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ORIGINAL ARTICLE

Mortality and morbidity after transcatheter aortic valve implantation compared to an age- and sex-matched control population: a population-based study from the SWEDEHEART registry

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Introduction Data are lacking about the risk for death and major adverse cardiovascular events (MACE) after transcatheter aortic valve implantation (TAVI), compared to the general population. Therefore, we assessed the risk for all-cause death and MACE after TAVI in patients aged 65 years and older, in comparison to an age- and sex-matched control population.

Methods and results In total, 5924 TAVI patients and 10 928 matched controls [mean age 82.1, standard deviation (SD) 6.0, and 81.9, SD 6.1, respectively] were included from 2014 to 2020. The SWEDEHEART registry and four mandatory national registers were used to collect data. Cox regression models were used to assess the association with all-cause mortality and MACE risk. In total, 1410 (23.8%) of the TAVI patients and 2115 (19.4%) controls died during the follow-up period. Median follow-up was 1.9 years (inter quartile range 0.9–3.3) respectively. The crude mortality and MACE risks were higher in TAVI patients than in controls {hazard ratios 1.27 [95% Confidence interval (CI): 1.19–1.36] and HR 1.44 (95% CI: 1.35–1.53), respectively}. After adjustment, there was a lower risk for both mortality and MACE in TAVI patients [adjusted hazard ratio (aHR) 0.77 (95% CI: 0.71–0.84) and aHR 0.90 (95% CI: 0.83–0.98), respectively].

Conclusion After adjustments for comorbidities, the mortality risk was lower in TAVI patients, compared with an age- and sex-matched control population. These findings suggest that the high burden of comorbidities in TAVI patients has a strong impact on the risk for mortality and MACE after TAVI.

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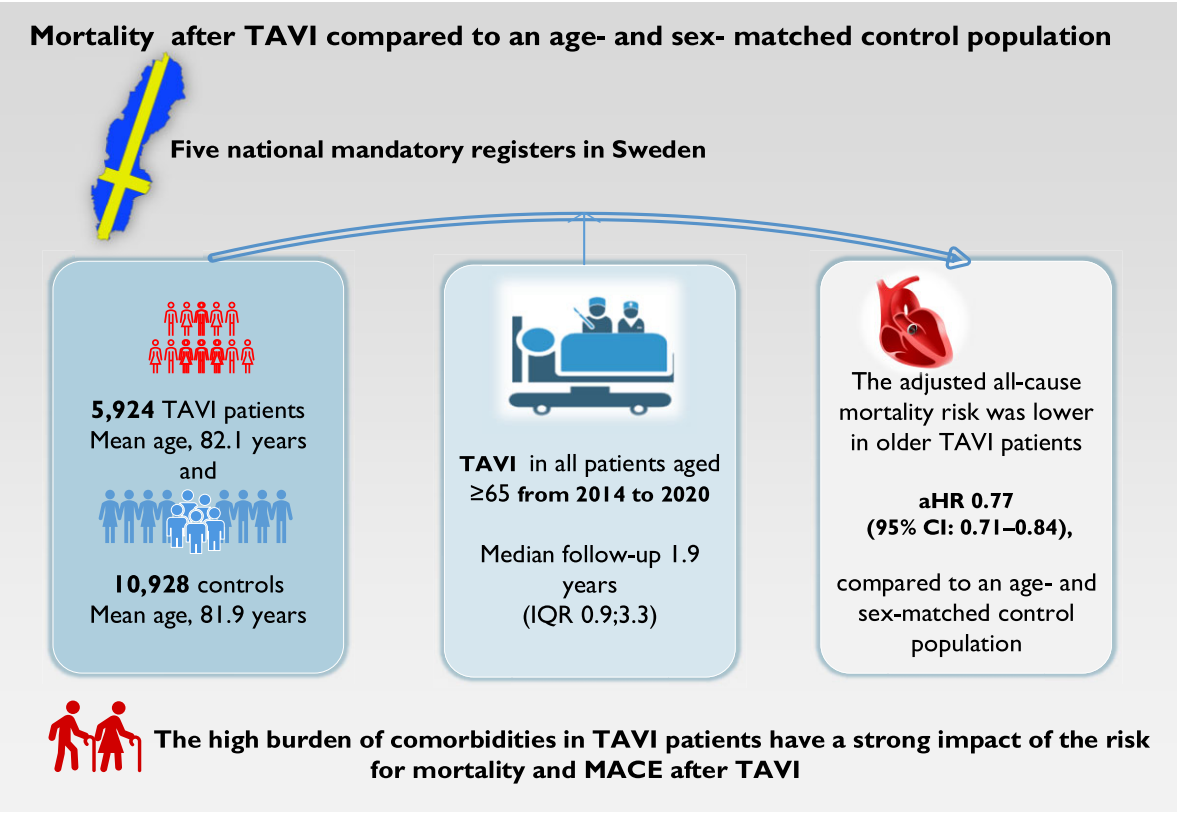
Graphical Abstract



Keywords Transcatheter aortic valve implantation • Cardiovascular risk factors • Morbidity • Mortality risk • Survival

Key learning points

What is already known?

