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Long-Term Risk of Infective Endocarditis After Transcatheter Aortic Valve Replacement

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ABSTRACT

BACKGROUND Patients undergoing surgical aortic valve replacement (SAVR) are considered at high risk of infective endocarditis (IE). However, data on the risk of IE following transcatheter aortic valve replacement (TAVR) are sparse and limited by the lack of long-term follow-up as well as a direct comparison with patients undergoing SAVR.

OBJECTIVES This study sought to investigate the long-term incidence of IE in patients undergoing TAVR and to compare the long-term risk of IE with patients undergoing isolated SAVR.

METHODS In this nationwide observational cohort study, all patients undergoing TAVR and isolated SAVR from January 1, 2008, to December 31, 2016, with no history of IE and alive at discharge were identified using data from Danish nationwide registries.

RESULTS A total of 2,632 patients undergoing TAVR and 3,777 patients undergoing isolated SAVR were identified. During a mean follow-up of 3.6 years, 115 patients (4.4%) with TAVR and 186 patients (4.9%) with SAVR were admitted with IE. The median time from procedure to IE hospitalization was 352 days (25th to 75th percentile: 133 to 778 days) in the TAVR group and 625 days (25th to 75th percentile: 209 to 1,385 days) in the SAVR group. The crude incidence rates of IE were 1.6 (95% confidence interval [CI]: 1.4 to 1.9) and 1.2 (95% CI: 1.0 to 1.4) events per 100 person-years in TAVR and SAVR patients, respectively. The cumulative 1-year risk of IE was 2.3% (95% CI: 1.8% to 2.9%) and 1.8% (95% CI: 1.4% to 2.3%) in TAVR and SAVR patients, respectively. Correspondingly, the cumulative 5-year risk of IE was 5.8% (95% CI: 4.7% to 7.0%) and 5.1% (95% CI: 4.4% to 6.0%), respectively. In multivariable Cox proportional hazard analysis, TAVR was not associated with a statistically significant different risk of IE compared with SAVR (hazard ratio: 1.12; 95% CI: 0.84 to 1.49).

CONCLUSIONS The 5-year incidence of IE following TAVR was 5.8% and not significantly different than the incidence following SAVR. (J Am Coll Cardiol 2019;73:1646-55) © 2019 by the American College of Cardiology Foundation.

Patients undergoing surgical aortic valve replacement (SAVR) are considered to be at high risk of infective endocarditis (IE) (1,2). During the last decade, transcatheter aortic valve replacement (TAVR) has been increasingly used for the treatment of severe symptomatic aortic stenosis in patients considered to be at high or excessive surgical risk. Although the risk of IE after surgical valve replacement is well-characterized (1-3), data on the risk of this complication in the setting of TAVR are sparse and limited by either lack of long-term follow-up or a small number of patients (4-11). Due

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to certain characteristics of patients eligible for TAVR (i.e., advanced age and greater burden of comorbidities), patients treated with TAVR may potentially carry a higher risk of IE compared with those undergoing SAVR. Further, the rapidly increasing number of patients with previous TAVR makes it important to assess the long-term clinical burden of this complication and to identify patients at high risk of IE.

The objective of this study was to investigate the long-term incidence of IE in a nationwide all-comers cohort of patients undergoing TAVR in Denmark and to compare the long-term risk of IE with a nationwide cohort of patients undergoing SAVR.

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METHODS

DATA SOURCES. All citizens in Denmark are assigned a unique and personal identification number, which allows accurate linkage of nationwide administrative registries at an individual level. For this study, data from the following nationwide administrative registries were obtained: The Danish National Patient Registry holds information on all hospital admissions and outpatient contacts according to the International Classification of Diseases (ICD) and all surgical procedures according to the NOMESCO Classification of Surgical Procedures (NCSP) (12). The Danish Registry of Medicinal Product Statistics (the Danish National Prescription Registry) comprises detailed information on dispensing date, strength, and quantity on all claimed drug prescriptions in Denmark (13); and The Danish Civil Registration System contains data on birth date, sex, and vital status (i.e., whether a person is alive and resident in Denmark, disappeared [persons whose residence is unknown to Danish authorities], emigrated, or dead, along with the date of these events) (14).

STUDY POPULATION. All Danish citizens undergoing first-time TAVR between January 1, 2008, and December 31, 2016, with no history of IE and alive at discharge were included in the study. In addition, a nationwide cohort of patients undergoing isolated SAVR (i.e., no concomitant cardiac surgery) between January 1, 2008, and December 31, 2016, with no history of IE and alive at discharge was included in the study.

