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Infective Endocarditis after Transcatheter Aortic Valve Replacement: a SwissTAVI Registry analysis

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Twitter & tweet: @StefanStortecky: Analysis from @SwissTavi – infective endocarditis frequently incurs early after TAVR, is commonly caused by Enterococcus species and results in considerable risks of mortality and stroke

ABSTRACT

Background Infective endocarditis may affect patients after transcatheter aortic valve replacement (TAVR).

Objectives To provide detailed information on incidence rates, types of microorganisms and outcomes of infective endocarditis after TAVR.

Methods Between February 2011 and July 2018, consecutive patients from the SwissTAVI Registry were eligible. Infective endocarditis was classified into early (peri-procedural (<100days) and delayed-early (100days to 1year)) and late (>1year) endocarditis. Clinical events were adjudicated according to the VARC-2 endpoint definitions.

Results During the observational period, 7,203 patients underwent TAVR at 15 hospitals in Switzerland. During follow-up of 14,832 patient-years, endocarditis occurred in 149 patients. The incidence for peri-procedural, delayed early and late endocarditis after TAVR was 2.59, 0.71 and 0.40 events per 100 person-years, respectively. Among patients with early endocarditis, *Enterococcus species* were the most frequently isolated microorganisms (30.1%). Among those with peri-procedural endocarditis, 47.9% of patients had a pathogen that was not susceptible to the peri-procedural antibiotic prophylaxis. Younger age (SHR 0.969; 95%CI 0.944-0.994), male sex (SHR 1.989; 95%CI 1.403-2.818), lack of predilatation (SHR 1.485; 95%CI 1.065-2.069) and treatment in a catheterization laboratory as opposed to hybrid OR (SHR 1.648; 95%CI 1.187-2.287) were independently associated with endocarditis. In a case-control matched analysis patients with endocarditis were at increased risk of mortality (HR 6.55; 95%CI 4.44-9.67) and stroke (HR 4.03; 95%CI 1.54–10.52).

Conclusions Infective endocarditis after TAVR most frequently incurs during the early period, is commonly caused by *Enterococcus species* and results in considerable risks of mortality and stroke.

ClinicalTrials.gov registration number NCT013682

CONDENSED ABSTRACT

Infective endocarditis after TAVR occurs at an incidence rate of 1.0 events per 100 person-years, and was associated with a 6.5-, and 4-fold increased risk of mortality and stroke, respectively. Patients in the peri-procedural period were at highest risk of infective endocarditis (incidence rate of 2.59 events per 100 person-years), and almost every second patient had a pathogen that was not susceptible to the peri-procedural antibiotic prophylaxis. Younger age, male sex, lack of predilatation and the treatment in a catheterization laboratory as opposed to a hybrid OR were independently associated with endocarditis after TAVR.

KEY WORDS:

Endocarditis, TAVR, Outcomes

ABBREVIATIONS AND ACRONYMS:

AS = aortic stenosis
BMI = body mass index
CCS angina = Canadian Cardiovascular Society grading of angina pectoris
CE = Conformité Européenne
CI = confidence interval
EF = ejection fraction
HR = hazard ratio
LV = left ventricular
NYHA = New York Heart Association
OR = operating room

PROM = Predicted Risk Of Mortality
SAVR = surgical aortic valve replacement
SD = standard deviation
SHR = subhazard ratio
SPP = species (plural)
STS = Society of Thoracic Surgeons
TAVR = transcatheter aortic valve replacement
VARC = Valve Academic Research Consortium
VRE = Vancomycin-resistant enterococci

INTRODUCTION

Prosthetic heart valve endocarditis is a well-recognized adverse event after surgical aortic valve replacement, which accounts for almost 20% of all infective endocarditis cases.(1,2) It has a relevant impact on morbidity and healthcare expenditures,(3) and mortality remains high despite early diagnosis and treatment.(1) Transcatheter aortic valve replacement (TAVR) has emerged as treatment alternative to surgical aortic valve replacement and has substantially affected the treatment of patients with severe, symptomatic aortic valve stenosis.(4) Technological advances, procedural simplification as well as reproducibly favorable results have contributed to the wide adoption of TAVR,(5) which has become the treatment of choice for elderly patients at high- and intermediate surgical risk. Following recent report of trials investigating TAVR in lower-risk surgical patients, it is likely that the use of TAVR will further expand.