- Transcatheter aortic valve implantation (TAVI) is the recommended treatment option for older patients with severe aortic stenosis and for patients with high surgical risk.
- TAVI implies a markedly increased survival probability and significantly reduced symptom burden.
- Comorbidities and socioeconomic factors are associated with an increased risk of mortality and major adverse events after TAVI.

What this study adds

- The high burden of comorbidities in TAVI patients has a strong impact on the risk for all-cause mortality and major adverse events after TAVI.
- Compared with an age- and sex-matched control population, the adjusted all-cause mortality risk is lower in older TAVI patients.

Introduction

Severe aortic stenosis (AS) is a very severe condition. The mortality without treatment is about 50% in a 2-year period after diagnosis.[1–3] Transcatheter aortic valve implantation (TAVI) is the recommended treatment option in older patients with severe AS and in patients with high surgical risk.[4,5] TAVI results in a markedly increased midterm and long-term survival for many of these patients.[2,6] A significant reduction of the symptom burden 1 year after TAVI has been demonstrated in previous studies.[7,8] However, frailty, heart failure, renal failure, pulmonary artery hypertension, and chronic obstructive lung disease are associated with an increased mortality after TAVI.[9,10] Two previous studies have shown that TAVI patients younger than 80 years had a worse survival compared to an age-matched control population, while the mortality risk in patients aged 80 years and older was comparable to their matched controls.[11,12] However, data are scarce about the impact of comorbidities, patient characteristics, including socioeconomic factors, and risk for mortality and major adverse events after TAVI, compared to those of the general population. Therefore, the aim of the present study was to examine the midterm risk of mortality, stroke, and myocardial infarction after TAVI in patients aged 65 years

and older, compared to an age- and sex-matched control population, before and after adjustment for comorbidities.

Methods

Study design, study population, and data sources

All patients aged 65 years and older ($n = 5924$), who underwent TAVI in Sweden during 2014 to 2020, and a sex- and age-matched control population ($n = 10\,928$) were included in a nationwide, observational population-based cohort study. The follow-up time varied from minimum 1 month to maximum 6.9 years. The follow-up time started at the date of discharge from the hospital after TAVI and ended at death or end of study (31 December 2020), whichever occurred first. Outcome measures were all-cause mortality, major adverse cardiovascular events (MACE), stroke, and myocardial infarction. The patients were identified in the Swedish Transcatheter Cardiac Intervention Registry (SWENTRY), which is a part of the Swedish Web System for Enhancement and Development of Evidence-based care in Heart disease Evaluated According to Recommended Therapies (SWEDEHEART). The SWENTRY registry includes all patients undergoing TAVI in Sweden since 2008.[13]

The Swedish Total Population Registry held by Statistics Sweden has complete coverage of basic demographic information of all citizens in Sweden.[14] This register was used to assign two controls without the TAVI procedure. The date of inclusion of the controls was the day of TAVI for the matching. Each TAVI patient and control individual were matched by the day of TAVI procedure (index date), sex, age, and home county. In the final match, it was not possible to find two controls for every TAVI patient because of the advanced age in the TAVI population; hence, for 920 patients, there was only one control participant.

The codes for surgical procedures in the International Classification of Diseases (ICD) system, version 10, were used to identify the TAVI procedures, which are FMD 12 and FMD 96, in combination with the diagnosis code for AS (I35.0). Since the follow-up period started at the date of discharge from the hospital after TAVI, patients who died before discharge were excluded ($n = 82$). A flowchart describing included and excluded patients is depicted in Supplementary material online, *Figure S1*.

Baseline characteristics and comorbidities were obtained from the Swedish National Patient Register (NPR), where registration is mandatory. The NPR has complete national coverage from 1987 for all patients hospitalized in Sweden, with an overall diagnosis validity of 85–95%.[15] In NPR, diagnoses are based on ICD codes from the 10th revision (ICD-10) of 1997. Diagnoses used for baseline characteristics are shown in Supplementary material online, *Table S1*. Marital status and educational level data were collected from the Longitudinal Integration Database for Health Insurance and Labor Market Studies register. The registry includes all citizens in Sweden aged 16 years and older and is updated annually.[16]

The date of death was obtained from The Swedish Cause of Death register, in which all deaths of Swedish citizens have been registered since 1952.[17] Data from the five national registers were linked through a personal 10-digit social security number, unique for all Swedish citizens.

Statistical methods

Baseline characteristics are presented as frequencies with percentages for categorical variables. Continuous variables are presented as means with standard deviations (SD). Follow-up time started at the date of discharge from the hospital after TAVI and continued until death or end-of-study period, whichever occurred first. Incidence rates (IRs) were estimated as total number of deaths, strokes, myocardial infarctions, and MACE (all-cause mortality, stroke, and myocardial infarction) divided by total follow-up time and reported as IR per 100 person-years with 95% confidence intervals (CIs).