COVARIATES. Comorbidity was obtained using in-hospital or out-patient diagnoses any time before discharge for TAVR/SAVR (Online Table 1 for ICD-8 and ICD-10 codes). Patients with diabetes and hypertension were identified using claimed drug prescriptions as described previously (15,16) (Online Table 2 for Anatomical Therapeutic Chemical codes). The presence of a cardiac implantable electronic device was defined as an implantation of a pacemaker or implantable cardioverter-defibrillator any time before discharge for TAVR/SAVR, including implantations during previous admissions (Online Table 1 for NCSP codes).

OUTCOMES. The primary outcome was incident IE. The diagnosis of IE in the Danish National Patient Registry has previously been validated with a positive predictive value of 90% in patients with a length of hospital stay of at least 14 days (17). In Denmark, all IE patients are admitted for at least 14 days. Consequently, patients with a diagnosis of IE and a length of hospital stay of <14 days were not considered as having IE, unless they died during admission. Patients were followed from the index date (defined as the date of discharge for TAVR/SAVR) until occurrence of IE, death, emigration, or end of the study (July 31, 2017), whichever came first.

STATISTICS. Descriptive data were reported as frequencies with percentages, medians with 25th to 75th percentiles, or mean ± SD. Differences in baseline characteristics between the TAVR and SAVR population were tested by the chi-square test for categorical variables and the Mann-Whitney test for continuous variables. Crude incidence rates of IE were calculated as number of events per 100 person-years. The cumulative incidence of IE according to groups was estimated using the Aalen-Johansen estimator, taking the competing risk of death into account, and differences between groups were assessed using Gray's test. Survival curves according to groups were constructed by the Kaplan-Meier method, and differences between groups were assessed using the log-rank test. Cox proportional hazard regression models were used to estimate hazard ratios (HR) with 95% confidence intervals (CIs), adjusted for age, sex, all comorbidities listed in **Table 1**, presence of a cardiac implantable electronic device, and year of procedure. Patients with SAVR served as the reference group in all models. The proportional hazards assumption was tested and found valid. Clinically relevant interactions, including age, sex, and several comorbidities were tested for and found insignificant, unless otherwise stated. Factors associated with the development of IE were identified using Cox proportional hazard regression. Covariates for the Cox regression models were selected a priori and only those considered most relevant based on current knowledge and literature were included (i.e., age, sex, comorbidity, presence of a cardiac implantable electronic device,

ABBREVIATIONS AND ACRONYMS

CI = confidence interval

HR = hazard ratio

ICD = International Classification of Diseases

IE = infective endocarditis

SAVR = surgical aortic valve replacement

TAVR = transcatheter aortic valve replacement

TABLE 1 Baseline Characteristics at Discharge in Patients Undergoing TAVR and Isolated SAVR

	SAVR (n = 3,777)	TAVR (n = 2,632)	p Value
Demographics			
Age, yrs	73 (68-78)	81 (77-85)	< 0.01
Male	2,241 (59.3)	1,378 (52.4)	< 0.01
Comorbidities			
Stroke	387 (10.3)	411 (15.6)	< 0.01
Ischemic heart disease	1,426 (37.8)	1,569 (59.6)	< 0.01
Heart failure	831 (22.0)	962 (36.6)	< 0.01
Atrial fibrillation	1,120 (29.7)	1,024 (38.9)	< 0.01
Hypertension	2,303 (61.0)	2,038 (77.4)	< 0.01
Diabetes	590 15.6)	484 (18.4)	< 0.01
Peripheral vascular disease	212 (5.6)	276 (10.5)	< 0.01
Malignancy	625 (16.6)	612 (23.3)	< 0.01
Chronic kidney disease	279 (7.4)	323 (12.3)	< 0.01
Chronic obstructive pulmonary disease	464 (12.3)	475 (18.1)	< 0.01
Liver disease	82 (2.2)	76 (2.9)	0.07
Cardiac implantable electronic device	288 (7.6)	629 (23.9)	< 0.01
Before admission	141 (3.7)	282 (10.7)	< 0.01
During admission	147 (3.9)	347 (13.2)	< 0.01
TAVR-in-SAVR	N/A	71 (1.1)	N/A
Access			
Transfemoral	N/A	2,028 (77.0)	N/A
Transapical	N/A	552 (21.0)	N/A
Transaortic	N/A	52 (2.0)	N/A
Year of procedure			N/A
2008	320 (8.5)	52 (2.0)	
2009	422 (11.2)	113 (4.3)	
2010	351 (9.3)	202 (7.7)	
2011	409 (10.8)	214 (8.1)	
2012	486 (12.9)	277 (10.5)	
2013	476 (12.6)	313 (11.9)	
2014	394 (13.1)	331 (12.9)	
2015	418 (11.1)	489 (18.6)	
2016	401 (10.6)	641 (24.4)	

Values are median (interquartile range) or n (%).

