

1 Infective Endocarditis Caused by Staphylococcus Aureus after

2 Transcatheter Aortic Valve Replacement

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1 **Brief Summary:** IE caused by *S aureus* after TAVR is a particular life-threatening complication
2 among patients with IE post-TAVR, with a very high in-hospital (~50%, two times higher than
3 non-SA-IE) and long-term (>70% at 2-years) mortality. The presence of some features (major
4 bleeding or sepsis complicating TAVR, neurological symptoms/embolism at index IE, the
5 involvement of devices other than the TAVR valve) determined a higher likelihood of SA-IE. The
6 results of this study suggest that surgical treatment may have a protective effect in SA-IE post-
7 TAVR patients.

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1 ABSTRACT

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3 **Background:** *Staphylococcus aureus* (*S aureus*) has been extensively studied as causative
4 microorganism of surgical prosthetic-valve infective endocarditis (IE). However, scarce evidence
5 exists on *S aureus* IE after transcatheter aortic valve replacement (TAVR).

6 **Methods:** Data was obtained from the Infectious Endocarditis after TAVR International Registry
7 including patients with definite IE following TAVR from 59 centers in 11 countries. Patients were
8 divided into two groups according to microbiological etiology (non-*S aureus*-IE, non-SA-IE vs. *S*
9 *aureus*-IE, SA-IE).

10 **Results:** SA-IE was identified in 141 out of 573 (24.6%) patients, methicillin-sensitive *S aureus*
11 in most cases (115/141, 81.6%). SEV were more common than BEV in patients with early SA-IE.
12 Major bleeding and sepsis complicating TAVR, neurological symptoms or systemic embolism at
13 admission and IE with cardiac device involvement other than the TAVR prosthesis were associated
14 with SA-IE ($p < 0.05$ for all). Among IE post-TAVR patients, the likelihood of SA-IE increased
15 from 19% in the absence of those risk factors to 84.6% if ≥ 3 risk factors were present. In-hospital
16 (47.8% vs. 26.9%, $p < 0.001$) and 2-year mortality (71.5% vs. 49.6%, $p < 0.001$) rates were higher
17 among SA-IE (vs. non-SA-IE) patients. Surgery at the time of index SA-IE was associated with a
18 lower mortality rate at follow-up (HR_{adj} : 0.46, 95% CI: 0.22-0.96, $p = 0.038$).

19 **Conclusions:** SA-IE represented ~ 25% of IE cases after TAVR and was associated with a very
20 high in-hospital and late mortality. The presence of some features determined a higher likelihood
21 of SA-IE and could help to orientate early antibiotic regimen selection. Surgery at index SA-IE
22 was associated with improved outcomes, and its role should be evaluated in future studies.

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1 INTRODUCTION

2
3 Transcatheter aortic valve replacement (TAVR) has revolutionized the management of
4 severe symptomatic aortic stenosis. Infective endocarditis (IE) following TAVR is a rare but life-
5 threatening complication associated with high in-hospital and long-term mortality rates.¹⁻³ Despite
6 the evolution of the TAVR procedure (simplified and less invasive) along with device iterations,
7 the overall incidence of IE after TAVR remained stable over time⁴. In the near future, the number
8 of TAVR procedures is expected to rise due to its expansion towards the treatment of younger and
9 lower surgical risk patients. Therefore, the total number of patients at risk of developing this life-
10 threatening complication may increase substantially.

11 *Staphylococcus aureus* (*S aureus*) remains the most frequent microorganism in both
12 community-acquired and hospital-acquired bacteremia, with mortality rates ranging from 10% to
13 30%.⁵⁻⁷ The increasing exposure to medical procedures along with the increasing number of
14 patients with implantable medical devices (prosthetic heart valves, implantable cardiac devices,
15 grafts) has translated into *S aureus* becoming the predominant causative microorganism of native-
16 or surgical prosthetic-valve endocarditis in developed countries.⁷⁻⁹ TAVR patients represent an
17 elderly population with a high comorbidity burden and exposure to healthcare-associated
18 procedures. Thus, these patients have a significant potential risk of bloodstream infections and IE
19 due to *S aureus*. In the surgical field, several studies have suggested that prosthetic-valve IE (PVE)
20 caused by *S aureus* is associated with worse clinical outcomes and high early mortality rates
21 compared with other forms of IE¹⁰. Nevertheless, scarce data exist on *S aureus* IE in TAVR
22 recipients, and fundamental features and prognosis of this particular group of patients remain
23 unknown. The purpose of this study was to evaluate the clinical characteristics, management, in-
24 hospital, and late outcomes of patients with *S aureus* IE after TAVR.

1 **METHODS**

2 **The Infectious Endocarditis after TAVR International Registry**

3 Data from the Infectious Endocarditis after TAVR International Registry were used for this study.
4 Briefly, the registry included data from 604 patients with definite IE determined by the modified
5 Duke criteria after TAVR (regardless of the structure involved) from 59 centers in 11 countries
6 across Europe, North America, and South America between June 2005 and December 2020.
7 Informed consent was obtained from all patients before the procedure and the individual
8 anonymized data sharing was performed according to the local ethics committee of each center, in
9 compliance with the Declaration of Helsinki.