For all-cause mortality and MACE, Kaplan–Meier survival curves were used to estimate the survival probability, with 95% CI, and median survival. Adjustment for the competing risk of death with the Fine-Gray method was performed for stroke and myocardial infarction, yielding cumulative incidence with 95% CI. For all analyses, a *P*-value of <0.05 was considered statistically significant.

Cox proportional hazards regression was used to calculate age- and sex-adjusted hazard ratio (HR) and fully adjusted hazard ratio (aHR) mortality risk, separately for the TAVI-cases and control participants. The multivariate models were adjusted for baseline characteristics (age, sex, myocardial infarction, diabetes, hypertension, heart failure, atrial fibrillation, previous stroke, chronic respiratory disease, peripheral vascular disease, renal failure, history of cancer, depression, dementia, marital status, and education). To test the robustness of the Cox regression model, a sensitivity analysis was performed using a propensity score model, matched for comorbidities using logistic regression with a 1:1 nearest-neighbour matching method. In the final propensity-score matched model, all TAVI patients ($n = 3635$) were successfully matched to a control ($n = 3635$). A good balance was achieved with all standardized mean differences of comorbidities below 0.1 after matching (Supplementary material online, *Figures S2* and *S3*).

All statistical analyses were performed using version 4.2.0 of R.[18] R—package 'dplyr' was used for data management,[19] 'survival' for Kaplain–Meier and Cox regression models,[20] 'prodlim' for competing risk, [21] and 'MatchIt' for propensity-score matching model.[22]

Ethical considerations

The present study was performed in line with the Declaration of Helsinki and was approved by the Swedish Ethical Review Authority (registration number: 2021–00122). All personal identifiers were replaced by codes before analysis to ensure anonymity. The need for individual patient consent was waived by the committee in accordance with current national regulations. This article follows the recommendations from the statement of Strengthening the Reporting of Observational Studies in Epidemiology (STROBE).[23]

Results

General

Baseline characteristics for the 5924 TAVI patients (47.3% women) and the 10 928 controls (50.1% women) are presented in *Table 1*. The median follow-up was 1.9 years (inter quartile range 0.9, 3.3) in both TAVI patients and controls. The mean age was 82.1 and 81.9 years (SD 6.0 and 6.1) in TAVI patients and controls, respectively. Compared to controls, TAVI patients had a higher proportion of comorbidities except for depression and dementia (*Table 1*). Patient characteristics after propensity-score matching are presented in Supplementary material online, *Table S2*.

Cumulative incidence of all-cause mortality, MACE, stroke, and myocardial infarction

In total, 23.8% of the TAVI patients and 19.4% of the controls died during the follow-up period. (Supplementary material online, *Table S3*). The cumulative incidence of all-cause mortality 5 years after TAVI was 46.2% (95% CI: 43.8–48.5) in TAVI patients and 35.7% (95% CI: 34.2–37.2) in controls (*Figure 1A*). For MACE, the cumulative incidence was 51.9% (95% CI: 49.6–54.2) in TAVI patients and 38.8% (95% CI: 37.2–40.3) in controls (*Figure 1B*). Corresponding numbers for stroke were 12.1% (95% CI: 10.8–13.5) in TAVI patients and 8.3% (95% CI: 7.4–9.1) in controls (*Figure 2A*). For myocardial infarction, the cumulative incidence was 7.5% (95% CI: 6.4–8.5) among TAVI patients and in controls, 2.5% (95% CI: 2.0–3.0) (*Figure 2B*).

In the propensity-score matched analysis 5 years after TAVI, the cumulative incidences of mortality and MACE showed higher incidences among the controls compared to the TAVI patients (*Figure 3*A and B).

Table 1 Baseline comorbidities in 5924 patients, aged ≥65 years who underwent transcatheter aortic valve implantation (TAVI) and in 10 928 sex- and age-matched control subjects