The incidence of infective endocarditis after TAVR has revealed a relevant variation over time in retrospective analyses.(6-8) Furthermore, different microorganisms underlying infective endocarditis at different time-points after TAVR have been identified, and the effectiveness of the standard antibiotic prophylaxis to prevent endocarditis remains unclear. The present study investigates incidence rates of infective endocarditis after TAVR and evaluates the spectrum of microorganisms at different time-points in a prospective evaluation of consecutive patients undergoing TAVR in Switzerland. Clinical outcomes in patients with endocarditis were investigated using a case-control matched patient population.

METHODS

DESIGN AND STUDY SETTING

The SwissTAVI Registry is a national, multicenter cohort study and was initiated by the Swiss Working Group of Interventional Cardiology and the Swiss Society of Cardiac and Thoracic Vascular surgery in 2011. Details of the rationale and design of the SwissTAVI

Registry have been described previously.(5,9) The Swiss Federal Office of Public Health (FOPH) monitors clinical outcomes after TAVR in Switzerland, and consecutive patient inclusion is mandatory and considered a prerequisite for reimbursement. Health insurance coverage requires Swiss heart valve centers to adhere to the protocol of the SwissTAVI Registry and submit patient information and clinical outcomes during follow-up to the database.

A web-based database (www.swisstavi.ch) with standardized case-report forms is used for data collection. Clinical events occurring during the procedure or follow-up are reviewed by a dedicated clinical event committee and are adjudicated according to the updated standardized endpoint definitions proposed by the Valve Academic Research Consortium (VARC-2).(10) An independent Clinical Trials Unit is responsible for central data monitoring to verify completeness and accuracy of data and independent statistical analysis. A list of participating sites and investigators is provided in the Online Supplement. The study protocol was approved by the local ethics committee at each site and written informed consent was provided.

Patient information and clinical outcomes of 7 patients (4.7%) from the present study have been previously shared with the "The Infectious Endocarditis after TAVR International Registry",(11) one patient casuistic of infective endocarditis with *Pseudomonas aeruginosa* was separately described,(12) and a case of *Candida endocarditis* was presented as "Image in Clinical Medicine".(13)

Study Population and Definitions

Between February 2011 and July 2018 all patients undergoing TAVR using Conformité Européenne (CE) -approved devices were considered eligible for this study. Infective endocarditis was reported by the Swiss infectious disease network. The Swiss infectious disease network is a group of board certified infectious disease specialists in

Switzerland – all of them were able to report cases of infective endocarditis to the SwissTAVI clinical event committee (CEC). Infective endocarditis was only considered after a three-step confirmation process. First, a local board certified infectious disease specialists from the Swiss infectious disease network reported cases of infective endocarditis to the SwissTAVI CEC. Second, an independent infectious disease specialist as part of the central Swiss TAVI CEC (AC) confirmed or rejected the diagnosis of infective endocarditis based on the information available taking into consideration clinical presentation, blood culture sampling, cardiac imaging, surgical reports and operative findings as well as post-mortem autopsy reports. Third, upon confirmation of infective endocarditis, a dedicated endocarditis event CRF was completed and transferred for event adjudication to the SwissTAVI CEC, consisting of independent cardiologists and cardiac surgeons. Again, source documents were critically revisited and only if there was consensus on the type and the severity of the event, infective endocarditis was confirmed and considered for this analysis. By including the Swiss infectious disease network into the event reporting process of infective endocarditis after TAVR, we are able to provide effective rates of infective endocarditis at any time after TAVR by minimizing event-reporting bias. The modified Duke criteria were assessed according to the available information and were added for comparative reasons.(14) Early and late infective endocarditis was defined as any infective endocarditis occurring during or beyond the first 12 months after TAVR, respectively.(15) Early infective endocarditis was categorized into peri-procedural (within 100 days) and early delayed (100 to 365 days after TAVR) infective endocarditis.

OUTCOMES

The primary outcome of the study was the incidence of infective endocarditis. Secondary endpoints included all-cause mortality and stroke (disabling and non-disabling

stroke) after diagnosis of infective endocarditis. Detailed information on microorganisms and antibiotic prophylaxis were collected.