N/A = not applicable; SAVR = surgical aortic valve replacement; TAVR = transcatheter aortic valve replacement.

and year of procedure). All statistical analyses were performed with SAS statistical software version 9.4 (SAS Institute, Cary, North Carolina). A 2-sided p value <0.05 was considered statistically significant. There were no missing data for any of the covariates or outcomes.

For sensitivity purposes, we identified a matched cohort of TAVR and SAVR patients to account for potential differences in baseline characteristics. Using risk-set matching, TAVR patients were matched by age (up to 1-year difference), sex, a history of stroke, ischemic heart disease, heart failure, diabetes, chronic kidney disease, atrial fibrillation, chronic obstructive pulmonary disease, and peripheral vascular disease, and the presence of a cardiac implantable electronic device with SAVR patients in a 1:1 ratio. The risk of IE was compared among groups using Cox proportional hazard regression models conditional on the matching (i.e., comparing cases with their matched controls) adjusted for comorbidities (all comorbidities listed in Table 1 not used for matching), presence of a cardiac implantable electronic device, and year of procedure.

ETHICS. The Danish Data Protection Agency approved this study (No. 2007-58-0015; internal reference: *GEH-2014-013,* I-Suite no. 02731). In Denmark, register-based studies, in which individuals cannot be identified, do not require ethical approval.

RESULTS

From January 1, 2008, to December 31, 2016, 2,680 patients underwent TAVR in Denmark. Of these, 2,632 patients did not have a history of IE and were alive at discharge. In addition, we identified 3,777 patients undergoing isolated SAVR who did not have a history of IE and were alive at discharge. Baseline characteristics of the TAVR and SAVR group are summarized in Table 1. The TAVR group was characterized by advanced age, lower proportion of men, and greater burden of comorbidities compared with the SAVR group.

INCIDENT IE. During a mean follow-up of 3.7 years (2.8 and 4.3 years in the TAVR and SAVR groups, respectively), 841 patients (32.0%) with TAVR and 720 patients (19.1%) with SAVR died. The crude incidence rates of death were 11.6 (95% CI: 10.8 to 12.4) and 4.4 (95% CI: 4.1 to 4.7) events per 100 person-years in TAVR and SAVR patients, respectively. Figure 1 depicts Kaplan-Meier curves for death for TAVR and SAVR patients. In multivariable Cox proportional hazard analysis, TAVR was associated with a higher risk of death compared with SAVR (HR: 2.05; 95% CI: 1.82 to 2.32). During a mean follow-up of 3.6 years (2.7 and 4.2 years in the TAVR and SAVR groups, respectively), 115 patients (4.4%) with TAVR and 186 patients (4.9%) with SAVR were admitted with IE. The crude incidence rates of IE were 1.6 (95% CI: 1.4 to 1.9) and 1.2 (95% CI: 1.0 to 1.4) events per 100 person-years in TAVR and SAVR patients, respectively. The cumulative incidences of IE according to groups are displayed in the Central Illustration. The cumulative 1-year risk of IE was 2.3% (95% CI: 1.8% to 2.9%) and 1.8% (95% CI: 1.4% to 2.3%) in TAVR and SAVR patients, respectively. Correspondingly, the cumulative 5-year risk of IE was 5.8% (95% CI: 4.7% to 7.0%) and 5.1% (95% CI: 4.4% to 6.0%), respectively. The crude incidence rates of IE from year 1 and onward were 1.2 (95% CI: 0.9 to 1.6) and 1.0 (95% CI: 0.8 to 1.1) events per 100 person-years in TAVR and SAVR patients,

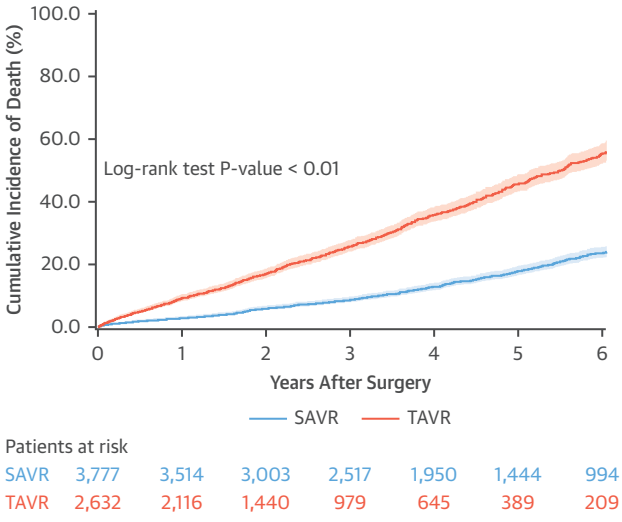
respectively. In multivariable Cox proportional hazard analysis, TAVR was not associated with a statistically significant different risk of IE compared with SAVR (HR: 1.12; 95% CI: 0.84 to 1.49).

