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ORIGINAL RESEARCH

Incidence and Outcomes of Infective Endocarditis After Transcatheter or Surgical Aortic Valve Replacement

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BACKGROUND: Data comparing the frequency and outcomes of infective endocarditis (IE) after transcatheter (TAVR) to surgical aortic valve replacement (SAVR) are scarce. The objective of this study is to compare the incidence and outcomes of IE after TAVR using a supra-annular, self-expanding platform (CoreValve and Evolut) to SAVR.

METHODS AND RESULTS: Data of 3 randomized clinical trials comparing TAVR to SAVR and a prospective continued TAVR access study were pooled. IE was defined on the basis of the modified Duke criteria. The cumulative incidence of IE was determined by modeling the cause-specific hazard. Estimates of all-cause mortality were calculated by means of the Kaplan–Meier method. Outcomes are reported for the valve-implant cohort. During a mean follow-up time of 2.17±1.51 years, 12 (0.5%) of 2249 patients undergoing TAVR and 21 (1.1%) of 1828 patients undergoing SAVR developed IE. Patients with IE more frequently had diabetes mellitus than those without (57.6% versus 34.2%; *P*=0.005). The cumulative incidence of IE was 1.01% (95% CI, 0.47%–1.96%) after TAVR and 1.58% (95% CI, 0.97%–2.46%) after SAVR (*P*=0.047) at 5 years. Among patients with IE, the rate of all-cause mortality was 27.3% (95% CI, 1.0%–53.6%) in the TAVR and 51.8% (95% CI, 28.2%–75.3%) in the SAVR group at 1 year (log-rank *P*=0.15).

CONCLUSIONS: Pooled prospectively collected data comparing TAVR with a supra-annular, self-expanding device to SAVR showed a low cumulative risk of IE irrespective of treatment modality, although the risk was lower in the TAVR implant group. Once IE occurred, mortality was high.

REGISTRATION: URL: https://www.clinicaltrials.gov; Unique identifiers: NCT01240902, NCT01586910, NCT02701283.

Key Words: endocarditis ■ incidence ■ mortality ■ SAVR ■ TAVR

Valve replacement is required in patients with symptomatic severe aortic stenosis to relieve symptoms and improve prognosis.[1] Transcatheter aortic valve replacement (TAVR) and surgical aortic valve replacement (SAVR) are well-established effective and safe treatment options for patients across the whole spectrum of surgical risk.[2–8] Infective endocarditis (IE) of the prosthetic valve is a deleterious complication after valve replacement, which can occur early or late and is associated with a high morbidity and mortality according to observational data.[9–15] Previous reports do not suggest an elevated risk of IE after TAVR compared with SAVR[10,11,13,16]; however, differences in valve design, such as the structure and composition of the stent frame or the tissue type and processing of the prosthetic leaflets, as well as differences in the preparatory steps, ways of valve delivery and implantation modes may all affect the risk of endocarditis

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CLINICAL PERSPECTIVE

What Is New?

- This study reports on the incidence and outcomes of infective endocarditis observed in pooled data of 3 randomized controlled trials and a prospective continued access registry comparing transcatheter aortic valve replacement using a self-expanding platform to surgical aortic valve replacement.
- Although infective endocarditis was infrequent after aortic valve replacement therapies, its cumulative incidence was lower after transcatheter aortic valve replacement with a self-expanding valve than after surgical aortic valve replacement.
- Annular abscess formation was more frequently encountered in endocarditis after surgical aortic valve replacement than transcatheter aortic valve replacement without evidence of a different spectrum of causative microorganisms in the 2 groups.

What Are the Clinical Implications?

- Among patients undergoing aortic valve replacement, the risk of infective endocarditis is low irrespective of the mode of replacement.
- Future studies should investigate whether the lower rates of endocarditis and abscess formation after transcatheter aortic valve replacement using a self-expanding valve compared with surgical aortic valve replacement can be corroborated.

Nonstandard Abbreviations and Acronyms

IE	infective endocarditis
PARTNER	Placement of Aortic Transcatheter Valves
SAVR	surgical aortic valve replacement
SURTAVI	Surgical Replacement and Transcatheter Aortic Valve Implantation
TAVR	transcatheter aortic valve replacement

associated with each specific TAVR device. This study aims to compare the frequency, timing, and outcomes of IE after TAVR with devices of a supra-annular, self-expanding platform (CoreValve and Evolut) to SAVR based on pooled data of 3 randomized controlled trials and a prospective continued access study in patients with severe symptomatic aortic stenosis covering the whole range of surgical risk.

METHODS

Study Design

Data of 3 multicenter randomized controlled trials comparing TAVR using devices of the self-expanding CoreValve family to SAVR in patients with symptomatic severe aortic stenosis at high (CoreValve high risk; clinicaltrials.gov, NCT01240902), intermediate (SURTAVI [Surgical Replacement and Transcatheter Aortic Valve Implantation]); clinicaltrials.gov, NCT01586910) and low (Evolut Low Risk; clinicaltrials.gov, NCT02701283) surgical risk, and data of the SURTAVI continued access study (clinicaltrials.gov, NCT01586910) were aggregated. The studies were conducted at tertiary, high-volume centers across North America, Asia, Europe, and Oceania, and patients were recruited between February 2011 and November 2018. Patients treated with TAVR received a self-expanding, supra-annular bioprosthesis of the CoreValve family (CoreValve, Evolut R, or Evolut PRO; Medtronic, Minneapolis, USA). Patients undergoing SAVR were treated with any bioprosthetic surgical valve at the discretion of the operator. All studies were approved by appropriately constituted competent ethics committees, study conduct complied with the Declaration of Helsinki, and all participants provided written informed consent before inclusion. Detailed information on the trials administrative structure and the specific protocols have been previously published.[3,6,7] Because of the sensitive nature of the data collected for this study, requests to access the data set from qualified researchers trained in human subject confidentiality protocols may be sent to Medtronic, SH&A Clinical Research & Medical Science (8200 Coral Street. MVS66, Mounds View, MN 55112).

Study Population

The study population comprises patients with symptomatic severe aortic stenosis at high, intermediate, or low surgical risk as assessed by the local heart team and the predicted risk of surgical mortality at 30 days based on the Society of Thoracic Surgeons Predicted Risk of Mortality score. All patients were deemed eligible for both TAVR and SAVR by the heart team, and anatomy had to be suitable for both treatment modalities accordingly. Patients with presence of ongoing sepsis were excluded. Details of the eligibility criteria of each included study have been published.[3,6,7]

Definitions and Follow-Up

IE was defined on the basis of the modified Duke criteria: For definite endocarditis, 2 major criteria, or 1 major and 3 minor criteria, or 5 minor criteria

were required; for possible endocarditis, 1 major and 1 minor criterion, or 3 minor criteria.[9] Endocarditis was classified as early if it occurred within a year of valve replacement, otherwise as late.[9] Clinical end points were defined according to the Valve Academic Research Consortium's (and Valve Academic Research Consortium 2) definitions and adjudicated by an independent clinical events committee. Follow-up was performed at least 3 times in the first year and yearly thereafter, with a maximum follow-up time of 5 years.

Statistical Analysis

Analyses were performed in the valve-implanted population comprising the patients in whom a TAVR valve or a surgical valve was actually implanted; sensitivity analyses were performed in the as-treated (attempted trial treatment according to allocation) populations as well as in the as-treated cohort excluding the patients of the SURTAVI continued access study. Patient and procedural characteristics are presented as counts (percentage) for categorical variables and mean (±SD) for continuous ones. *P* values were derived from Student's *t*-tests for comparisons of continuous data and Fisher's exact tests when the observed count was <5 and otherwise with the chi-square test for categorical variables. Cumulative incidence estimates were derived by modeling the cause-specific hazard, taking into account the competing risk of death, and curves were compared using Gray's test.[17] Incidence rates and CIs were obtained using normal approximation to the Poisson distribution. Clinical outcomes after endocarditis were assessed by means of the Kaplan–Meier method stratified by the mode of valve replacement and survival curves were compared using the log-rank test. All statistical analyses were performed with the use of SAS software, version 9.4 (SAS Institute Inc, Cary, NC).