Statistical Analysis

Discrete data are presented as frequencies (% of patients) and continuous data are summarized as means ± standard deviations (SD). P-values were calculated using unpaired t-tests, chi-square tests, or Fisher's exact tests. Predictors of infective endocarditis were selected from univariable competing risk regressions (time-to-endocarditis, competing event is all-cause death), from which variables with univariable $p<0.20$ were presented in the multivariable competing risk regression model. Matched sets of endocarditis cases at time t vs same-sex control patients alive and still at risk for endocarditis on time t were constructed (t = days since TAVR when endocarditis occurred) in a 1:4 fashion (for every patient with endocarditis, 4 respective control patients without endocarditis were identified and followed). Sets were propensity score matched for age, year of TAVR and STS PROM (n=138 cases); age and STS PROM (n=10 cases with not enough matches close to the year of TAVR of the case); and n=1 case could not be matched with any suitable control (male case below 50 years of age). Clinical outcomes up to 1 year post-endocarditis could then be compared using these matched sets, and were expressed as counts and incidence rates and computed using the Kaplan–Meier method (censored at 1 year). Statistical analyses were performed using Stata 15.1 (College Station, TX: StataCorp LP). Statistical significance was considered at $p <0.05$.

Results

Incident infective endocarditis

Between February 2011 and July 2018, 7,203 patients underwent TAVR at 15 hospitals in Switzerland. During a follow-up duration of 14,832 patient years (median follow-up time 529 days [25%-75% IQR 362 – 2850 days]), infective endocarditis occurred in 149 patients. During 5 years of follow-up, 148 patients (5.8%) developed infective endocarditis

with an incidence rate of 1.0 (95% CI 0.85 – 1.17) events per 100 person years (**Figure 1**). The median time from TAVR to infective endocarditis amounted to 196 [80 to 577] days. The incidence rate for early infective endocarditis was 1.48 (95% CI 1.21 – 1.81) while late endocarditis occurred with an incidence rate of 0.40 (95% CI 0.31 – 0.53) events per 100 person years after one year of follow-up. The highest risk of endocarditis after TAVR was observed during the early peri-procedural period (1,853 patient years at risk) with an incidence rate of 2.59 (95% CI 1.95 – 3.44), followed by the delayed early period (6,229 patient years at risk) with an incidence rate of 0.72 (95% CI 0.54 – 0.97) events per 100 person years (**Central Illustration**).

PATIENT CHARACTERISTICS

Baseline clinical characteristics of patients with and without infective endocarditis are provided in **Supplemental Table 1**. Patients with endocarditis were younger (80.1 ± 8.0 vs 82.0 ± 6.4 years, p<0.001) and more frequently male (68.5% vs 49.9%, p<0.001) than patients without infective endocarditis. Cardiac risk factors and past medical history including diabetes mellitus, previous cardiac surgery and previous pacemaker implantation were similar between groups, as was the estimated risk of peri-procedural mortality using the STS PROM (5.0% ± 3.9 vs. 5.2% ± 4.1, p=0.21).

Procedural characteristics are presented in **Supplemental Table 2.** Procedure time and type of vascular access site were comparable between patient groups. Patients with infective endocarditis had undergone TAVR more frequently in the catheterization laboratory as opposed to the hybrid operating room (55.7% vs. 42.8%, p=0.024), had more frequently received a mechanically expandable transcatheter prosthesis (13.3% vs. 4.2%, p<0.001) and more frequently had TAVR without predilatation balloon aortic valvuloplasty (57.0% vs. 63.5%, p=0.003). They more frequently had received packed red blood cell transfusion during hospitalization (19.5% vs. 13.4%, p=0.01), however there was no difference in the

number of packed red blood cell transfusions received. Aortic regurgitation after TAVR was similar for patients with and without infective endocarditis.