The median time from procedure to IE hospitalization was 352 days (25th to 75th percentile: 133 to 778 days) in the TAVR group and 625 days (25th to 75th percentile: 209 to 1,385 days) in the SAVR group. In total, 5 patients (4.4%) in the TAVR group and 24 patients (12.9%) in the SAVR group, respectively, underwent SAVR during IE hospitalization. In-hospital mortality during IE hospitalization was 20.9% and 14.0% in patients with TAVR and SAVR, respectively. One-year mortality in patients with IE was 40.0% and 23.1% in the TAVR and SAVR groups, respectively.

FACTORS ASSOCIATED WITH IE. Figure 2A shows factors associated with the development of IE in patients undergoing TAVR or SAVR. Male sex, liver disease, and the presence of a cardiac implantable electronic device were associated with a greater risk of IE. Factors associated with IE in patients undergoing TAVR are displayed in Figure 2B. Male sex and a history of chronic kidney disease were associated with a greater risk of IE in TAVR patients. Figure 2C displays factors associated with the development of IE in patients undergoing SAVR. Male sex and a history of diabetes were associated with a greater risk of IE in SAVR patients.

SENSITIVITY ANALYSIS. To test the robustness of our findings, we created a matched cohort of TAVR and SAVR patients to account for differences in baseline characteristics. Using risk-set matching, TAVR patients were matched by age (up to 1-year difference); sex; a history of stroke, ischemic heart disease, heart failure, diabetes, chronic kidney disease, atrial fibrillation, chronic obstructive pulmonary disease, peripheral vascular disease; and the presence of a cardiac implantable electronic device, with SAVR patients in a 1:1 ratio. We identified 1,151 patients undergoing TAVR who could be matched with 1,151 patients undergoing SAVR. The baseline characteristics of the matched population are summarized in Table 2. The median age of the population was 79 years (25th to 75th percentile: 74 to 82 years), and 53.8% were men. The cumulative incidences of IE according to groups are shown in Figure 3. There was no significant difference in the cumulative risk of IE between the TAVR and SAVR group. In multivariable Cox proportional hazard analysis, TAVR was not associated with a statistically significant different risk of IE compared with SAVR (HR: 1.02; 95% CI: 0.59 to 1.79).

FIGURE 1 Death After TAVR and SAVR



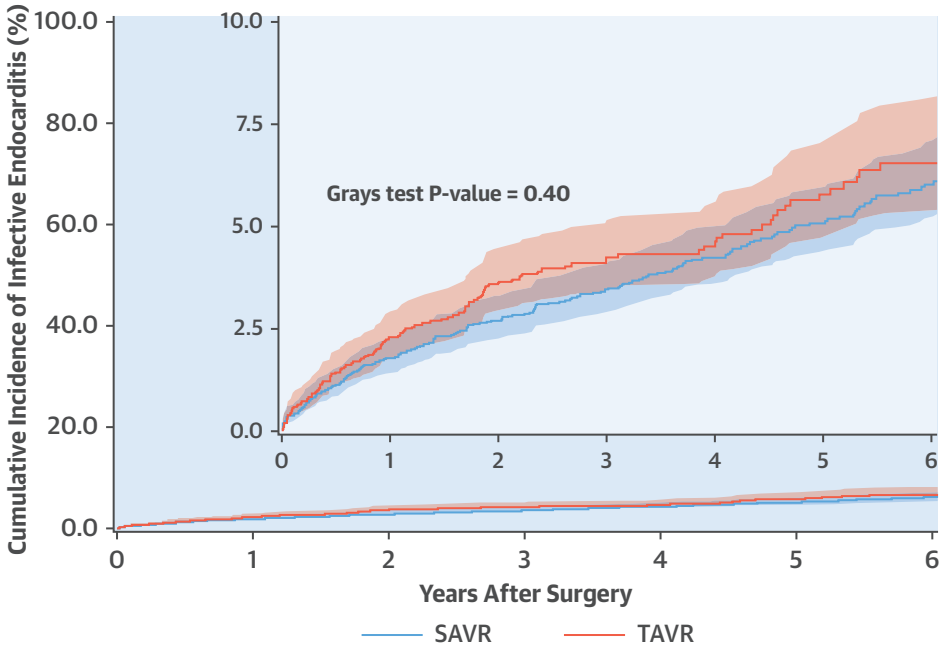
Kaplan-Meier curves for death in patients undergoing TAVR and SAVR. SAVR = surgical aortic valve replacement; TAVR = transcatheter aortic valve replacement.