	TAVI *n* (%)	Controls *n* (%)	*P*-value
Number of patients	5924 (35.2)	10 928 (64.8)	
Women	2801 (47.3)	5476 (50.1)	<0.001
Mean age ± SD	82.1 ± 6.0	81.9 ± 6.1	0.007
Median follow-up, IQR	1.9 [0.9:3.3]	1.9 [0.9:3.3]	0.109
Comorbidities			
Myocardial infarction	1292 (21.8)	247 (2.3)	<0.001
Diabetes	1758 (29.7)	1434 (13.1)	<0.001
Hypertension	5020 (84.7)	4855 (44.4)	<0.001
Heart failure	2679 (45.2)	868 (7.9)	<0.001
Atrial fibrillation	2536 (42.8)	1840 (16.8)	<0.001
Hyperlipidaemia	2284 (38.6)	1124 (10.3)	<0.001
Previous stroke	918 (15.5)	1312 (12.0)	<0.001
Chronic respiratory disease	1262 (21.3)	1085 (9.9)	<0.001
Peripheral vascular disease	951 (16.1)	578 (5.3)	<0.001
Renal failure	1037 (17.5)	544 (5,0)	<0.001
History of cancer	2165 (36.5)	3383 (31.0)	<0.001
History of depression	298 (5.0)	593 (5.4)	0.289
Dementia	55 (0.9)	664 (6.1)	<0.001
Prior PCI	1559 (26.4)		
Prior cardiac surgery	1019 (17.2)		
Marital status			0.002
Married/cohabiting	2836 (47.9)	5194 (47.5)	
Never married	381 (6.4)	854 (7.8)	
Divorced	893 (15.1)	1720 (15.7)	
Widowed	1814 (30.6)	3160 (28.9)	
Education			0.015
<10 years	2433 (41.5)	4228 (39.8)	
10–12 years	2191 (37.4)	3958 (37.3)	
>12 years	1238 (21.1)	2439 (23.0)	

IQR, inter quartile range.

The numbers for the cumulative incidence of stroke at 5 years showed no significant difference when comparing TAVI patients and controls, 11.6% (95% CI: 9.9–13.3) vs. 9.3% (95% CI: 7.9–10.7) (*Figure 4A*). The incidence of myocardial infarction was higher among the TAVI patients in the propensity-score matched model during the follow-up period and started to differ at 1 year after TAVI, 1.9% (95% CI: 1.4–2.3) and 1.0% (95% CI: 0.6–1.3), respectively (*Figure 4* B).

Risk for all-cause mortality, stroke, and myocardial infarction

The overall IR for all-cause mortality, MACE, stroke, and myocardial infarction is presented in *Table 2*. The event rate of all-cause death was 10.57 (95% CI: 10.02–11.13) and 8.36 (95% CI: 8.00–8.72) per 100 person-years in TAVI patients and control participants, respectively (*Table 2*).

The age- and sex-adjusted HR model showed that TAVI patients had an increased risk of all-cause mortality and MACE compared to controls [HR 1.27 (95% CI: 1.19–1.36) vs. HR 1.44 (95% CI: 1.35–1.53)]. This increased risk was markedly attenuated when co-morbidities, marital status and education were included in the fully adjusted model [aHR 0.77 (95% CI: 0.71–0.84) and aHR 0.90, (95% CI: 0.83–0.98)] (*Table 2*).

The risk for stroke and myocardial infarction was higher in TAVI patients compared to controls in the age- and sex-adjusted model [HR 1.61 (95% CI: 1.41–1.83) vs. HR 3.31 (95% CI: 2.70–4.06)]. This increased risk in TAVI patients persisted for myocardial infarction in the multi-adjusted model [aHR 1.67 (95% CI: 1.29–2.16)] but not for stroke [aHR 1.14 (95% CI: 0.96–1.34)].

Similar findings were found in the propensity-score matched model where TAVI patients had a lower risk for all-cause mortality and for MACE compared to controls [aHR 0.71 (95% CI: 0.64–0.78) and aHR 0.84 (95% CI: 0.77–0.92), respectively]. A higher risk for myocardial infarction was observed in TAVI patients compared to controls [aHR 1.85 (95% CI: 1.39–2.46)] but not for stroke [aHR 1.13 (95% CI: 0.94–1.36)] (Supplementary material online, *Table S4*).

Discussion

In this national observational cohort study, which included 5924 TAVI patients and 10 928 age- and sex-matched controls, there are two main findings: (i) TAVI patients had a higher unadjusted mortality risk compared to an age- and sex-matched control group. This increased risk did not persist in the multi-adjusted model, which included co-morbidities and social factors, or in the propensity-score matched model. (ii) Compared to control participants, TAVI patients had an increased risk for myocardial infarction in both the age- and sex-adjusted model, the multi-adjusted models, and the propensity-score matched model. However, an increased risk for stroke in the age- and sex-adjusted model did not persist in the fully adjusted model or in the propensity-score matched model.

The higher mortality risk in TAVI patients, compared to controls in the model adjusted for age and sex only, is likely attributable to the high proportion of comorbidities in TAVI patients. When comorbidities at baseline, education, and marital status were included in the fully adjusted model, as in the propensity-score matched model, the excess risk of mortality and MACE in TAVI patients did not persist. Instead, we observed a lower risk compared to controls. Possible explanations of the lower mortality risk, observed in the present study among TAVI patients, may be related to an underuse of statins and antihypertensive therapy in general in older patients with hyperlipidaemia and hypertension.[24,25] In the present study, no information regarding the use of pharmacological therapy was available. However, it is possible that patients undergoing TAVI have better blood-pressure control and lower cholesterol levels, owing to the follow-up strategies after TAVI compared to controls. Previous studies, without comparisons to a matched control population, have also demonstrated an association between high burden of comorbidities and increased mortality risk after TAVI.[9,10] Moreover, frequent readmissions after TAVI, caused by both cardiovascular and non-cardiovascular comorbidities, have also shown to be strongly associated with an increased risk of mortality.[10,26,27]