Details of Infective Endocarditis

Details of infective endocarditis are summarized in **Table 1**. Using the modified Duke criteria, infective endocarditis was definite in 63.1% and possible in 36.9% of patients (**Supplemental Table 3**). Echocardiographic images were considered normal or inconclusive in 47.7% of echocardiographic studies (transthoracic (n=114) and transesophageal echocardiography (n=119)). At the timepoint of echocardiography, 36.2% of patients with infective endocarditis had evidence of vegetations, 9.4% abscess formation and 8.7% had new signs of bioprosthetic regurgitation. Overall, 148 out of 149 patients (99.3%) were blood-culture positive; details on causative microorganisms can be found in **Table 1**. Overall, *Streptococcus spp.* were most frequently isolated in 28.9%, *Enterococcus spp.* in 26.2% and *Staphylococcus aureus* in 21.5% of cases. Among patients with peri-procedural infective endocarditis *Enterococcus spp.* were the most frequent causative microorganisms (33.3%) followed by *S. aureus* (22.9%), coagulase-negative staphylococci (18.8%) and *Streptococcus spp.* (18.8%). The majority of patients with infective endocarditis had received antibiotic prophylaxis (92.6%). Antimicrobial susceptibility testing revealed endocarditis prophylaxis ineffective in 47.9% of patients with peri-procedural endocarditis (details on pre-operative antibiotic prophylaxis are provided in **Supplemental Figure 1**). No significant differences in baseline clinical (**Supplemental Table 4)** and procedural characteristics (**Supplemental Table 5)** were observed between TAVR patients with early endocarditis (peri-procedural and early delayed) despite effective antibiotic prophylaxis and TAVR patients without endocarditis during subgroup analyses.

Outcomes and Predictors of Infective Endocarditis

Baseline clinical information of the matched patient cohort (matched TAVR patients with infective endocarditis vs TAVR controls) is provided in **Supplemental Table 6**. Patients with infective endocarditis were at substantial risk for all-cause mortality (HR 6.55; 95%CI 4.44-9.67) and stroke (HR 4.03; 95%CI 1.54–10.52) compared to a case-matched patient population without endocarditis (**Figure 2**). While patients with infective endocarditis were at risk of all-cause mortality irrespective of whether it occurred during the early or late time period, the risk of stroke associated with infective endocarditis emerged during the late time period (HR 11.92; 95%CI 2.76-51.53). Clinical outcomes for patients with "definite" endocarditis according to the Duke diagnostic criteria are summarized in **Supplemental Figure 2**.

Table 2 shows independent predictors of infective endocarditis after TAVR. Younger age (subhazard ratio SHR 0.969; 95%CI 0.944-0.994), male sex (SHR 1.989; 95%CI 1.403-2.818), lack of predilatation balloon aortic valvuloplasty before valve implantation (SHR 1.485; 95%CI 1.065-2.069) and treatment in a catheterization laboratory as opposed to hybrid operating room (SHR 1.648; 95%CI 1.187-2.287) were found to be independently associated with infective endocarditis after TAVR.

DISCUSSION

The salient findings of the present study investigating infective endocarditis after TAVR can be summarized as follows:

- The overall incidence rate of infective endocarditis during 5-year follow-up after TAVR was 1.0 events per 100 person years. Patients in the early peri-procedural phase after TAVR were at highest risk of infective endocarditis.
- Among patients with early peri-procedural infective endocarditis, *Enterococcus spp.* were the most frequently isolated microorganisms.

- Every second patient developing peri-procedural endocarditis had a pathogen not susceptible to the peri-procedural antibiotic prophylaxis.
- Independent predictors of infective endocarditis included younger age, male sex, lack of balloon aortic valvuloplasty before transcatheter valve implantation and treatment in a catheterization laboratory as opposed to hybrid operating room.
- Patients with infective endocarditis were at almost seven-fold increased risk of mortality and four-fold increased risk of stroke compared with a case-matched control group.

Infective endocarditis is estimated to occur at rates between 0.3% and 1% per patient year after surgical prosthetic heart valve replacement.(1,16) The risk of infective endocarditis is higher in patients with bioprosthetic rather than mechanical heart valves and increased during the first year after the procedure.(16,17) The SwissTAVI study results are in line with the surgical literature providing an incidence rate of 1.0 events per 100 person – years during the first 5 years after TAVR. Similar to surgery, the risk of infective endocarditis is higher during the first year after TAVR (incidence rate of 1.48 events per 100 person-years) and highest during the early peri-procedural phase (incidence rate of 2.59 events per 100 person-years). Incidence rates of infective endocarditis after TAVR have been reported varying between 0.3% and 5.8% during long-term follow-up in retrospective analyses.(6-8) Most recently, a multicenter registry including 53 patients with infective endocarditis after TAVR showed an overall incidence rate of 0.67%, which is half the rate of the prospective SwissTAVI patient cohort.(18) However, after extending this retrospective cohort and adding the data of several other heart centers, the overall incidence rate increased to 1.1%.(11)