DISCUSSION

In this nationwide cohort study, we examined the long-term incidence of IE in an all-comers cohort of patients undergoing TAVR in Denmark and compared the long-term risk of IE with a nationwide cohort of patients undergoing isolated SAVR. The study yielded the following major findings: First, the 5-year incidence of IE in patients undergoing TAVR was 5.8%, with the highest risk within the first year. Second, TAVR was not associated with a statistically significant different risk of IE compared with SAVR. Third, male sex and a history of chronic kidney disease were associated with a greater risk of IE in patients undergoing TAVR.

INCIDENCE OF IE FOLLOWING TAVR. With ongoing research aimed at further evolvement of the TAVR procedure and expansion of its indications, the volume of procedures is expected to increase rapidly, making it even more important to assess the clinical burden of IE. A number of clinical trials and observational studies have examined the short-term incidence of IE following TAVR (4,5,8–11,18–22). However, these data are conflicting, with a reported 1-year incidence of IE ranging from 0.5% to 3.4%. Possible explanations for the discrepancy are differences in risk profiles and predisposing conditions in patients across studies, different definitions of IE (i.e., some studies included possible IE in addition to

CENTRAL ILLUSTRATION **Infective Endocarditis After Transcatheter Aortic Valve Replacement and Surgical Aortic Valve Replacement**



Patients at risk							
SAVR	3,777	3,457	2,936	2,452	1,896	1,394	955
TAVR	2,632	2,083	1,401	950	625	373	200

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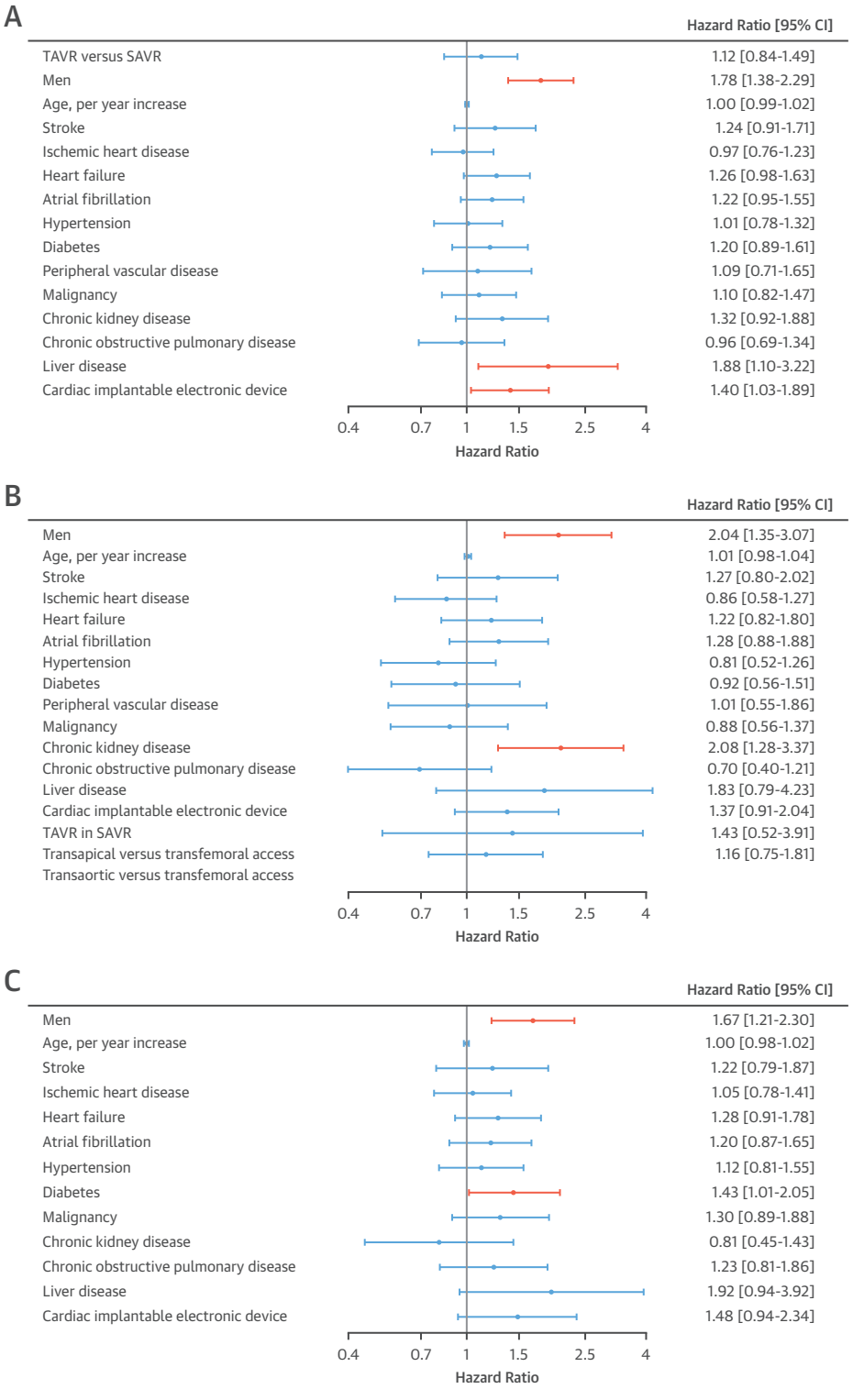
Cumulative incidence of infective endocarditis in patients undergoing TAVR and SAVR. SAVR = surgical aortic valve replacement; TAVR = transcatheter aortic valve replacement.