RESULTS

Baseline and Procedural Characteristics

A total of 4301 patients were randomly assigned to TAVR or SAVR in the trials or enrolled in the continued access study. In 4088 patients the assigned valve replacement procedure was attempted, and in 4077 patients a valve was implanted (Figure 1). In the valve-implant cohort 33 cases of endocarditis occurred; 12

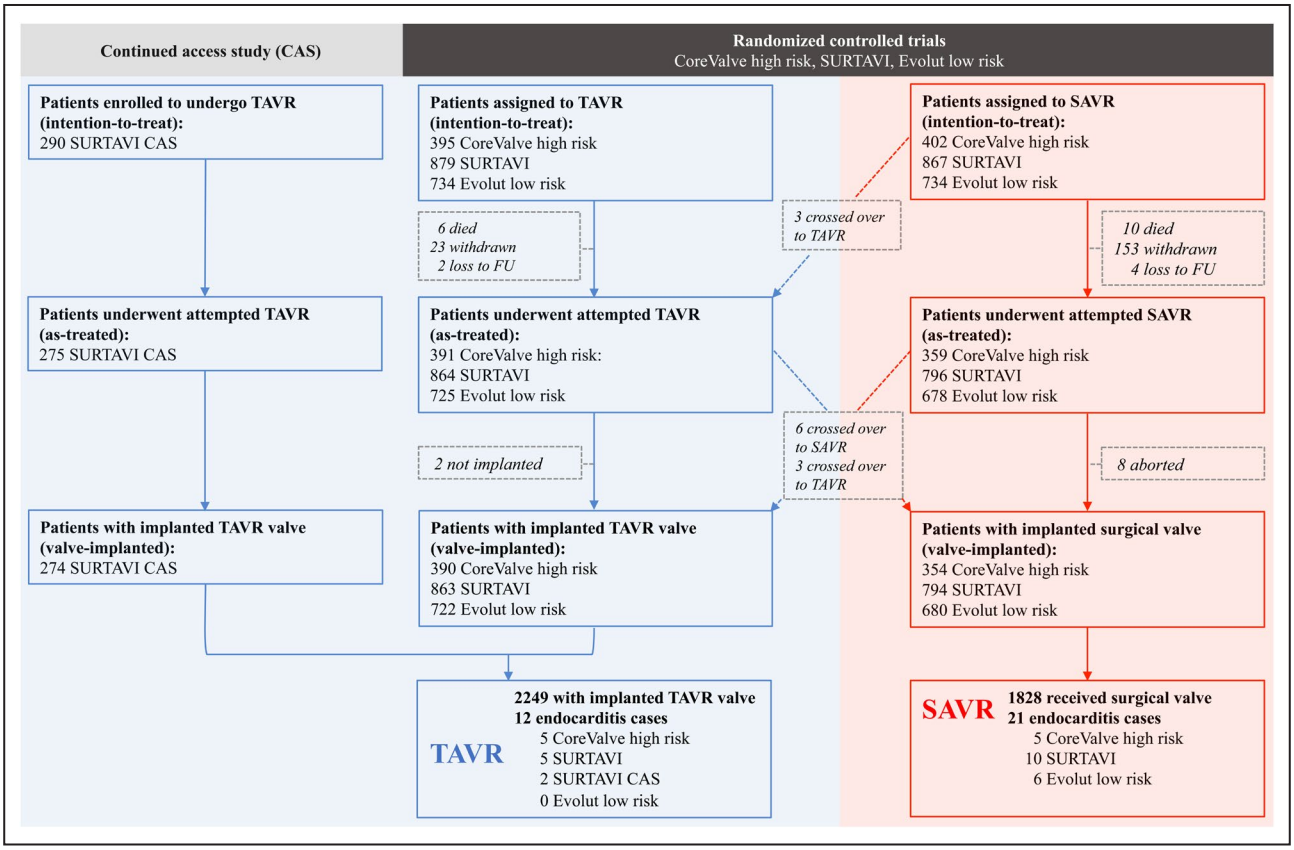

Figure 1. Flowchart depicting the patient flow from the intention-to-treat to the as-treated and valve-implanted cohorts in the randomized trials and the SURTAVI continued access study.
FU indicates follow-up; SAVR, surgical aortic valve replacement; SURTAVI, Surgical Replacement and Transcatheter Aortic Valve Implantation; and TAVR, transcatheter aortic valve replacement.

(0.5%) in 2249 in the TAVR group during a mean follow-up of 2.15 (±1.49) years and 21 (1.1%) in 1828 patients in the SAVR group during a mean follow-up of 2.17 (±1.54) years.

The mean age of the valve-implant cohort was 78.3±7.1 years, 42.1% were women (Table 1). Mean Society of Thoracic Surgeons Predicted Risk of Mortality score was 4.1±2.6. Patients with endocarditis experienced on average more heart failure symptoms (New York Heart Association class III/IV: 72.7% versus 51.8%; *P*=0.022), and were more likely to suffer from diabetes mellitus (57.6% versus 34.2%; *P*=0.005) at baseline (Table 1). There were no significant differences in the distribution of baseline characteristics comparing TAVR and SAVR patients with IE (Table S1). The mean time in the catheterization laboratory or operating room did not differ between patients developing endocarditis and those who did not (Table S2.) There was a numerical trend toward a higher proportion of concomitant percutaneous revascularization procedures among patients who developed subsequent endocarditis compared with those without endocarditis in the TAVR group (25% versus 8.3%; *P*=0.07); this was not observed for surgical revascularization in patients treated with SAVR (Table S2).

Incidence of IE

The incidence rate of IE amounted to 3.74 (95% CI, 2.46–5.01) per 1000 patient-years in the total cohort, 2.47 (95% CI, 1.07–3.87) per 1000 patient-years in the TAVR, and 5.28 (95% CI, 3.02–7.54) per 1000 patient-years in the SAVR group. The overall estimated cumulative incidence of endocarditis at 5 years amounted to 1.28% (95% CI, 0.83%–1.88%), taking into account the competing risk of death. In the TAVR group, the cumulative incidence of endocarditis at 5 years was 1.01% (95% CI, 0.47%–1.96%) and 1.58% (95% CI, 0.97%–2.46%) in the SAVR group (*P*= 0.047) (Figure 2). Sensitivity analyses showed that in the as-treated cohort cumulative incidence was 1.05% (95% CI, 0.50%–1.99%) in the TAVR and 1.59% (95% CI, 0.98%–2.46%%) in the SAVR group at 5 years (*P*=0.07) (Figure S1); cumulative incidence estimates were 1.00% in the TAVR and 1.59% in the SAVR group at 5 years if patients of the SURTAVI continued access study were excluded (*P*=0.049) (Figure S2). Cumulative incidence rates at 2 years stratified by surgical risk categories are reported in Table S3. There was no indication of a difference in the incidence of IE according to bioprosthetic leaflet tissue type (Figure S3).

Table 1. Baseline Clinical Characteristics Stratified by Outcome

Characteristic	Endocarditis (N=33)	No Endocarditis (N=4044)	*P* Value
Age, y	77.2±7.3	78.3±7.1	0.37
Female sex	36.4 (12/33)	42.1 (1702/4044)	0.51
Body mass index, kg/m^2	30.7±5.0	29.7±6.0	0.35
STS score, %	4.4±2.2	4.1±2.6	0.47
NYHA class			0.024
I	0.0 (0/33)	3.4 (139/4044)	
II	27.3 (9/33)	44.7 (180/4044)	
III	66.7 (22/33)	45.7 (1847/4044)	
IV	6.1 (2/33)	6.2 (249/4044)	
Diabetes mellitus	57.6 (19/33)	34.2 (1382/4044)	0.005
Serum creatinine >2 mg/dL	3.0 (1/33)	1.6 (65/4044)	0.42
Chronic lung disease	45.5 (15/33)	30.8 (1226/3982)	0.07
Peripheral vascular disease	48.1 (13/27)	32.7 (864/2643)	0.09
Cerebrovascular disease	18.2 (6/33)	16.4 (662/4035)	0.78
History of hypertension	100.0 (33/33)	89.6 (3622/4042)	0.051
Previous PCI	21.2 (7/33)	21.6 (872/4044)	0.96
Previous CABG	15.2 (5/33)	14.0 (565/4044)	0.85
Previous MI	21.2 (7/33)	13.1 (528/4044)	0.17
Atrial fibrillation/flutter	27.3 (9/33)	25.7 (1036/4038)	0.83
Immunosuppressive therapy	9.1 (3/33)	5.9 (237/4042)	0.44
Preexisting pacemaker or ICD	3.0 (1/33)	9.9 (400/4043)	0.25

Data comprise all patients from the CoreValve Pivotal High Risk, SURTAVI, and Evolut Low Risk trials as well as the SURTAVI continued access registry. Data are presented as % (number/denominator) or as mean±SD. *P* values are derived from Fisher's exact tests for categorical variables and Student *t*-tests for continuous variables.