Cardiovascular diseases are progressive within a lifetime perspective and cardiovascular risk factors are associated with worsening long-term outcomes.[28] Multimorbidity, including cardiovascular disease, stroke, diabetes, chronic lung and kidney diseases, frailty, living alone, and cognitive impairment, is strongly associated with increased mortality risk among older people in the general population.[29–32] Also, patients with dementia with the concomitant presence of cardiovascular disease have a poor prognosis.[31] Current guidelines recommend TAVI according to the patient's life expectancy and improvement in quality of life.[4] Therefore, patients with AS and a disseminated cancer, severe frailty, or suffering from a disabling stroke were likely not accepted for the procedure. Accordingly, death caused by malignancy was more prevalent among the controls. Furthermore, dementia

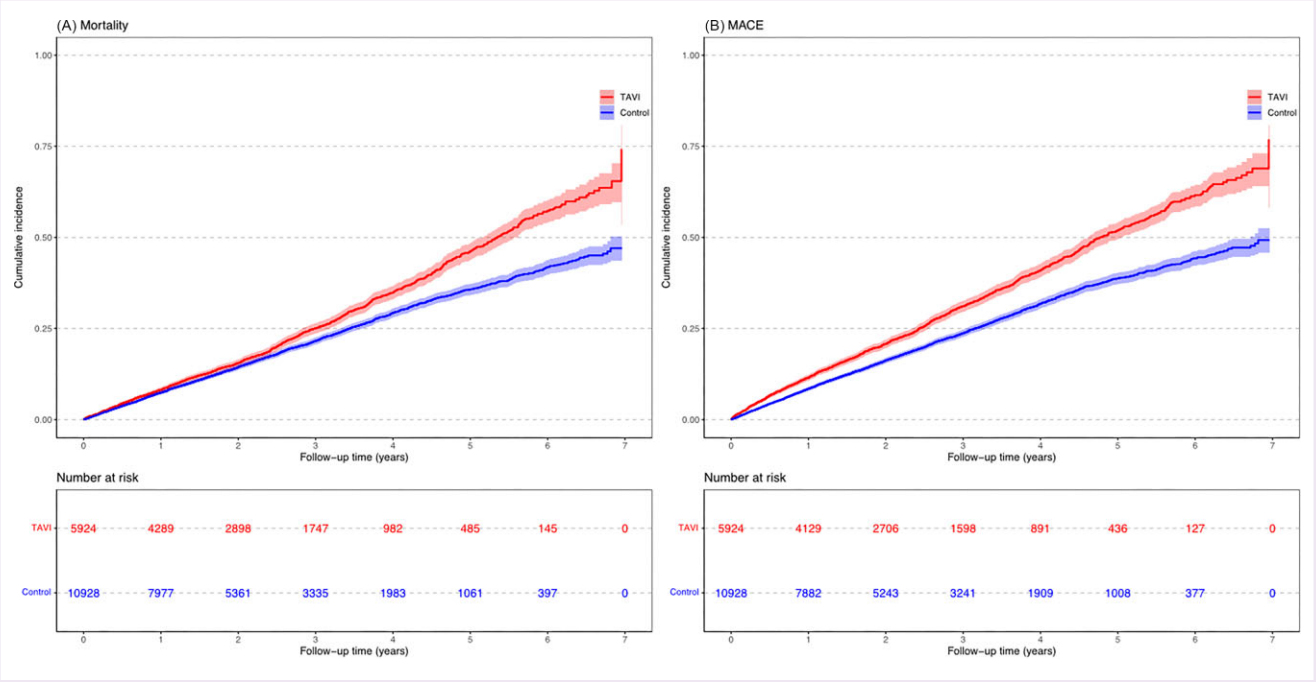


Figure 1 Panel A, Cumulative incidence for all-cause death. Panel B, Cumulative incidence for MACE (all-cause death, stroke, myocardial infarction).