After surgical valve replacement, *S. aureus* (34.0%) and coagulase-negative staphylococci (25.6%) are the most common microorganisms isolated in cases of prosthetic valve endocarditis, whereas low rates of enterococcal (9.4%) and viridans group streptococcal infections (4.9%) have been reported.(1) In contrast, we found relevant

differences in causative pathogens according to the time of occurrence of infective endocarditis after TAVR. *Enterococcus spp.* were among the most frequently isolated microorganisms in patients with early infective endocarditis (30.1%), whereas *S. aureus* (26.8%) and viridans group streptococcal infections (26.8%) were predominantly found in infective endocarditis occurring more than one year after TAVR. Although this observation is consistent with the published literature and previous observational data, we can only speculate as to potential explanations for the difference in microbiota composition of endocarditis after TAVR and surgery. While advanced age itself could be considered a confounding factor and one of the reasons for the observed difference in microbiological spectrum of infective endocarditis,(19) another explanation might be found in differences of bacterial colonization of the sternal as compared with the femoral skin. A recent observational study comparing the microbiota of elderly and frail adults living in nursing homes to those in the community reported more frequently culture positive Enterobacteriaceae in elderly adults and nursing home residents than in the community control group,(20) pointing to potential differences related to baseline characteristics (elderly patients and frail patients have been more likely to undergo TAVR than SAVR). Moreover, when assessing the colonization of Vancomycin-resistant enterococci (VRE) in critically – ill patients in a medical intensive care unit setting, the femoral region was contaminated in almost 90% of colonized patients.(21) Whether improved and intensified disinfection and hygiene of the femoral skin or other preventive hygiene measures might be able to decrease the levels of bacterial contamination related to the access site needs to be studied in well-designed, prospective studies.

Based on previous evidence and infective endocarditis after surgical valve replacement, current professional guidelines recommend the administration of perioperative antibiotic prophylaxis covering the most frequent microorganisms underlying early prosthetic

valve infections after surgery (coagulase-negative staphylococci and staphylococcus aureus) for both, surgical or transcatheter valve procedures.(15) Of note, antimicrobial susceptibility testing proved that 47.9% of patients with early peri-procedural infective endocarditis after TAVR in the present study had a pathogen that was not susceptible to the antibiotic prophylaxis administered before or during TAVR. This is mainly explained by the increased rate of enterococcal infections during the peri-procedural period, that are not covered by the prophylactic regimen consisting of first or second generation cephalosporins. Based on the observed differences in the spectrum of pathogens between surgical and transcatheter heart valve interventions, a change in antibiotic prophylaxis for transcatheter heart valve interventions to an intravenous dose of amoxicillin/clavulanic acid, ampicillin/sulbactam or vancomycin in patients allergic to penicillin may be reasonable. However, while broadening antibiotic prophylaxis is a simple intervention with minimal acute risk and cost, the growing problem of antibiotic resistance must be taken into consideration, and it remains to be demonstrated whether a change in antibiotic prophylaxis is effective to mitigate the risk of peri-procedural endocarditis.

Independent predictors of infective endocarditis after TAVR included younger age, male sex, absence of predilatation balloon aortic valvuloplasty before valve implantation and the treatment in a catheterization laboratory as opposed to a hybrid operating room. While the clinical characteristics of age and sex corroborate the findings of a previous multicenter analysis,(11) the procedural characteristics of lack of predilatation balloon aortic valvuloplasty and the treatment in a catheterization laboratory rather than hybrid operating room are newly identified risk factors for infective endocarditis after TAVR. During the early TAVR experience, balloon aortic valvuloplasty was common practice and considered a prerequisite in preparing the native, calcified aortic valve to increase the likelihood of a circular deployment and homogenous apposition of the stented valve frame.(22,23) However,

as additional manipulation in the ascending aorta including pre- and postdilatation of the native valve may increase the risk for cerebrovascular events,(24) and owing to technological advances with reduced profile delivery catheters, rates of predilatation balloon aortic valvuloplasty before delivering the transcatheter heart valve prosthesis continuously decreased, and are nowadays performed in only every other patient.(5)