definite IE as defined by the modified Duke criteria, whereas other studies included all cases of IE and not only prosthetic valve IE), and a low number of patients in the majority of studies. The diagnosis is further challenged by the difficulties in echocardiography imaging due to the stent frame of the prosthesis causing shadowing artefacts. In our study, we found a 1-year cumulative risk of IE of 2.3% in patients undergoing TAVR, suggesting that the risk of IE during the first year following TAVR is not trivial.

Long-term data on the risk of IE following TAVR are sparse and limited by a small number of patients. In a study including only 70 patients who underwent TAVR, the incidence of IE was 1.4% (n = 1) during a median follow-up of 3.7 years (7). In addition, in the multicenter, randomized PARTNER (Placement of Aortic Transcatheter Valves) cohort A clinical trial comparing TAVR and SAVR in patients with aortic stenosis at high surgical risk, the cumulative 5-year incidence of prosthetic valve IE in patients undergoing TAVR and patients undergoing SAVR was 2.0% (5 of 348) and 2.5% (6 of 351), respectively (4). By contrast, the NOTION (Nordic Aortic Valve Intervention) multicenter, randomized trial comparing TAVR and SAVR in an all-comers cohort of patients with severe aortic stenosis reported a 5-year incidence of prosthetic valve IE of 6.9% in the TAVR group and 5.0% in the SAVR group (23). In our all-comers nationwide cohort of 2,632 patients with no history of IE undergoing TAVR, the cumulative 5-year incidence of IE was 5.8%. These data are more in line with those reported from the NOTION trial. Our findings underline that IE is not uncommon in patients undergoing TAVR during long-term follow-up, and preventive efforts aimed at reducing the rate of IE in this population are therefore warranted, especially within the first year following TAVR.

COMPARATIVE RISK OF IE FOLLOWING TAVR AND SAVR. Both the European and American guidelines consider patients undergoing prosthetic valve replacement to be at high risk of IE (1,24,25). Whether TAVR is associated with a different risk of IE than

FIGURE 2 Factors Associated With Infective Endocarditis



(A) Patients undergoing TAVR or SAVR. **(B)** Patients undergoing TAVR. **(C)** Patients undergoing SAVR. CI = confidence interval; other abbreviations as in Figure 1.

TABLE 2 Baseline Characteristics at Discharge in the Matched Cohort of Patients Undergoing TAVR and Isolated SAVR

	SAVR (n = 1,151)	TAVR (n = 1,151)	p Value
Demographics			
Age, yrs	79 (74–82)	79 (74–82)	N/A
Male	619 (53.8)	619 (53.8)	N/A
Comorbidities			
Stroke	115 (10.0)	115 (10.0)	N/A
Ischemic heart disease	584 (50.7)	584 (50.7)	N/A
Heart failure	293 (25.5)	293 (25.5)	N/A
Atrial fibrillation	376 (32.7)	376 (32.7)	N/A
Hypertension	762 (66.2)	846 (73.5)	<0.01
Diabetes	156 (13.6)	156 (13.6)	N/A
Peripheral vascular disease	36 (3.1)	36 (3.1)	N/A
Malignancy	216 (18.8)	232 (20.2)	0.40
Chronic kidney disease	56 (4.9)	56 (4.9)	N/A
Chronic obstructive pulmonary disease	145 (12.6)	145 (12.6)	N/A
Liver disease	21 (1.8)	38 (3.3)	0.03
Cardiac implantable electronic device	125 (10.9)	125 (10.9)	N/A
Year of procedure			N/A
2008	99 (8.6)	21 (1.8)	
2009	136 (11.8)	45 (3.9)	
2010	121 (10.5)	87 (7.6)	
2011	140 (12.2)	90 (7.8)	
2012	137 (11.9)	111 (9.6)	
2013	131 (11.4)	123 (10.7)	
2014	164 (14.3)	141 (12.3)	
2015	110 (9.6)	222 (19.3)	
2016	113 (9.8)	311 (27.0)	

Values are median (25th to 75th percentile) or n (%).
Abbreviations as in Table 1.