CABG indicates coronary artery bypass grafting; CCS, Canadian Cardiovascular Society; ICD, intracardiac defibrillator; MI, myocardial infarction; NYHA, New York Heart Association; PCI, percutaneous coronary intervention; and SURTAVI, Surgical Replacement and Transcatheter Aortic Valve Implantation.

Characteristics of IE

A total of 27 (81.8%) of 33 patients fulfilled the modified Duke criteria for definite IE, the remaining the criteria for possible endocarditis (Table 2). Half of the IE cases occurred early (≤365 days), the other half late (>365 days) after valve replacement. Among patients with endocarditis, abscess formation was observed more frequently after SAVR than after TAVR (47.6% versus 8.3%; *P*=0.027) (Table 2). The most frequent causative microorganisms were *Streptococcus* (33.3%) and *Enterococcus* species (30.3%), followed by coagulase-negative staphylococci (18.2%), and *Staphylococcus aureus* (15.2%) (Table 2). No notable differences were observed between the TAVR and SAVR groups with regard to the detected microorganisms. In both groups, roughly two-thirds of the patients with IE were treated conservatively with antibiotic treatment only, whereas one-third underwent surgical intervention in addition (Table 2).

Outcomes of IE

In the overall cohort, all-cause mortality after the occurrence of IE was 42.3% (95% CI, 24.5%–60.1%) at 1 year. In the TAVR cohort, 1-year all-cause mortality amounted to 27.3% (95% CI, 1.0%–53.6%), in the SAVR group to 51.8% (95% CI, 28.2%–75.3%) (*P*=0.15) (Figure 3). The composite of all-cause mortality and stroke occurred in 55.0% (95% CI, 24.5%–85.5%) in the TAVR and 64.6% (95% CI, 32.1%–97.1%) in the SAVR group at 2 years (*P*=0.71) (Figure S4). Mortality in the cohort including only patients of the randomized trials is shown in Figure S5. One-year mortality did not differ between patients with endocarditis with and without abscess formation (45.5% versus 40.7%; *P*=0.50) (Figure S6). One-year mortality rates stratified by surgical risk category are reported in Table S4.

DISCUSSION

This analysis of pooled data of 3 large randomized clinical trials and a prospective continued access study showed a higher prevalence of diabetes mellitus and symptoms of heart failure in patients developing IE after aortic valve replacement at baseline than in those who do not. Incidence rates of IE were 2.47 per 1000 person-years with TAVR and 5.28 per 1000 person-years with SAVR. In the valve-implanted cohort, the cumulative incidence at 5 years was lower in those who underwent TAVR (1.01%) than those who received SAVR (1.58%). Half of the endocarditis cases occurred within a year of valve replacement. Abscess formation was more frequently reported in patients with endocarditis after SAVR than after TAVR (47.6% versus 8.3%). *Streptococcus* and *Enterococcus* species were the most frequent causative microorganisms

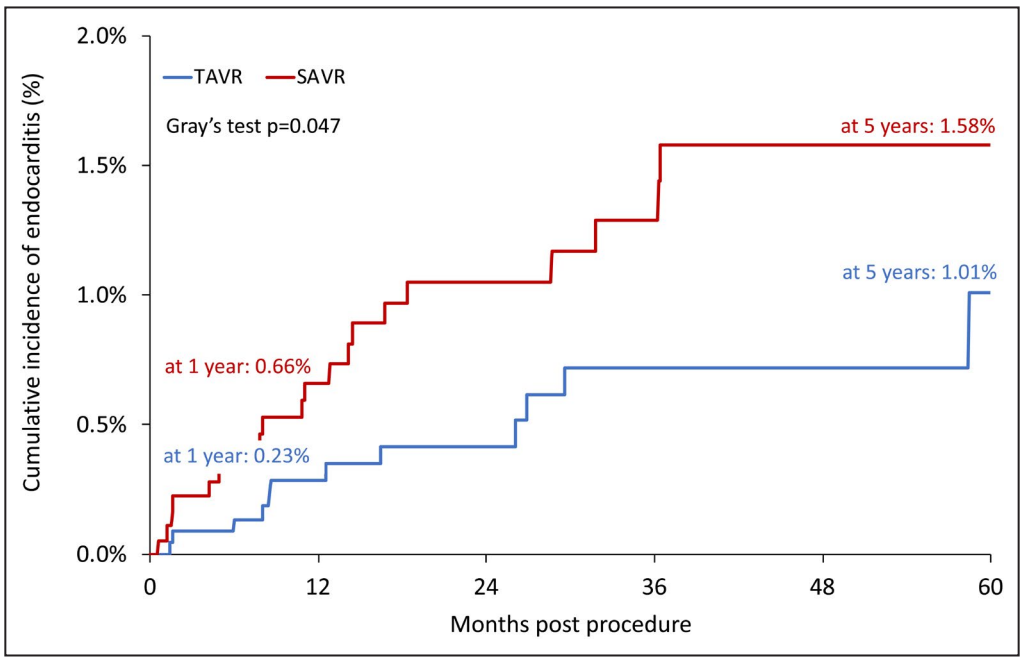

Figure 2. Cumulative incidence of endocarditis taking into account the competing risk of death in the SAVR group amounted to 0.66% (95% CI, 0.35%–1.15%) at 1 year, and 1.58% (95% CI, 0.97%–2.46%) at 5 years, in the TAVR group to 0.23% (95% CI, 0.12%–0.61%) at 1 year and 1.01% (95% CI, 0.47%–1.96%) at 5 years.
SAVR indicates surgical aortic valve replacement; and TAVR, transcatheter aortic valve replacement.

Table 2. Characteristics of Endocarditis Stratified by Mode of Valve Replacement

Characteristic	TAVR (N=12), n (%)	SAVR (N=21), n (%)	*P* Value
Early*	6 (50)	11 (52.4)	>0.99
Late*	6 (50)	10 (47.6)	>0.99
Definite†	10 (83.3)	17 (81)	>0.99
Possible†	2 (16.7)	4 (19)	>0.99
Echocardiographic findings			
Vegetation	10 (83.3)	11 (52.4)	0.13
Abscess	1 (8.3)	10 (47.6)	0.027
Moderate or more valve regurgitation	2 (16.7)	5 (23.8)	0.99
Microorganism‡			
Gram-positive bacilli	12 (92.3)	20§ (100)	0.39
Staphylococcus aureus	2 (15.4)	3 (15)	>0.99
Coagulase-negative staphylococci	2 (15.4)	4 (20)	>0.99
Streptococcus species	5 (38.5)	5§ (25)	0.46
Viridans group streptococci	5 (38.5)	2 (10)	0.08
Non-viridans group streptococci	0 (0)	2 (10)	0.51
Enterococcus species	3 (23.1)	7 (35)	0.70
Gram-negative bacilli	1 (7.7)	0 (0)	0.39
Polymicrobial (≥2 microorganisms)	1 (7.7)	3 (15)	>0.99
Not documented	0 (0)	4 (20)	0.14
Treatment			
Antibiotic only	8 (66.7)	13 (61.9)	>0.99
Valve surgery	4 (33.3)	8 (38.1)	>0.99

*Early ≤365 days, late >365 days after the index intervention.
†According to modified Duke criteria.
‡In this section, percentages refer to total number of identified microorganisms and not patients.
§One microorganism not further specified.
SAVR indicates surgical aortic valve replacement; TAVR, transcatheter aortic valve replacement.

followed by *Staphylococcus aureus*. About a third of the endocarditis patients underwent surgical intervention. All-cause mortality after endocarditis was 42.3% at 1 year, with a numerically higher rate in the SAVR than the TAVR group (51.8% versus 27.3%).