In the SwissTAVI patient cohort, the treatment in a hybrid OR was independently associated with a reduction in infective endocarditis. This finding might be explained by the aseptic infrastructure and specific OR standards, that are available for a hybrid OR environment but not for a standard catheterization laboratory. Hybrid ORs have similar standards compared with ORs for cardiac surgery and are equipped with dedicated high efficiency particulate air filters. Moreover, a restricted access policy for hybrid ORs minimizes the traffic of healthcare workers and open doors within this sterile environment. In addition, OR guidelines include a specific training for staff members, who might be more familiar with access site disinfection, the sterile management of heart valve prostheses, and potentially better trained in surgical hand hygiene and the management of sterile gowns and gloves. Although these measures sound intuitive in the prevention of bacterial contamination and septic complications after an invasive treatment, recent findings from the France TAVI multicenter registry do not support the expected benefits of a hybrid OR.(25) Higher rates of post-procedural infection were found in patients treated in the hybrid OR when compared with patients treated in a catheterization laboratory. The investigators related this observation to an increase in pulmonary and urinary tract infections related to the increased procedural complexity including endotracheal intubation and bladder catheterization and not to an increase in infectious complications at the access site. As there is conflicting evidence on the benefits of a hybrid OR setting, well-designed prospective studies are required to further inform the discussion on the added value of a specific hybrid OR environment, dedicated

hygiene standards including improved and intensified disinfection, specific hygiene treatment of the femoral skin or other preventive hygiene measures to decrease the levels of bacterial contamination and prevent infective endocarditis after TAVR.

Prosthetic heart valve endocarditis is associated with a significant impact on morbidity and mortality, irrespective of previous surgical or transcatheter heart valve treatment.(1,11) Rates of in-hospital mortality are reported with 22.8% after surgical and 36% after transcatheter valve replacement,(1,11) which is comparable with the rate in the SwissTAVI patient population. Moreover, patients with infective endocarditis had a seven-fold increased risk of mortality during the first year after diagnosis of endocarditis compared with a case-matched population, and this effect was consistent for peri-procedural, delayed early and late endocarditis events. Of interest, patients with infective endocarditis were at four-fold increased risk of stroke, which was mainly related to events after late occurrence of infective endocarditis. The incidence of embolic stroke during infective endocarditis ranges between 10 and 50% and the risk of embolization is associated with specific pathogens as *S. aureus*, *S. bovis* and *Candida spp.(26)* It is reasonable that the increased risk of stroke during late endocarditis is related to the higher rate of *S. aureus* endocarditis in the SwissTAVI patient population.

Study limitations

The results of the present study should be interpreted in light of the following limitations: First, the SwissTAVI Registry is a national, multicenter cohort study and differences in institutional practice and clinical decision algorithms might impact treatment and clinical outcomes of patients with infective endocarditis. Second, infective endocarditis was diagnosed according to the clinical presentation of the patient, laboratory findings and blood culture sampling, echocardiographic images and post-mortem autopsy reports. Positron emission tomography–computed tomography was not routinely performed and the respective

information not collected in the study specific case report form. Third, the information on transcatheter heart valve expansion is not collected in the registry and potential effects of incomplete valve expansion, or asymmetric valve deployment and the potential effect of pre- or postdilation of the prosthesis on infective endocarditis cannot be investigated within this dataset. Fourth, incidence rates for late endocarditis (beyond one year after TAVR) might be underrepresented in this analysis due to the pre-specified follow-up modalities in SwissTAVI, which include mandatory visits at 1 and 5 years and optional follow-ups scheduled at 2, 3, and 4 years after TAVR. However, as clinical endpoints including infective endocarditis can be submitted to the SwissTAVI clinical event committee at any time after TAVR, estimates should be as precise as possible.

Conclusions

Infective endocarditis most frequently incurs during the early period after TAVR, is commonly caused by *Enterococcus species* and results in considerable risks of mortality and stroke. Future studies need to address whether changes in antibiotic prophylaxis, treatment in a Hybrid OR setting, and other measures such as improved disinfection, hygiene of the femoral skin or other preventive hygiene measures are able to decrease the levels of bacterial contamination and as a result infective endocarditis.

Perspectives

Competency in Medical Knowledge: Infective endocarditis most frequently incurs during the early period after TAVR, is commonly caused by *Enterococcus species* and results in considerable risks of mortality and stroke

Translational Outlook: Future studies need to address whether changes in antibiotic prophylaxis, treatment in a Hybrid OR setting, and other measures such as improved disinfection, hygiene of the femoral skin or other preventive hygiene measures are able to decrease the levels of bacterial contamination and as a result infective endocarditis.