SAVR has not been investigated previously. Randomized trials did not find any significant difference in the risk of IE between TAVR and SAVR, though the number of patients and the absolute risk of this complication in these trials was low, and patients participating in randomized trials tend to be selected patients (4-6,21,23). Further, data directly comparing unselected patients undergoing TAVR and SAVR with regard to the risk of IE in a real-world setting are scarce. It has been speculated that the less invasive nature of TAVR may be associated with a lower risk of IE (10,26). though, on the other hand, the high exposure to health care procedures, certain patient characteristics (i.e., advanced age and greater burden of comorbidities) and procedural characteristics (i.e., more metal frame in the transcatheter heart valve) may contribute to increase the risk of IE in patients undergoing TAVR (10). In our study, we compared patients undergoing TAVR with patients undergoing SAVR. In line with the randomized trials, we did not find TAVR to be associated with a statistically significant different risk of IE compared with SAVR. These results confirm the current guidelines in considering patients undergoing prosthetic valve replacement, irrespective of implantation strategy, at high risk of IE.

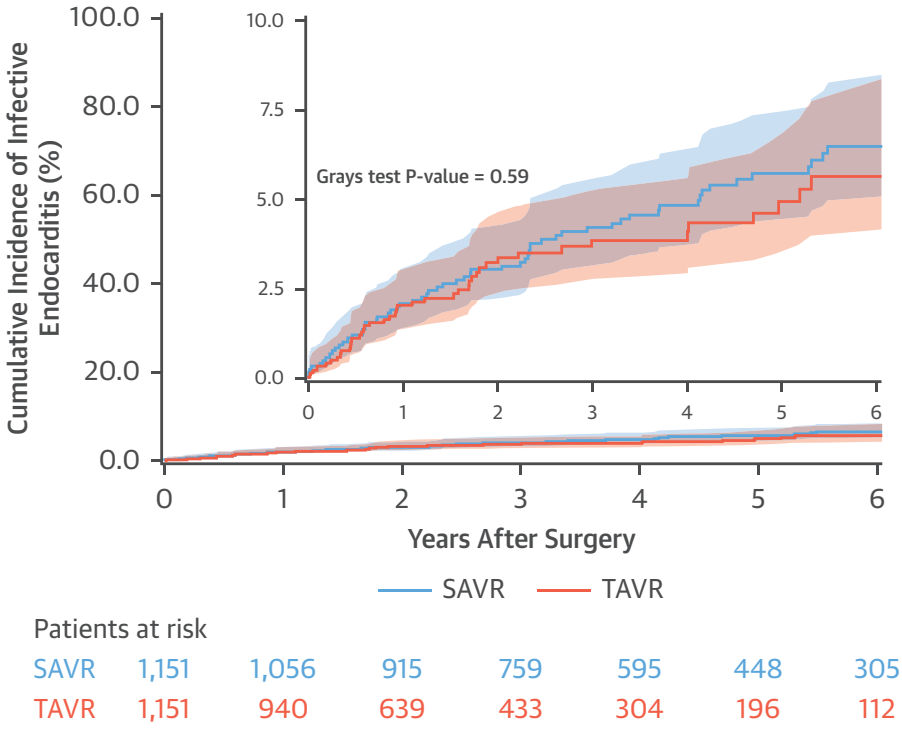
IN-HOSPITAL MORTALITY ASSOCIATED WITH IE. Previous studies have reported IE-related in-hospital mortality rates in patients undergoing TAVR between 11% and up to 67% (9-11,18,27). We found that IE following TAVR was associated with a poor prognosis with an in-hospital mortality of 20.9%. By contrast, SAVR patients who developed IE fared better than TAVR patients, with an in-hospital mortality of only 14.0%. The higher IE-related in-hospital mortality in TAVR patients compared with SAVR patients may in part reflect the primarily conservative treatment strategy applied as well as the higher age and burden of comorbidities.

FACTORS ASSOCIATED WITH IE FOLLOWING TAVR. Identifying patients at particular high risk of IE following TAVR has important implications for preventive efforts aimed at reducing the rate of IE. In line with previous studies (9,11,28), our data revealed that male sex was associated with a significantly increased risk of IE in patients undergoing TAVR. There are no clear explanations to this association, though it has been speculated that differences in comorbid conditions and outcomes as well as sex-specific hormones (a possible endothelial protection of estrogen) in part may explain the observed sex difference in the risk of IE (28-30).

