.01 (0.97-1.06)
Age groups												
20-24	0	0.25	-	0	0.01	-	0	0.02	-	0	0.22	-
25-29	3	0.54	5.59 (1.80-17.3)	1	0.03	32.59 (4.59-231)	0	0.05	-	2	0.46	4.39 (1.10-17.5)
30-34	5	0.90	5.55 (2.31-13.3)	1	0.06	15.57 (2.19-111)	0	0.12	-	4	0.71	5.61 (2.11-14.9)
35-39	17	1.7	9.92 (6.17-15.9)	7	0.2	36.3 (17.3-76.2)	2	0.3	5.82 (1.46-23.3)	8	1.2	6.79 (3.40-13.6)
40-44	17	3.9	4.36 (2.71-7.02)	9	0.7	13.52 (7.03-26.0)	2	0.9	2.11 (0.53-8.43)	6	2.3	2.63 (1.18-5.85)
45-49	37	9.4	3.93 (2.85-5.42)	14	2.1	6.75 (4.00-11.4)	7	2.6	2.66 (1.27-5.57)	16	4.7	3.39 (2.08-5.54)
50-54	64	24.1	2.66 (2.08-3.39)	28	6.0	4.64 (3.20-6.72)	10	7.9	1.27 (0.68-2.36)	26	10.2	2.55 (1.74-3.74)
55-59	174	64.7	2.69 (2.32-3.12)	91	18.0	5.06 (4.12-6.21)	36	24.3	1.48 (1.07-2.06)	47	22.4	2.10 (1.57-2.79)
60-64	365	169.1	2.16 (1.95-2.39)	173	49.5	3.50 (3.01-4.06)	96	68.8	1.40 (1.14-1.71)	96	50.8	1.89 (1.55-2.31)

65-69	713	389.5	1.83 (1.70-1.97)	345	119.5	2.89 (2.60-3.21)	185	160.9	1.15 (1.00-1.33)	183	109.0	1.68 (1.45-1.94)
70-74	1371	822.1	1.67 (1.58-1.76)	649	271.3	2.39 (2.21-2.58)	358	322.7	1.11 (1.00-1.23)	364	228.1	1.60 (1.44-1.77)
75-79	2134	1668.6	1.28 (1.23-1.33)	1093	616.5	1.77 (1.67-1.88)	518	549.5	0.94 (0.86-1.03)	523	502.6	1.04 (0.96-1.13)
80-84	3313	2742.6	1.21 (1.17-1.25)	1697	1126.7	1.51 (1.44-1.58)	681	686.9	0.99 (0.92-1.07)	935	928.9	1.01 (0.94-1.07)
85+	4847	4584.2	1.06 (1.03-1.09)	2656	2134.5	1.24 (1.20-1.29)	572	646.4	0.88 (0.82-0.96)	1619	1803.3	0.90 (0.86-0.94)

SMR = standardized mortality ratio, CI = confidence interval

Figure S1. Number of operations per year in Sweden from 1997 to 2018.