The reported incidence rates of IE after TAVR and SAVR range between 1% and 2% per year in the vast majority of observational studies.[10,12,15,16,18–21] An analysis of pooled data encompassing 8530 patients included in the PARTNER (Placement of Aortic Transcatheter Valves) I and II trial series and registries reported a lower overall incidence rate of IE with 0.5% per year.[11] The incidence rates observed in our analysis are in line with these latter findings (0.4% per year). Whether the rates observed in randomized controlled trials are lower because of a reduction in misclassification as a consequence of the independent adjudication of events or rather because of an underreporting of events in these trials as endocarditis was merely a secondary outcome remains unknown.

Several studies have compared the incidence of IE after TAVR with SAVR. Neither crude incidence rates nor studies that performed adjustment for potential confounders by means of regression analysis or propensity-score matching suggest significantly different rates of IE after surgical or transcatheter valve replacement.[10,11,16,18,22] In this context, the lower cumulative incidence of endocarditis observed in the TAVR group in this study has to be interpreted with caution.

The potential predictors of IE after aortic valve replacement reported in the literature vary considerably[11–13,15,16,21,22]; on the one hand, this heterogeneity can be explained by the fact that endocarditis is a rare event, and on the other hand by a lack of granularity of data with respect to patient- and procedure-related factors.

Two-thirds of the endocarditis cases observed in our cohort were caused by typical microorganisms as defined by the modified Duke criteria.[9] The high proportion of enterococci species observed as causative microorganisms is consistent with previous reports; the proportion of *Staphylococcus aureus* appears lower, but inferences are precluded by the low number of overall cases.[11,12,14–16,20,23,24]

Data comparing the incidence of periannular abscess formation observed in endocarditis cases after SAVR to TAVR are scarce. An observational study that investigated endocarditis cases after aortic valve replacement in Finland also reported higher rates of abscesses detected by echocardiography in the SAVR group (0% versus 32.1% [*P*=0.011]).[22] Rates of periannular aortic abscesses detected in patients undergoing TAVR with diagnosed endocarditis range between 3.6% to 19.1% in the literature,[12,16,20,25] whereas reported rates in patients undergoing SAVR vary from 30% to 55%.[26–28] Whether the higher proportion of periannular abscesses found in the SAVR group is related to procedural differences such as the resection of the native aortic valve and deeper wound trauma incurred during SAVR or whether this finding is by chance or caused by detection bias remains unknown and warrants further investigation in future studies.

In contrast to the discrepancies observed between randomized and observational studies regarding the incidence rates of endocarditis, the 1-year all-cause mortality rate of 42.3% in our cohort is in accordance with the rates observed in observational studies.[12,14,18,21,22] Studies consistently report a rapid increase in mortality during the first months after the

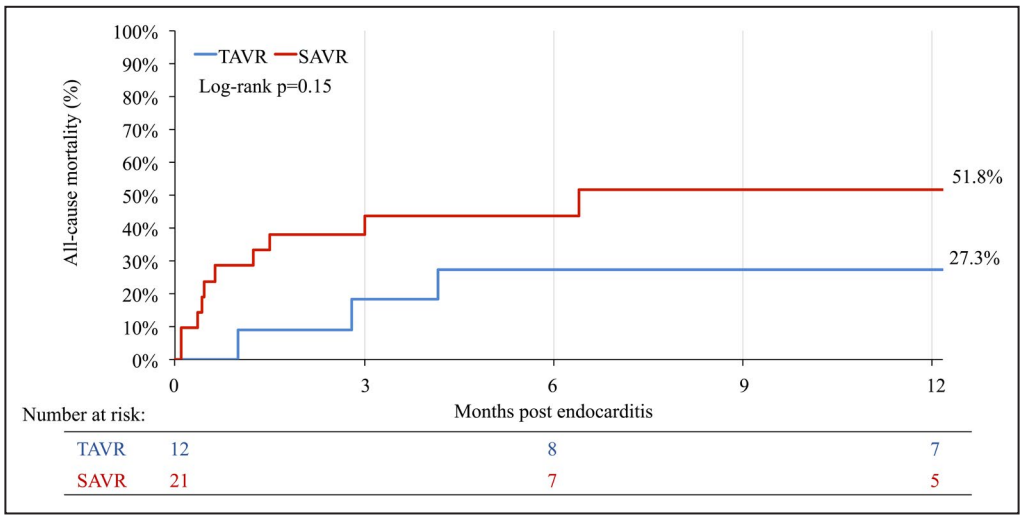

Figure 3. Kaplan–Meier curves depicting all-cause mortality after endocarditis stratified by mode of valve replacement.
In the TAVR cohort, 1-year all-cause mortality was 27.3% (95% CI, 1.0%–53.6%) and in the SAVR group 51.8% (95% CI, 28.2%–75.3%). SAVR indicates surgical aortic valve replacement; and TAVR, transcatheter aortic valve replacement.

occurrence of endocarditis, and a mortality of 30% to 50% of the affected population at 1 year and 50% to 70% at 2 years.[12,14,18,21,22] The numerical difference in 1-year mortality after TAVR and SAVR observed in our study did not reach statistical significance and was not attributable to the higher prevalence of abscess formation observed in patients with endocarditis after SAVR.

Although this analysis was based on data obtained from rigorously conducted prospective randomized trials and studies, there are certain limitations. Notwithstanding the independent adjudication of all events by an independent clinical event committee, diagnosis of endocarditis is complex and misclassification is possible as the diagnostic value of the modified Duke criteria is limited, and multimodality imaging, which could enhance diagnostic sensitivity, is not performed frequently enough.[29,30] Treatment crossovers may distort results of the comparison between TAVR and SAVR; however, robustness of findings in the valve-implant cohort was assessed by performing sensitivity analyses in the as-treated study population and by excluding the patients of the nonrandomized continued access study. A further limitation of the presented analysis is the lack of information on antimicrobial prophylaxis. The low number of cases precludes the inference of predictors, a more detailed analysis of causative microorganisms in relation to the timing of endocarditis as well as assessment of differences in IE rates between surgical risk categories.

In conclusion, this analysis of pooled prospective data comparing TAVR with a supra-annular, self-expanding device to SAVR showed a low cumulative risk of IE in both groups, although it was lower in the TAVR implant group. If endocarditis occurred, mortality rates were high irrespective of the mode of valve replacement.