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FIGURE LEGENDS

Figure 1. Incidence of Infective Endocarditis

Incidence of infective endocarditis up to 5 years of follow-up. Incidence rates (%) including 95% confidence intervals. n=1 endocarditis event not shown, occurred 1895 days after TAVR.

Figure 2. Clinical outcomes at 1 year post infective endocarditis

Case-control matching on time t of the endocarditis case since TAVR. Controls did not have endocarditis up to time t. Case : Control 1:4 matching using age, gender, year of TAVR and STS PROM.

(1) n = 1 in one young male late endocarditis case no suitable controls at risk on time t could be matched; (2) n=9 very old and/or very high STS PROM cases - not enough suitable matches within the year still at risk on time t, so up to 4 control matches were acquired from all years.

Central Illustration. Infective Endocarditis after TAVR

Incidence rates of infective endocarditis according to different time points after TAVR – rates per 100 patient-years; causative microorganisms are presented according to early and late occurrence of infective endocarditis; and all–cause mortality after infective endocarditis after case : control matching.

TABLE 1. CHARACTERISTICS OF INFECTIVE ENDOCARDITIS

	ENDOCARDITIS N = 149	EARLY N = 93	PERI-PROCEDURAL N = 48	DELAYED N = 45	LATE N = 56	P-VALUE PERI-PROCEDURAL VS DELAYED	P-VALUE PERI-PROCEDURAL VS LATE	P-VALUE EARLY VS LATE
Endocarditis								
Duke criteria - definite	94 (63.1%)	61 (65.6%)	31 (64.6%)	30 (66.7%)	33 (58.9%)	1.00	0.69	0.48
Duke criteria - possible	55 (36.9%)	32 (34.4%)	17 (35.4%)	15 (33.3%)	23 (41.1%)	1.00	0.69	0.48
Echocardiographic details								
Normal	12 (8.1%)	8 (8.6%)	4 (8.3%)	4 (8.9%)	4 (7.1%)	1.00	1.00	1.00
Not conclusive	59 (39.6%)	35 (37.6%)	19 (39.6%)	16 (35.6%)	24 (42.9%)	0.83	0.84	0.61
Vegetation	54 (36.2%)	35 (37.6%)	15 (31.3%)	20 (44.4%)	19 (33.9%)	0.21	0.84	0.73
Abscess formation	14 (9.4%)	11 (11.8%)	6 (12.5%)	5 (11.1%)	3 (5.4%)	1.00	0.30	0.25
New valve regurgitation	13 (8.7%)	8 (8.6%)	5 (10.4%)	3 (6.7%)	5 (8.9%)	0.72	1.00	1.00
Fistula	1 (0.7%)	1 (1.1%)	0 (0.0%)	1 (2.2%)	0 (0.0%)	0.48		1.00
Causative Microorganisms						0.25	0.14	0.15
Staphylococcus aureus	32 (21.5%)	17 (18.3%)	11 (22.9%)	6 (13.3%)	15 (26.8%)			
Coagulase-negative staphylococci	19 (12.8%)	15 (16.1%)	9 (18.8%)	6 (13.3%)	4 (7.1%)			
Viridans-group streptococci	34 (22.8%)	19 (20.4%)	6 (12.5%)	13 (28.9%)	15 (26.8%)			
Non-viridans group streptococci	9 (6.0%)	6 (6.5%)	3 (6.3%)	3 (6.7%)	3 (5.4%)			
Enterococcus faecalis	36 (24.2%)	25 (26.9%)	14 (29.2%)	11 (24.4%)	11 (19.6%)			
Enterococcus faecium	3 (2.0%)	3 (3.2%)	2 (4.2%)	1 (2.2%)	0 (0.0%)			
Gram – negative bacilli	8 (5.4%)	4 (4.3%)	3 (6.3%)	1 (2.2%)	4 (7.1%)			
Candida species	3 (2.0%)	2 (2.2%)	0 (0.0%)	2 (4.4%)	1 (1.8%)			
Polymicrobial (≥2 microorganisms)	3 (2.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (5.4%)			
Other	2 (1.3%)	2 (2.2%)	0 (0.0%)	2 (4.4%)	0 (0.0%)			