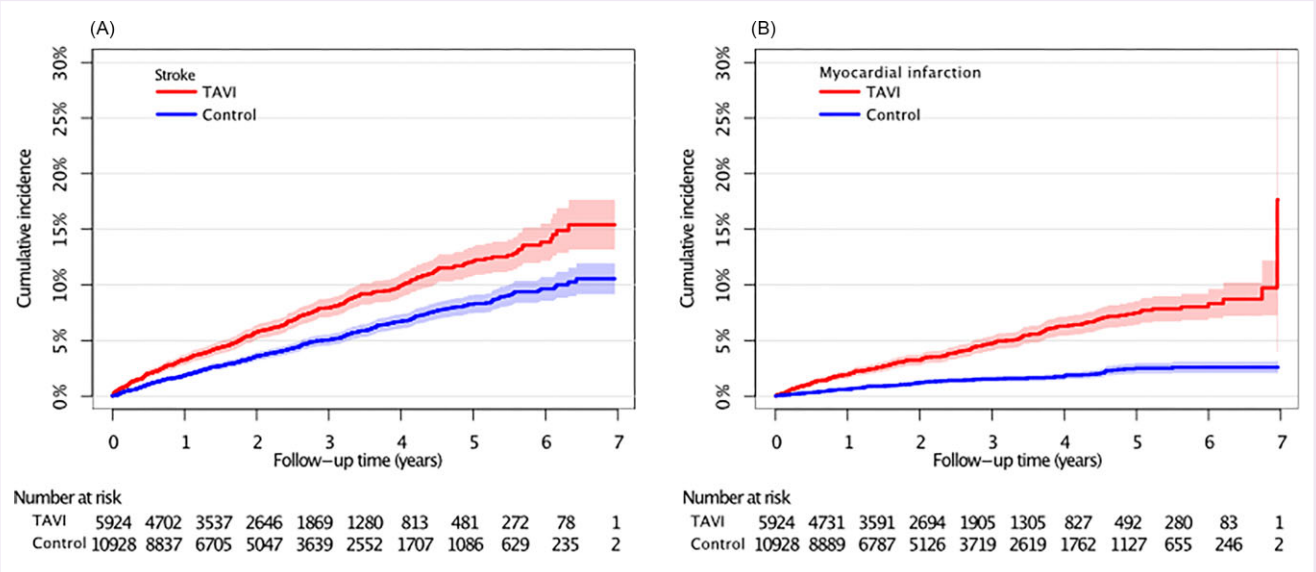


Figure 2 Panel A, Cumulative incidence for stroke. Panel B, Cumulative incidence for myocardial infarction.

was rare in TAVI patients, which might be explained by a careful preoperative patient selection process. Previous studies, comparing TAVI patients to matched participants from the general population, have shown an increased mortality risk in younger but not in older TAVI patients (>80 years).[11,12] The results from the present study extend this observation to TAVI patients regardless of age and adds information about the impact of comorbidities at baseline in TAVI patients.

To our knowledge, no previous study has examined the long-term risk for stroke and myocardial infarction after TAVI, compared to a sex- and age-matched population. Compared to controls, the overall risk for stroke in TAVI patients was twice as high. However, after the multivariable adjustment, the risk did not persist. The overall risk for myocardial infarction was three-fold higher but attenuated after multi-adjustment and was slightly increased in the propensity-score matched sensitivity analysis. Patients undergoing TAVI had a higher incidence of myocardial infarction than the matched control population. One possible explanation is that patients undergoing TAVI have a higher burden of coronary artery disease than the age- and sex-matched controls. Previous myocardial infarction was included in the propensity score matched model, but the present dataset lacks information on the extent of coronary disease. A previous study has