ARTICLE INFORMATION

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Supplementary Material

Tables S1–S4
Figures S1–S6

REFERENCES

1. Otto CM, Prendergast B. Aortic-valve stenosis — from patients at risk to severe valve obstruction. *N Engl J Med*. 2014;371:744–756. DOI: 10.1056/NEJMra1313875.
2. Smith CR, Leon MB, Mack MJ, Miller DC, Moses JW, Svensson LG, Tuzcu EM, Webb JG, Fontana GP, Makkar RR, et al. Transcatheter versus surgical aortic-valve replacement in high-risk patients. *N Engl J Med*. 2011;364:2187–2198. DOI: 10.1056/NEJMoa1103510.
3. Adams DH, Popma JJ, Reardon MJ, Yakubov SJ, Coselli JS, Deeb GM, Gleason TG, Buchbinder M, Hermiller J, Kleiman NS, et al. Transcatheter aortic-valve replacement with a self-expanding prosthesis. *N Engl J Med*. 2014;370:1790–1798. DOI: 10.1056/NEJMoa1400590.
4. Thyregod HG, Steinbruchel DA, Ihlemann N, Nissen H, Kjeldsen BJ, Petursson P, Chang Y, Franzen OW, Engstrom T, Clemmensen P, et al. Transcatheter versus surgical aortic valve replacement in patients with severe aortic valve stenosis: 1-year results from the all-comers notion randomized clinical trial. *J Am Coll Cardiol*. 2015;65:2184–2194. DOI: 10.1016/j.jacc.2015.03.014.
5. Leon MB, Smith CR, Mack MJ, Makkar RR, Svensson LG, Kodali SK, Thourani VH, Tuzcu EM, Miller DC, Herrmann HC, et al. Transcatheter or surgical aortic-valve replacement in intermediate-risk patients. *N Engl J Med*. 2016;374:1609–1620. DOI: 10.1056/NEJMoa1514616.
6. Reardon MJ, Van Mieghem NM, Popma JJ, Kleiman NS, Søndergaard L, Mumtaz M, Adams DH, Deeb GM, Maini B, Gada H, et al. Surgical or transcatheter aortic-valve replacement in intermediate-risk patients. *N Engl J Med*. 2017;376:1321–1331. DOI: 10.1056/NEJMoa1700456.
7. Mack MJ, Leon MB, Thourani VH, Makkar R, Kodali SK, Russo M, Kapadia SR, Malaisrie SC, Cohen DJ, Pibarot P, et al. Transcatheter aortic-valve replacement with a balloon-expandable valve in low-risk patients. *N Engl J Med*. 2019;380:1695–1705. DOI: 10.1056/NEJMoa1814052.
8. Popma JJ, Deeb GM, Yakubov SJ, Mumtaz M, Gada H, O'Hair D, Bajwa T, Heiser JC, Merhi W, Kleiman NS, et al. Transcatheter aortic-valve replacement with a self-expanding valve in low-risk patients. *N Engl J Med*. 2019;380:1706–1715. DOI: 10.1056/NEJMoa1816885.
9. Baddour LM, Wilson WR, Bayer AS, Fowler VG, Tleyjeh IM, Rybak MJ, Barsic B, Lockhart PB, Gewitz MH, Levison ME, et al. Infective endocarditis in adults: diagnosis, antimicrobial therapy, and management of complications. *Circulation*. 2015;132:1435–1486. DOI: 10.1161/CIR.0000000000000296.
10. Butt JH, Ihlemann N, De Backer O, Søndergaard L, Havers-Borgersen E, Gislason GH, Torp-Pedersen C, Køber L, Fosbøl EL. Long-term risk of infective endocarditis after transcatheter aortic valve replacement. *J Am Coll Cardiol*. 2019;73:1646–1655. DOI: 10.1016/j.jacc.2018.12.078.
11. Summers MR, Leon MB, Smith CR, Kodali SK, Thourani VH, Herrmann HC, Makkar RR, Pibarot P, Webb JG, Leipsic J, et al. Prosthetic valve endocarditis after TAVR and SAVR. *Circulation*. 2019;140:1984–1994. DOI: 10.1161/CIRCULATIONAHA.119.041399.
12. Bjursten H, Rasmussen M, Nozohoor S, Götberg M, Olaison L, Rück A, Ragnarsson S. Infective endocarditis after transcatheter aortic valve implantation: a nationwide study. *Eur Heart J*. 2019;40:3263–3269. DOI: 10.1093/eurheartj/ehz588.
13. Ando T, Ashraf S, Villablanca PA, Telila TA, Takagi H, Grines CL, Afonso L, Briasoulis A. Meta-analysis comparing the incidence of infective endocarditis following transcatheter aortic valve implantation versus surgical aortic valve replacement. *Am J Cardiol*. 2019;123:827–832. DOI: 10.1016/j.amjcard.2018.11.031.
14. Regueiro A, Linke A, Latib A, Ihlemann N, Urena M, Walther T, Husser O, Herrmann HC, Nombela-Franco L, Cheema A, et al. Infective endocarditis following transcatheter aortic valve replacement. *Circ Cardiovasc Interv*. 2019;12:e007938. DOI: 10.1161/CIRCINTERVENTIONS.119.007938.
15. Stortecky S, Heg D, Tueller D, Pilgrim T, Muller O, Noble S, Jeger R, Toggweiler S, Ferrari E, Taramasso M, et al. Infective endocarditis after transcatheter aortic valve replacement. *J Am Coll Cardiol*. 2020;75:3020–3030. DOI: 10.1016/j.jacc.2020.04.044.
16. Kolte D, Goldsweig A, Kennedy KF, Abbott JD, Gordon PC, Sellke FW, Ehsan A, Sodha N, Sharaf BL, Aronow HD. Comparison of incidence, predictors, and outcomes of early infective endocarditis after transcatheter aortic valve implantation versus surgical aortic valve replacement in the united states. *Am J Cardiol*. 2018;122:2112–2119. DOI: 10.1016/j.amjcard.2018.08.054.
17. Pintilie M. Analysing and interpreting competing risk data. *Stat Med*. 2007;26:1360–1367. DOI: 10.1002/sim.2655.
18. Fauchier L, Bisson A, Herbert J, Lacour T, Bourguignon T, Saint Etienne C, Bernard A, Deharo P, Bernard L, Babuty D. Incidence and outcomes of infective endocarditis after transcatheter aortic valve implantation versus surgical aortic valve replacement. *Clin Microbiol Infect*. 2020;26:1368–1374. DOI: 10.1016/j.cmi.2020.01.036.
19. Latib A, Naim C, De Bonis M, Sinning JM, Maisano F, Barbanti M, Parolari A, Lorusso R, Testa L, Actis Dato GM, et al. TAVR-associated prosthetic valve infective endocarditis. *J Am Coll Cardiol*. 2014;64:2176. DOI: 10.1016/j.jacc.2014.09.021.
20. Mangner N, Woitek F, Haussig S, Schlotter F, Stachel G, Höllriegel R, Wilde J, Lindner A, Holzhey D, Leontyev S, et al. Incidence, predictors, and outcome of patients developing infective endocarditis following transfemoral transcatheter aortic valve replacement. *J Am Coll Cardiol*. 2016;67:2907. DOI: 10.1016/j.jacc.2016.03.588.
21. Regueiro A, Linke A, Latib A, Ihlemann N, Urena M, Walther T, Husser O, Herrmann HC, Nombela-Franco L, Cheema AN, et al. Association between transcatheter aortic valve replacement and subsequent infective endocarditis and in-hospital death. *JAMA*. 2016;316:1083–1092. DOI: 10.1001/jama.2016.12347.
22. Moriyama N, Laakso T, Biancari F, Raivio P, Jalava MP, Jaakkola J, Dahlbacka S, Kinnunen E-M, Juvonen T, Husso A, et al. Prosthetic valve endocarditis after transcatheter or surgical aortic valve replacement with a bioprosthesis: results from the FinnValve registry. *EuroIntervention*. 2019;15:e500–e507. DOI: 10.4244/EIJ-D-19-00247.
23. Cahill TJ, Baddour LM, Habib G, Hoen B, Salaun E, Pettersson GB, Schäfers HJ, Prendergast BD. Challenges in infective endocarditis. *J Am Coll Cardiol*. 2017;69:325. DOI: 10.1016/j.jacc.2016.10.066.
24. Khan A, Aslam A, Satti KN, Ashiq S. Infective endocarditis post-transcatheter aortic valve implantation (TAVI), microbiological profile and clinical outcomes: a systematic review. *PLoS One*. 2020;15:e0225077. DOI: 10.1371/journal.pone.0225077.
25. Amat-Santos IJ, Messika-Zeitoun D, Eltchaninoff H, Kapadia S, Lerakis S, Cheema AN, Gutiérrez-Ibanes E, Munoz-Garcia AJ, Pan M, Webb JG, et al. Infective endocarditis after transcatheter aortic valve implantation. *Circulation*. 2015;131:1566–1574. DOI: 10.1161/CIRCULATIONAHA.114.014089.
26. Graupner C, Vilacosta I, SanRomán J, Ronderos R, Sarriá C, Fernández C, Mújica R, Sanz O, Sanmartín JV, Pinto AG. Periannular extension of infective endocarditis. *J Am Coll Cardiol*. 2002;39:1204–1211. DOI: 10.1016/S0735-1097(02)01747-3.
27. Anguera I, Miro JM, Cabell CH, Abrutyn E, Fowler VG, Hoen B, Olaison L, Pappas PA, de Lazzari E, Eykyn S, et al. Clinical characteristics and outcome of aortic endocarditis with periannular abscess in the international collaboration on endocarditis merged database. *Am J Cardiol*. 2005;96:976–981. DOI: 10.1016/j.amjcard.2005.05.056.
28. Wang A, Athan E, Pappas PA, Fowler VG, Olaison L, Paré C, Almirante B, Muñoz P, Rizzi M, Naber C. Contemporary clinical profile and outcome of prosthetic valve endocarditis. *J Am Med Assoc*. 2007;297:1354–1361. DOI: 10.1001/jama.297.12.1354.
29. Habib G, Lancellotti P, Antunes MJ, Bongiorni MG, Casalta J-P, Del Zotti F, Dulgheru R, El Khoury G, Erba PA, Iung B, et al. 2015 esc guidelines for the management of infective endocarditis: The task force for the management of infective endocarditis of the European Society of Cardiology (ESC). Endorsed by: European Association for Cardio-thoracic Surgery (EACTS), the European Association of Nuclear Medicine (EANM). *Eur Heart J*. 2015;36:3075–3128. DOI: 10.1093/eurheartj/ehv319.
30. Salaun E, Sportouch L, Barral P-A, Hubert S, Lavoute C, Casalta A-C, Pradier J, Ouk D, Casalta J-P, Lambert M, et al. Diagnosis of infective endocarditis after TAVR. *JACC Cardiovasc Imaging*. 2018;11:143–146. DOI: 10.1016/j.jcmg.2017.05.016.