Antibiotic prophylaxis								
Antibiotic prophylaxis received	138 (92.6%)	87 (93.5%)	45 (93.8%)	42 (93.3%)	51 (91.1%)	1.00	0.72	0.75
Antibiotic prophylaxis effective	83 (55.7%)	47 (50.5%)	25 (52.1%)	22 (48.9%)	36 (64.3%)	0.84	0.24	0.13
Timing of prophylaxis						*0.64*	*0.82*	*0.58*
after TAVR	1 (0.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.0%)			
pre < 30min	44 (31.9%)	29 (33.3%)	13 (28.9%)	16 (38.1%)	15 (29.4%)			
pre 30-60min	84 (60.9%)	52 (59.8%)	29 (64.4%)	23 (54.8%)	32 (62.7%)			
pre >60min	9 (6.5%)	6 (6.9%)	3 (6.7%)	3 (7.1%)	3 (5.9%)			

Depicted are means with standard deviations or counts (% of all patients). P-values from t-tests or chisquare tests (multiple categories) or Fisher's tests (two categories). Echocardiographic details include the information from transthoracic and transesophageal echocardiographic studies.

n=1 endocarditis case in the Late group occurred very late: 1895 days after TAVI.

TABLE 2. INDEPENDENT PREDICTORS OF INFECTIVE ENDOCARDITIS

	UNIVARIABLE		MULTIVARIABLE		
	SUBHAZARD RATIO (95% CI)	P-VALUE		SUBHAZARD RATIO (95% CI)	P-VALUE
Age (years)	0.960 (0.939-0.980)	<0.001	Age (years)	0.969 (0.944-0.994)	0.014
Sex (male)	2.156 (1.526-3.046)	<0.001	Sex (male)	1.989 (1.403-2.818)	<0.001
Body mass index (kg/cm²)	1.028 (0.999-1.057)	0.06	Body mass index (kg/cm²)	1.016 (0.984-1.049)	0.34
Diabetes mellitus	1.246 (0.876-1.772)	0.22	Arterial hypertension	1.388 (0.880-2.188)	0.16
Dyslipidemia	1.055 (0.764-1.456)	0.75	CCS Angina	0.730 (0.469-1.136)	0.16
Arterial hypertension	1.349 (0.871-2.088)	0.18	STS PROM	0.989 (0.951-1.029)	0.59
Previous pacemaker implantation	1.012 (0.594-1.724)	0.97	Femoral access	0.839 (0.530-1.327)	0.45
History of myocardial infarction	0.854 (0.523-1.395)	0.53	Non-Hybrid OR (catheterization laboratory)	1.648 (1.187-2.287)	0.003
History of cardiac surgery	1.021 (0.650-1.605)	0.93	Lack of balloon aortic valvuloplasty	1.485 (1.065-2.069)	0.020
History of cerebrovascular accident	1.027 (0.627-1.684)	0.92			
Peripheral artery disease	0.906 (0.581-1.413)	0.66			
COPD	1.092 (0.682-1.747)	0.71			
Coronary artery disease	0.883 (0.640-1.220)	0.45			
LVEF (%)	0.993 (0.981-1.005)	0.24			
Aortic Valve Area (cm²)	0.894 (0.512-1.560)	0.69			
Mean Gradient (mmHg)	1.002 (0.993-1.010)	0.74			
NYHA (III or IV)	0.824 (0.593-1.146)	0.25			
CCS Angina	0.708 (0.457-1.097)	0.12			
STS PROM	0.963 (0.916-1.011)	0.13			
Procedure time (min)	1.002 (0.999-1.005)	0.28			
Total contrast administered (cc)	1.000 (0.998-1.002)	0.91			
Percutaneous access	0.801 (0.540-1.189)	0.27			
Femoral access	0.716 (0.455-1.127)	0.15			
Non-Hybrid OR (catheterization laboratory)	1.570 (1.136-2.169)	0.006			
Lack of balloon aortic valvuloplasty	1.550 (1.117-2.151)	0.009			

Procedural complication (any)	1.112 (0.711-1.739)	0.64

Results from Competing risk time-to-event analyses; competing event is all-cause death. Tabulated are subhazard ratios (95 confidence interval CI) with p-values.