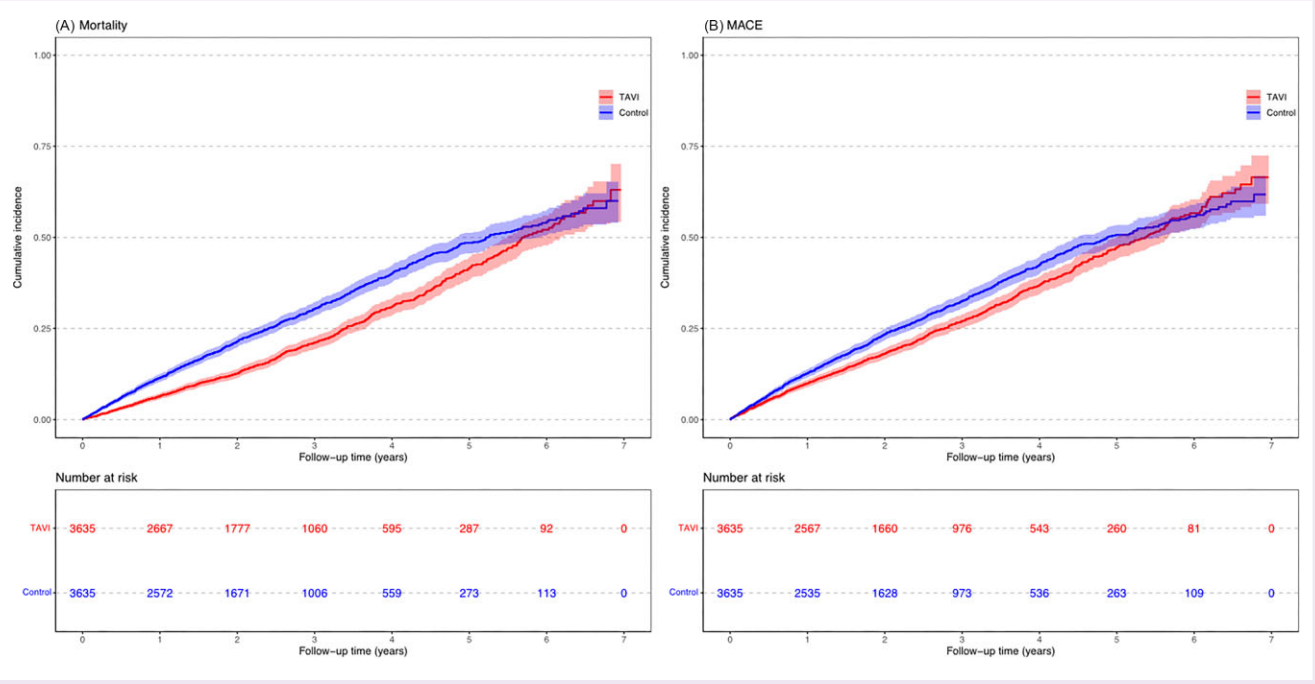


Figure 3 Panel A, Cumulative survival incidence for all-cause death in the propensity-score matched population. Panel B, Cumulative incidence for MACE (all-cause death, stroke, myocardial infarction) in the propensity-score matched population.

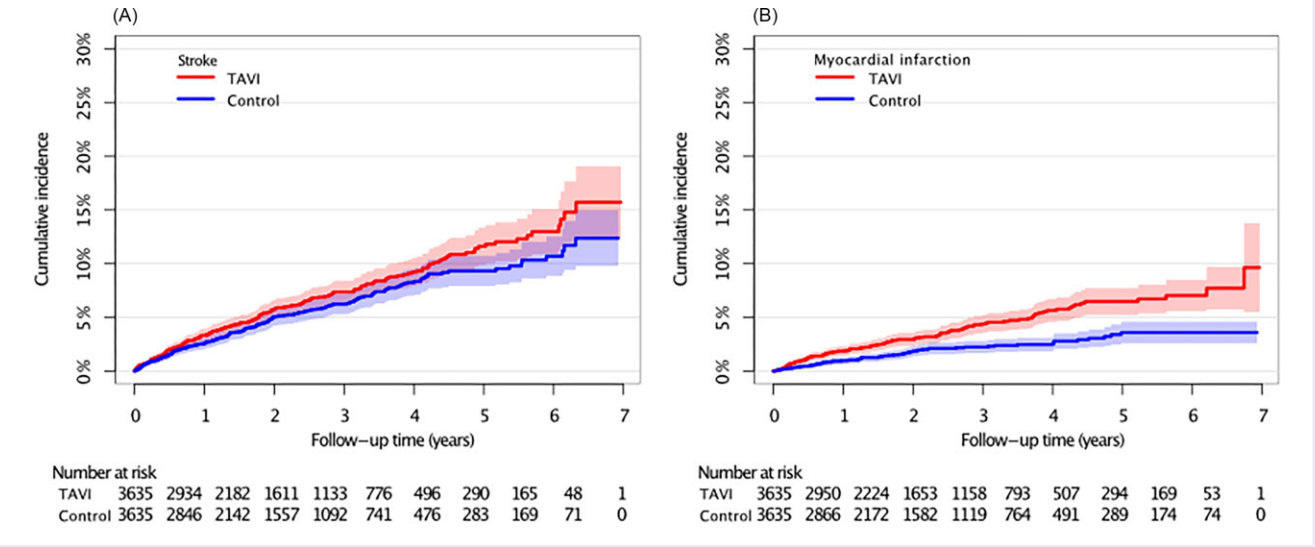


Figure 4 Panel A, Cumulative incidence for stroke propensity-score matched population. Panel B, Cumulative incidence for myocardial infarction in the propensity-score matched population.

shown that significant coronary disease is present in 40–75% of those undergoing TAVI.[33] Furthermore, cardiac comorbidities at baseline were more common among TAVI patients, which reflect that the TAVI group had a more severe cardiac disease burden than controls.[34] The increased risk for myocardial infarction after TAVI may thus also be attributed to a more progressive development of the patients' cardiovascular risk factors at baseline. In this study, the presence of hypertension was almost twice as high (85% vs. 45%) in TAVI patients compared to controls. Also, the proportions of diabetes and atrial fibrillation were nearly three times higher among the TAVI patients. Hypertension may lead to left ventricular fibrosis and hypertrophy, which cause cardiac damage prior to TAVI.[35] Furthermore, the presence of atrial fibrillation post TAVI may impair cardiac remodelling after TAVI.[36] There is growing evidence that remaining cardiac damage 1 year after TAVI, and the extent of cardiac damage at the time of TAVI, are associated with adverse events and increased mortality 2 years after TAVI.[36–38] In addition, a recent study found that heart failure and myocardial infarction, prior to TAVI, were associated with an increased risk of mortality and rehospitalization after TAVI.[39] Cardiovascular risk factors for stroke and myocardial infarction in

Table 2 Incidence rates and hazard ratios with 95% confidence intervals in 5924 patients, aged ≥65 years who underwent transcatheter aortic valve implantation and in 10 928 controls