SUPPLEMENTAL MATERIAL

Table S1. Baseline characteristics stratified by mode of valve replacement and outcome in the valve-implant cohort.

	TAVR			SAVR			
Characteristic	**Endocarditis (N = 12)**	**No endocarditis (N = 2237)**	**P value**	**Endocarditis (N = 21)**	**No endocarditis (N = 1807)**	**P value**	**P value** (TAVR vs SAVR with endocarditis)
Age (yrs)	78.5 ± 5.6	78.5 ± 7.1	0.9992	76.5 ± 8.1	78.2 ± 7.1	0.30	0.46
Female sex	41.7% (5)	42.6% (953)	0.9479	33.3% (7)	41.4% (749)	0.45	0.63
Body mass index (kg/m^2)	30.9 ± 5.2	29.7 ± 6.1	0.5044	30.6 ± 5.0	29.7 ± 5.9	0.50	0.86
STS Score (%)	4.9 ± 1.9	4.1 ± 2.5	0.2291	4.1 ± 2.4	4.1 ± 2.8	0.99	0.32
NYHA class			0.1080			0.12	0.73
I	0.0% (0)	3.4% (76)		0.0% (0)	3.5% (63)		
II	25.0% (3)	45.2% (1011)		28.6% (6)	44.2% (798)		
III	66.7% (8)	45.4% (1016)		66.7% (14)	46.0% (831)		
IV	8.3% (1)	6.0% (134)		4.8% (1)	6.4% (115)		
Diabetes	58.3% (7)	33.6% (751)	0.0703	57.1% (12)	34.9% (631)	0.034	0.95
Serum creatinine >2 mg/dl	0.0% (0)	1.4% (31)	0.6813	4.8% (1)	1.9% (34)	0.34	> 0.99

Chronic lung disease	50.0% (6)	31.5% (695)	0.1701	42.9% (9)	29.9% (531)	0.20	0.69
Peripheral vascular disease	50.0% (6)	32.3% (489)	0.1932	46.7% (7)	33.2% (375)	0.27	0.86
Cerebrovascular disease	25.0% (3)	16.5% (369)	0.4321	14.3% (3)	16.3% (293)	> 0.99	0.64
History of hypertension	100.0% (12)	90.6% (2025)	0.2636	100.0% (21)	88.4% (1597)	0.10	NA
Previous PCI	25.0% (3)	21.6% (484)	0.7299	19.0% (4)	21.5% (388)	> 0.99	0.69
Previous CABG	16.7% (2)	13.8% (308)	0.6761	14.3% (3)	14.2% (257)	> 0.99	> 0.99
Previous MI	25.0% (3)	13.2% (296)	0.2068	19.0% (4)	12.8% (232)	0.34	0.69
Atrial fibrillation/flutter	25.0% (3)	25.6% (572)	> 0.9999	28.6% (6)	25.7% (464)	0.77	> 0.99
Immunosuppressive therapy	0.0% (0)	6.1% (137)	0.3764	14.3% (3)	5.5% (100)	0.11	0.28
Pre-existing PM or ICD	8.3% (1)	9.8% (219)	> 0.9999	0.0% (0)	10.0% (181)	0.13	0.36

Data comprises all patients from the CoreValve Pivotal High Risk, SURTAVI and Low Risk trials as well as the SURTAVI continued access study. Data is presented as % (number/denominator) or as mean ± standard deviation. P values are derived from Fisher`s exact tests for categorical variables and Student`s t-tests for continuous variables. NYHA, New York Heart Association; CCS, Canadian Cardiovascular Society; PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting; TIA, transient ischemic attack; PM, pacemaker; ICD, intracardiac defibrillator.

Table S2. Procedural characteristics stratified by mode of valve replacement and outcome.

	TAVR			SAVR		
Characteristic	**Endocarditis (N = 12)**	**No endocarditis (N = 2237)**	**P value**	**Endocarditis (N = 21)**	**No endocarditis (N = 1807)**	**P value**
Total Time in Cath Lab or OR						
N	11	2232		21	1790	
Mean ± SD (minutes)	169.4 ± 36.9	176.8 ± 63.5	0.70	283.6 ± 62.2	293.0 ± 84.5	0.61
Access Route			0.88			NA
Femoro-iliac	100% (12/12)	93.8% (2097/2236)		NA	NA	
Subclavian/axillary	0.0% (0/12)	2.1% (47/2236)		NA	NA	
Direct aortic	0.0% (0/12)	4.1% (91/2236)		NA	NA	
Concomitant revascularization*	25.0% (3/12)	8.3% (186/2237)	0.07	15.0% (3/20)	15.6% (282/1803)	> 0.99

* Concomitant percutaneous coronary intervention with TAVR, concomitant aorto-coronary bypass with SAVR. TAVR, transcatheter aortic valve replacement; SAVR, surgical aortic valve replacement; N, number; SD, standard deviation; NA, not applicable.

Table S3. Cumulative incidence of infective endocarditis at 2 years stratified by surgical risk category.

	TAVR % (95%CI)	**SAVR** % (95%CI)	**TAVR+SAVR** % (95%CI)	**P value** (comparing SAVR to TAVR)	**P value** (comparing risk categories in overall cohort)
High risk	0.77% (0.22%-2.11%)	1.15% (0.39%-2.77%)	0.95% (0.43%-1.88%)	0.59	
Intermediate risk*	0.47% (0.18%-1.06%)	0.78% (0.33%-1.62%)	0.60% (0.32%-1.04%)	0.39	
Low risk	0.000% (NA, NA)	2.032% (0.710%-4.649%)	0.961% (0.344%-2.231%)	0.010	
Overall	0.42% (0.20%-0.80%)	1.05% (0.63%-1.68%)	0.71% (0.46%-1.04%)	0.030	0.64

Cumulative incidence takes into account the competing risk of death. For p-values Gray`s tests were used. TAVR, transcatheter aortic valve replacement; SAVR, surgical aortic valve replacement. * SURTAVI und SURTAVI continued access registry.

Table S4. All-cause mortality from infective endocarditis through 1 year stratified by surgical risk category.

	TAVR % (95%CI)	**SAVR** % (95%CI)	**TAVR+SAVR** % (95%CI)	**P value** (comparing SAVR to TAVR)	**P value** (comparing risk categories in overall cohort)
High risk	20.0% (0.0%, 55.1%)	100.0% (NA, NA)	53.3% (20.8%, 85.8%)	0.06	
Intermediate risk*	33.3% (0.0%, 71.1%)	40.0% (9.6%, 70.4%)	36.9% (13.2%, 60.6%)	0.50	
Low risk	NA†	33.3% (0.0%, 71.1%)	33.3% (0.0%, 71.1%)		
Overall	27.3% (1.0%, 53.6%)	51.8% (28.2%, 75.3%)	42.3% (24.5%, 60.1%)	0.15	0.85

Kaplan Meier rates of all-cause mortality with day 0 set at the day of infective endocarditis diagnosis. 95% confidence intervals were calculated based on linear transformation with the Greenwood variance estimate. P values were derived by Log-rank tests. TAVR, transcatheter aortic valve replacement; SAVR, surgical aortic valve replacement. NA, not applicable. * SURTAVI und SURTAVI continued access registry. † no cases of endocarditis.