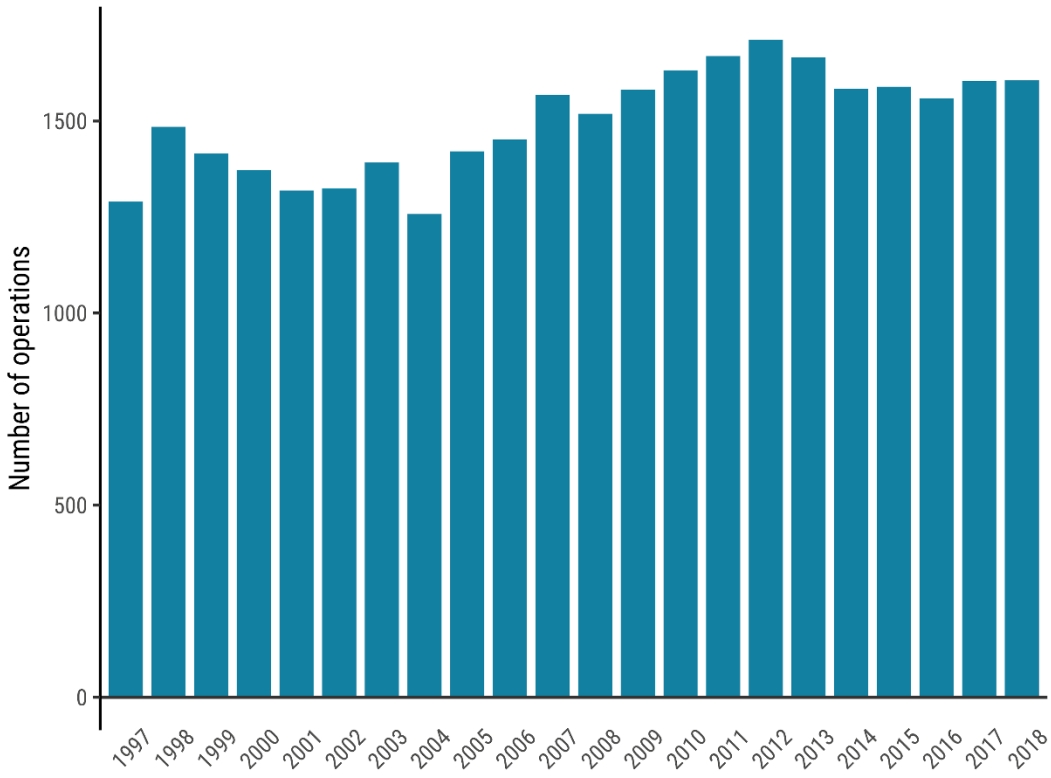
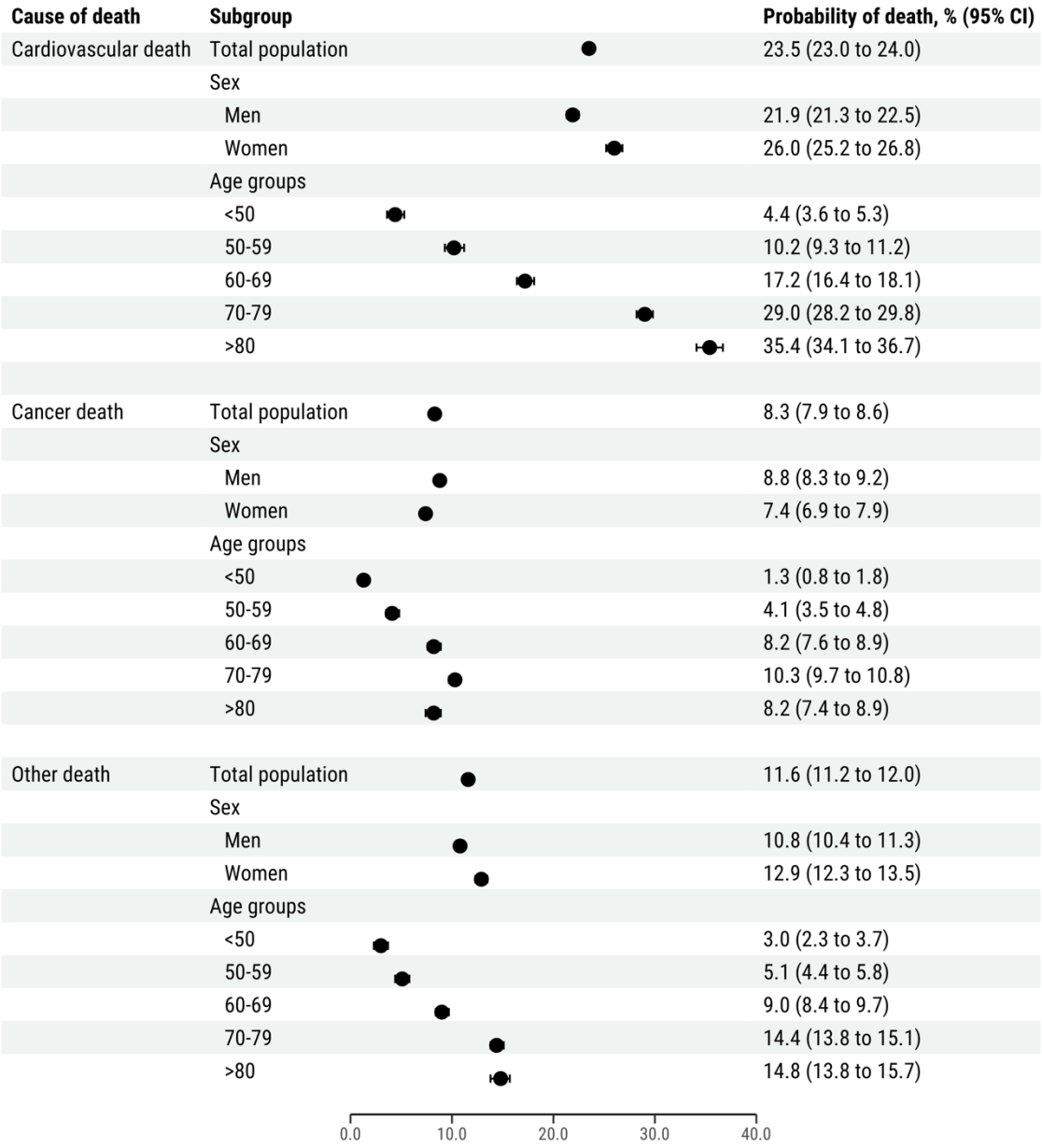