	Number of events, *n* (%)		Incidence rate per 100 person-years (95% CI)		HR (95% CI) TAVI vs. controls	
Outcomes	TAVI	Controls	TAVI	Controls	Age- and sex adjusted[a]	Multi-adjusted[b]
Mortality						
All-cause mortality	1410 (23.8)	2115 (19.4)	10.57 (10.02–11.13)	8.36 (8.00–8.72)	1.27 (1.19–1.36)	0.77 (0.71–0.84)
Morbidity						
MACE	1677 (28.3)	2306 (21.1)	13.25 (12.62–13.89)	9.28 (8.91–9.67)	1.44 (1.35–1.53)	0.90 (0.83–0.98)
Stroke	417 (7.0)	501 (4.6)	3.23 (2.93–3.56)	2.01 (1.84–2.20)	1.61 (1.41–1.83)	1.14 (0.96–1.34)
Myocardial infarction	252 (4.3)	147 (1.4)	1.93 (1.70–2.18)	0.58 (0.49–0.68)	3.31 (2.70–4.06)	1.67 (1.29–2.16)

TAVI, transcatheter aortic valve implantation; HR, hazard ratio; CI, confidence interval; MACE, major adverse cardiovascular events defined by mortality of any cause, myocardial infarction, and stroke.
[a]Adjusted for age and sex.
[b]Multivariable model adjusted for age, sex, marital status, education, with baseline comorbidities: myocardial infarction, hypertension, diabetes, heart failure, atrial fibrillation, stroke, renal failure, chronic respiratory disease, peripheral vascular disease, history of cancer, hyperlipidaemia, depression, and dementia.

older TAVI patients have been described in previous studies, with similar proportions for myocardial infarctions as in our study.[10,40,41] A previous study has shown an annual risk for stroke of 2.0–3.1% during an 8-year follow-up after TAVI.[42] In the present study, the incidence of stroke was 7.0% during the follow-up period. The risk of stroke 2 years after TAVI has been demonstrated with a 6.2–9.5% prevalence in two previous landmark studies, and the corresponding number for myocardial infarction was 2.8–3.6%.[43,44] However, patient selection and procedural factors have improved over time, and have proven to be important in the reduction of major complications and mortality 1 year after TAVI.[45] In addition, in the propensity-score matched analysis we did not observe any significant difference in the incidence of stroke after TAVI, and the incidence of myocardial infarction showed a significant difference first at one year after TAVI. This result indicates that the higher proportion of myocardial infarction among the TAVI patients was related to a higher burden of severe cardiovascular comorbidities, in comparison to the controls, and not primarily due to the TAVI procedure. After multi-adjustment for comorbidities in our analysis of MACE, the results also indicate a high proportion of non-fatal strokes or myocardial infarctions in the TAVI group during the follow-up period. Further studies are warranted with an extended follow-up period to examine the long-term probability of survival and adverse events after TAVI.

Strengths of this study include the large population-based cohort, a long follow-up time, no patients lost to follow-up, high-quality registry data including comorbidities and social factors both for the TAVI population and the age- and sex-matched study population. However, we did not include the patients' income level as a part of their social status, since the large majority of the patients were retired. Social status includes multiple components, and we did not have information regarding living area and information of ethnicity. Limitations also include no estimation of frailty being available for either group, and information lacking regarding Euroscore II or STS-score, extent of coronary disease, and ejection fraction in the TAVI group. Another limitation is that the retrospective study design carries an inherent risk of selection bias and residual confounding.

Conclusions

After adjustments for comorbidities and social factors, the mortality risk was lower in TAVI patients, compared with an age- and sex-matched control population. These results show that the high burden of comorbidities in TAVI patients had a strong impact on the mortality risk. TAVI patients had a higher risk for myocardial infarction both in the sex-and age-adjusted model and in the fully adjusted model, but only a higher risk for stroke in the unadjusted model. These findings are also likely caused by the higher proportion of severe comorbidities in TAVI patients.

Supplementary material

Supplementary material was available at *European Heart Journal—Quality of Care and Clinical Outcomes* online.

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Conflict of interest: A.J. has received fees for consultancy from AstraZeneca, Novo Nordisk, Bayer, Boehringer Ingelheim, Werfen, and LFB Biotechnologies outside the present work. S.J. has received institutional research grants from Medtronic and Edwards and personal compensation for valve proctoring from Medtronic. M.S. has received fees for consultancy from Abbott Vascular, Boston Scientific, Edwards, Medtronic, Anteris, W.L. Gore, Cardiomech, and Smartcella outside of the present work. P.P. has received lectures fees from Medtronic and received personal compensation for valve proctoring from Abbott. None of the other authors has anything to disclose.

Data availability

Data will be shared on reasonable request to the corresponding author if permissions are obtained from SWEDEHEART and the Swedish National Board of Health and Welfare.

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