Figure S1. Cumulative incidence of endocarditis taking into account the competing risk of stroke stratified by mode of valve replacement in as-treated cohort. The cumulative incidence amounted to 1.05% (95% confidence interval (95% CI): 0.50 to 1.99%) in the TAVR group and 1.59% (95% CI: 0.98 to 2.46%) in the SAVR group at 5 years.

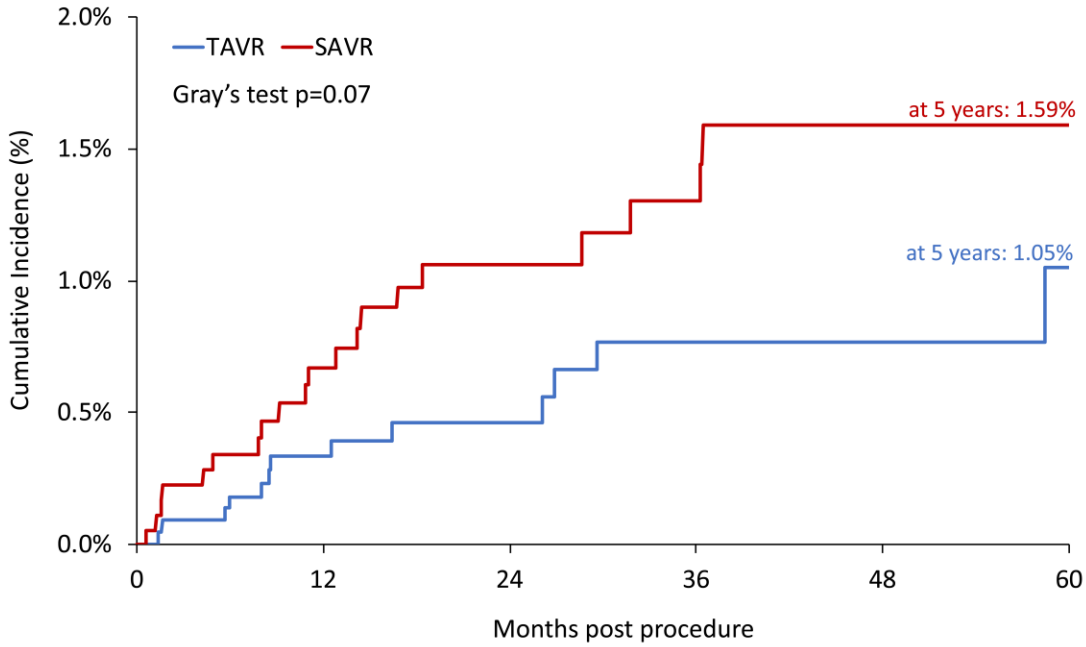


Figure S2. Cumulative incidence of endocarditis taking into account the competing risk of stroke stratified by mode of valve replacement in as-treated cohort including only patients of the randomized trials but not the SURTAVI continued access study.

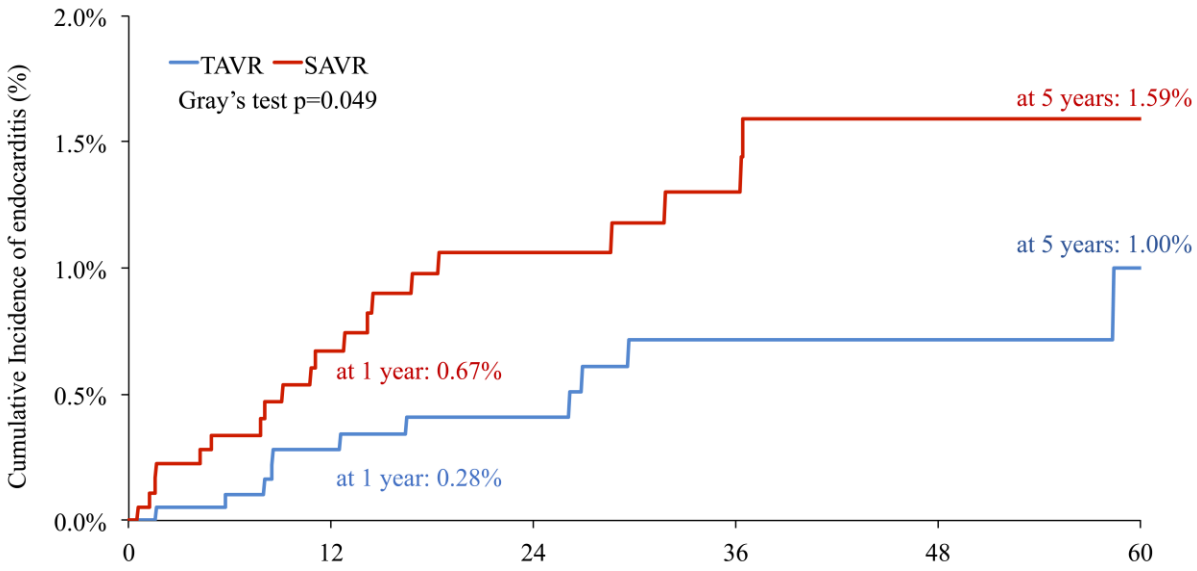


Figure S3. Cumulative incidence of endocarditis taking into account the competing risk of stroke stratified by type of bioprosthetic leaflet tissue.

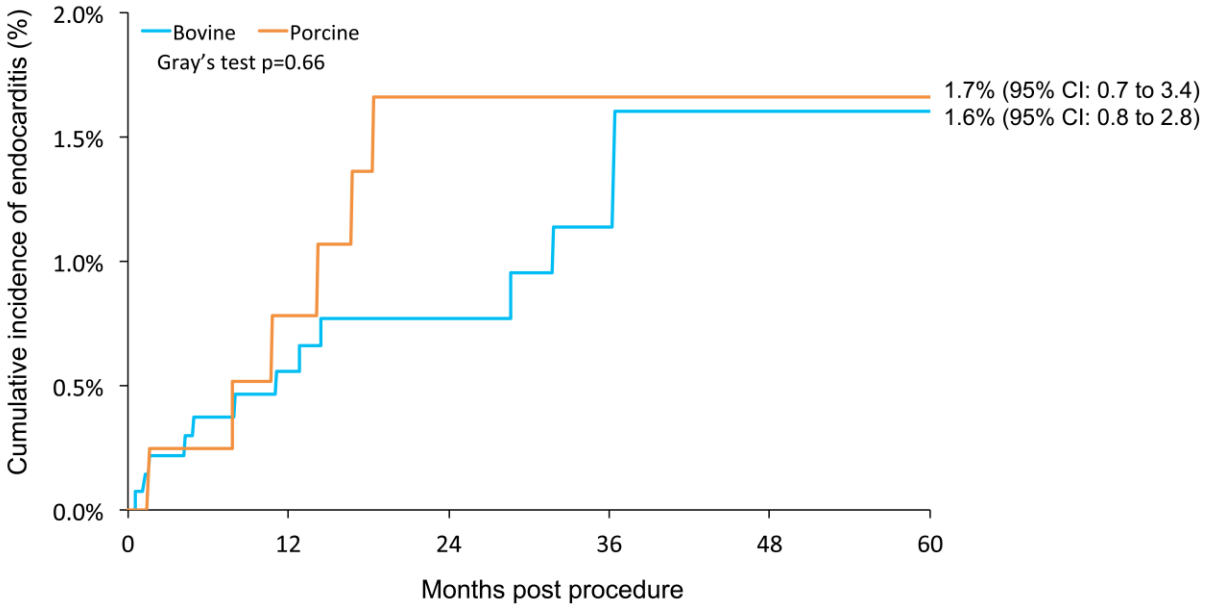


Figure S4. Kaplan Meier curves depicting all-cause mortality and stroke after endocarditis stratified by mode of valve replacement. In the TAVR cohort 2-year cumulative incidence was 55.0% (95% CI: 24.5 to 85.5%), in the SAVR group 64.6% (95% CI: 32.1 to 97.1%).