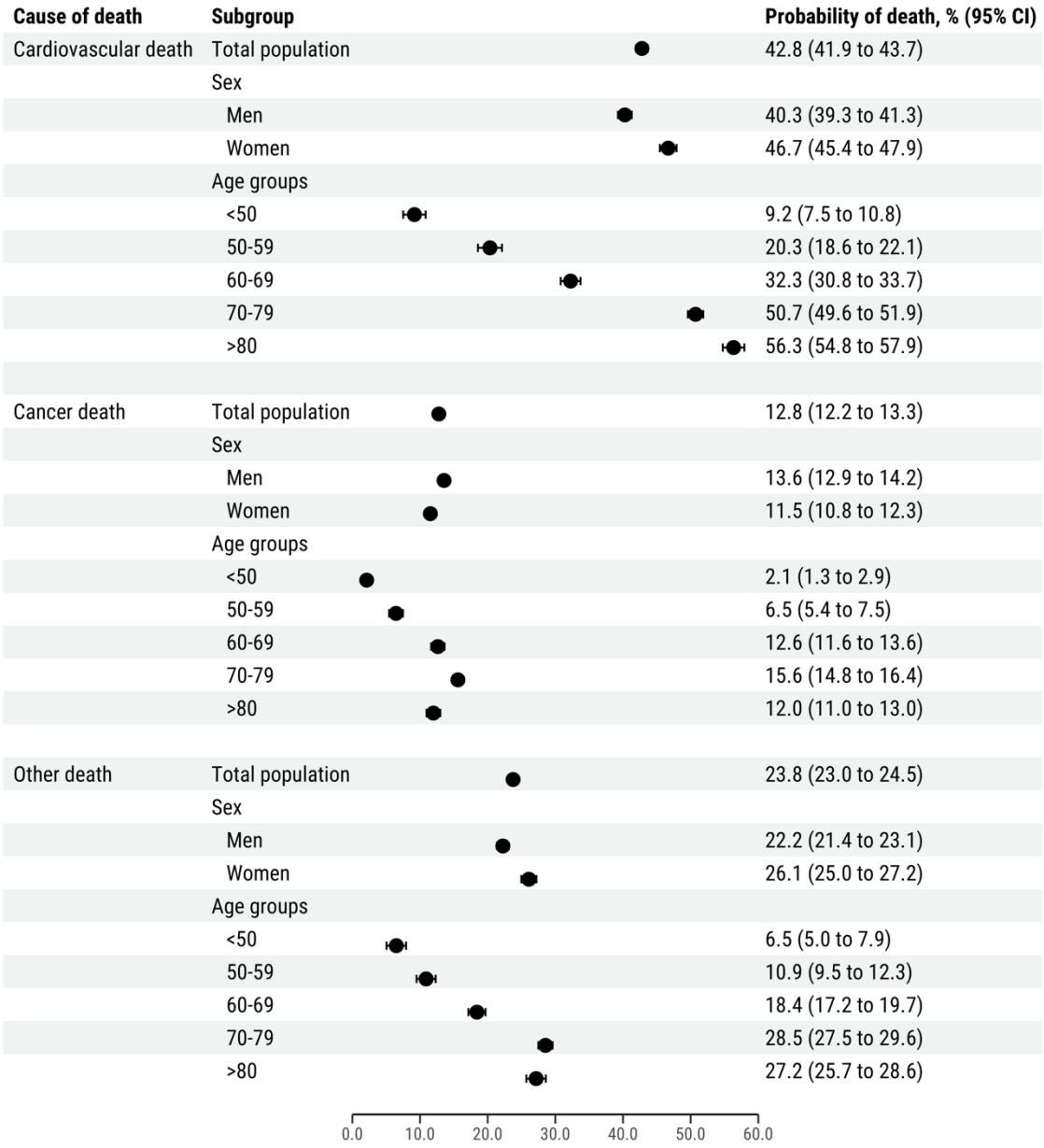