Chronic kidney disease affects general immunity, causing intestinal barrier dysfunction, systemic inflammation, and immunodeficiency, and thereby increases susceptibility to infection (31). In a large cohort of older adults, chronic kidney disease not being treated with dialysis was associated with an increased risk of bloodstream infection (32). In line with these results, we found that chronic kidney disease, independent of age and comorbidities, was associated with a significantly increased risk of developing IE following TAVR. Potential strategies aimed at reducing the risk of IE in patients with chronic kidney disease may therefore include greater surveillance, identification and thorough management of infections, eradication of unnecessary invasive procedures, and reinforcement of preventive measures to reduce the risk of bacteremia.

Other studies evaluating predictors of IE in patients undergoing TAVR have also found diabetes, chronic hemodialysis, peripheral artery disease, orotracheal intubation, and a number of procedural factors and complications, including low valve implantation, residual moderate-to-severe aortic regurgitation or paravalvular leakage, and vascular complications to be associated with a greater risk of

FIGURE 3 **Infective Endocarditis in the Matched Cohort**



Cumulative incidence of infective endocarditis in the matched cohort of patients undergoing TAVR and SAVR. Abbreviations as in **Figure 1**.

IE (9–11,27). In this regard, the procedural characteristics and complications are of particular interest. Compared with the first-generation devices, the newer-generation transcatheter valve devices are specifically designed to address these complications. Therefore, the increasing use of newer-generation devices is expected to translate into lower rates of IE in this specific population. However, long-term follow-up data in patients with newer-generation transcatheter valve devices are warranted to confirm this prospect.

STUDY STRENGTHS AND LIMITATIONS. The main strength of this study is the completeness of data in a large nationwide unselected cohort of patients undergoing TAVR followed in a real-world setting with long-term follow-up. The Danish health care system, funded by taxes, provides equal access to health care services for all residents regardless of socioeconomic or insurance status. The findings of this study should be viewed in the context of a number of limitations. Data on procedural characteristics and complications in relation to the TAVR and SAVR procedures were not available. Patients with IE were identified through the Danish National Patient Registry, which is based on ICD codes. However, the diagnoses of IE and prosthetic valve IE in the Danish National Patient Registry have previously been validated with high positive predictive values (17). In addition, the rates of IE in TAVR patients reported in our study are similar to those from the NOTION trial, conducted at 2 centers in Denmark and 1 in Sweden, in which all clinical events were adjudicated by an independent clinical events committee. We were not able to differentiate between the location of IE (i.e., prosthetic or native valve, or cardiac implantable electronic device). In addition, data on microbiology, use of antibiotic therapy, and findings from echocardiograms and other imaging modalities (e.g., positron emission tomography-computed tomography scans) in patients with IE were not available. The observational nature of this study precludes the assessment of cause-effect relationships, and the possibility of residual confounding cannot be excluded despite adjustment for potential confounders in the Cox regression models comparing TAVR and SAVR with regard to the risk of IE.

Despite the lack of any significant difference with respect to the risk of IE among groups, we found that

TAVR was associated with a higher risk of death compared with SAVR despite adjusting for age, sex, and major comorbid conditions. This finding is not surprising because patients referred for TAVR often are older, carry a higher burden of comorbidities, and particularly are frailer than patients referred for surgical intervention. Consequently, adjusting for all the differences between patients undergoing TAVR and SAVR in the multivariable mortality analysis is not possible. The difference in the risk of mortality among groups may influence the interpretation of the estimates of the comparative risk of IE. However, the cumulative incidences of IE were estimated using the Aalen-Johansen estimator and compared using Gray's test, taking the competing risk of death into account. In addition, we did not find any significant difference with respect to the risk of IE in a thoroughly matched cohort of patients undergoing TAVR and SAVR.

CONCLUSIONS

The 5-year incidence of IE in a large nationwide all-comers cohort of patients undergoing TAVR was 5.8%. TAVR was not associated with a significantly different risk of IE compared with SAVR.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: In a nationwide observational cohort study, the 5-year incidence of IE did not differ significantly between patients undergoing transcatheter or surgical aortic valve replacement.

TRANSLATIONAL OUTLOOK: Additional studies are needed to identify predictors of IE in patients who have undergone aortic valve replacement and enhance strategies for effective prophylaxis.

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KEY WORDS aortic valve replacement, epidemiology, infective endocarditis

APPENDIX For supplemental tables, please see the online version of this paper.