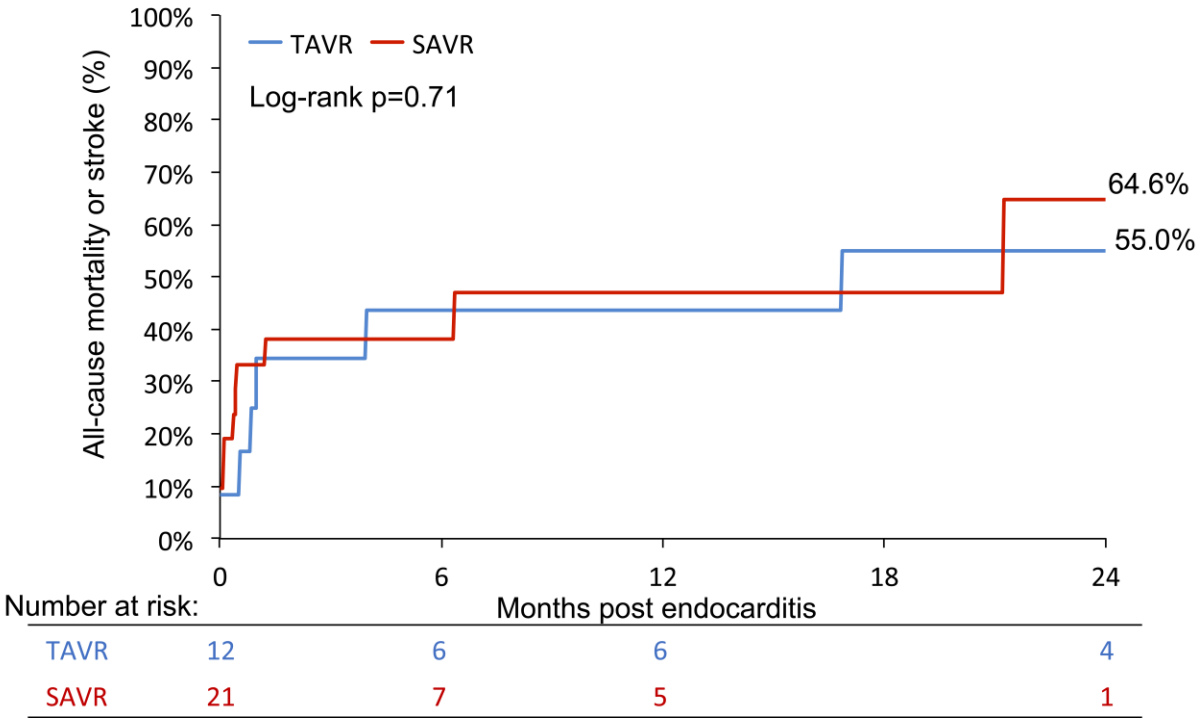


Figure S5. Kaplan Meier curves depicting all-cause mortality after endocarditis in the valve-implanted cohort stratified by mode of valve replacement including only patients of the randomized trials but not the SURTAVI continued access study.

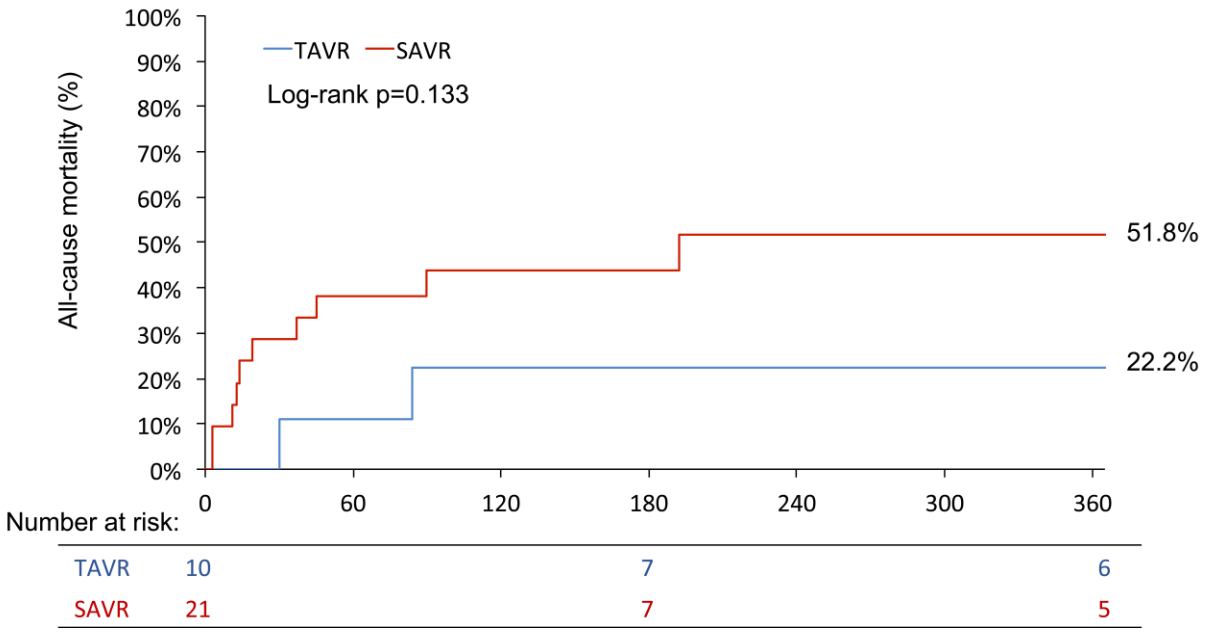
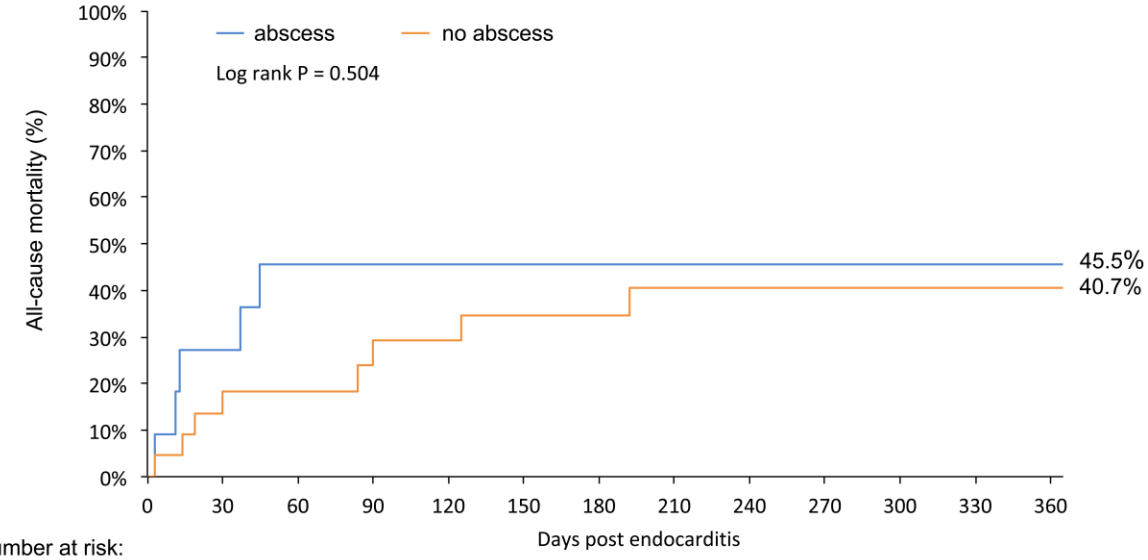


Figure S6. Kaplan Meier curves depicting all-cause mortality at 1 year in endocarditis patients stratified by presence or absence of paravalvular abscess formation.



Number at risk:			
with abscess	11	4	3
no abscess	22	11	9