Figure S2. Crude probability of death at 10 years after surgery according to cause of death by age group and sex in 33108 patients who underwent aortic valve replacement in Sweden between 1997 and 2018.



CI = confidence interval

Figure S3. Crude probability of death at 20 years after surgery according to cause of death by age group and sex in 33108 patients who underwent aortic valve replacement in Sweden between 1997 and 2018.



CI = confidence interval

Figure S4. Crude probability of cause-specific death over time since surgery according to surgical procedure and valve type in 33108 patients who underwent aortic valve replacement in Sweden between 1997 and 2018. The white area shows the probability of being alive.

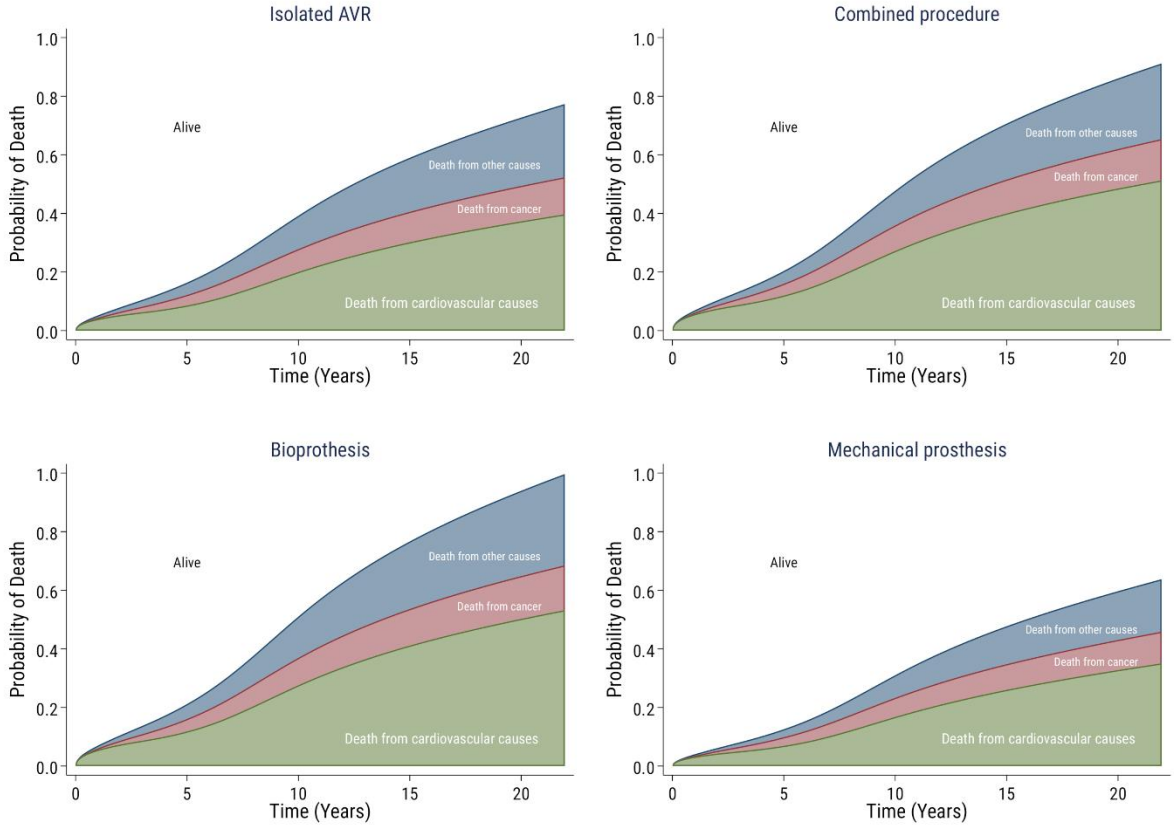
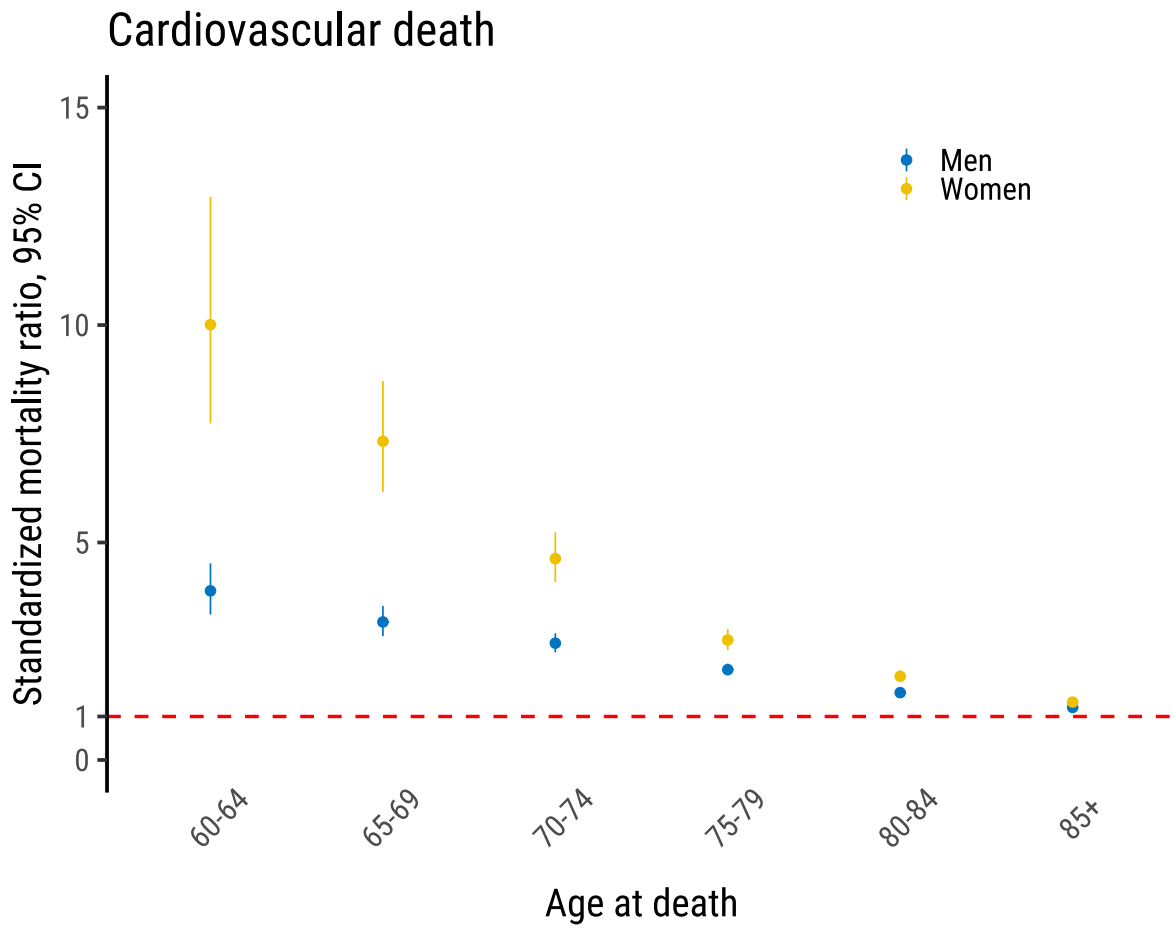


Figure S5. Standardized mortality ratios with 95% confidence intervals for cardiovascular cause of death according to sex and age groups in patients who underwent aortic valve replacement in Sweden between 1997 and 2018.



CI = confidence interval