10 **Patient selection and Data Collection**

11 Each center retrospectively identified patients according to the modified Duke criteria. Only
12 TAVR patients developing definite IE were included irrespective of the structure affected
13 (native/prosthetic valve or implantable cardiac device). Also, only the first episode of IE recorded
14 for an individual patient was included in the analysis. A dedicated case report form (database) was
15 used at all sites for data collection that included baseline and periprocedural TAVR features, as
16 well as IE characteristics, microbiological profile, management and in-hospital and follow-up
17 outcomes (191 variables). Based on the microbiological profile, the global cohort was divided into
18 two groups of patients: (i) patients developing IE post-TAVR caused by *S aureus* (SA-IE) and (ii)
19 patients suffering from IE post-TAVR caused by another microorganism (non-SA-IE). Non-SA-
20 IE included enterococci (33.6%), coagulase-negative Staphylococci (24.1%), oral streptococci
21 (18.3%), *Streptococcus gallolyticus* (6.9%), other streptococci (5.3%), culture-negative IE (8.3%)
22 and other pathogens (4.5%). A total of 573 patients with well-documented data on IE's etiology

1 (94.9% of the entire cohort) were included in the analysis. After index IE, the mean follow-up was
2 15.4 months, and follow-up was complete in 96.7% of the patients (19 patients lost to follow-up).

4 **Definitions**

5 Definite infective endocarditis definition was based on the modified Duke criteria.¹¹ Perioperative
6 mortality risk was defined according to the logistic EuroSCORE. Transcatheter aortic valve type
7 was divided into two groups: balloon-expandable and self-expanding or mechanically- expandable
8 valves (Supplementary data). Clinical endpoints were defined according to the Valve Academic
9 Research Consortium-2 criteria.¹² Periannular complications and other systemic embolization
10 were defined as previously reported.¹³ Persistent bacteremia was defined as positive blood cultures
11 despite appropriate antibiotic therapy for > 7 days. Healthcare-associated infective endocarditis
12 was defined using the Friedman criteria.¹⁴ Early prosthetic valve endocarditis was defined as
13 occurring within 12 months from TAVR. The presumed source of entry was determined by each
14 site investigator based on medical records.

16 **Statistical Analysis**

17 Depending on the variable distribution, which was assessed using the Shapiro-Wilk test,
18 continuous variables were expressed as mean \pm standard deviation or median (interquartile range,
19 IQR). Categorical variables were expressed as number (%). Group comparison between groups
20 was analyzed using the Student t test or Wilcoxon rank-sum test for continuous variables and χ^2
21 or Fisher exact test for categorical variables. For bivariable analysis, patients with missing data
22 were excluded. A multivariable Cox proportional hazard model was performed to determine the
23 factors independently associated with 2-year mortality among patients with SA-IE. This model

1 included all variables considered a priori to contribute to in-hospital mortality. A multivariable
2 logistic model was also performed to determine the associated factors of SA-IE. Likewise, all
3 variables considered a priori to contribute to SA-IE were included in the multivariable model. The
4 variables with a P value < 0.10 in the bivariate analysis were included in the multivariable models.
5 Both models were built by backward stepwise (likelihood ratio) selection, and IE with TAVR
6 involvement and surgery during IE hospitalization were forced to remain in the Cox model. We
7 used the Kaplan–Meier method to provide survival estimates, assessed with a log-rank test. Event
8 times were measured from initial IE symptoms to the date of death or last follow-up. Differences
9 in the incidence of mortality were determined using the log-rank test. A 2-sided P value of <0.05
10 was considered statistically significant. Data analyses were performed using the Stata software
11 (version 15.1, Stata Corp, College Station, TX, USA) and Prism (GraphPad Software, San Diego,
12 CA, USA).

13

14 RESULTS

15 **Baseline and TAVR procedural characteristics.** Definite IE was diagnosed in 604 patients after
16 TAVR (31 patients with missing data of IE post-TAVR microbiologic etiology). The flowchart of
17 the study population is depicted in **Figure 1**. SA-IE was detected in 141 out of 573 (24.6%) patients
18 in whom the causative microorganism was identified. Most of these patients presented methicillin-
19 sensitive *S aureus* (115 patients, 81.6%). Baseline and procedural features of the study population
20 grouped according to the microbiological profile (SA-IE vs. non-SA-IE) are shown in **Table 1**.
21 Underlying comorbidities and surgical risk determined by the logistic EuroSCORE were well-
22 balanced in both groups, except for higher median body mass index in non-SA-IE patients (SA-
23 IE: 25.6 Kg/m² [IQR: 23.4-28.9] vs. non-SA-IE: 27.2 Kg/m² [IQR: 24.4-30.9], p=0.001). While
24 there were no differences regarding the type of valve and IE etiology in the overall cohort, patients

1 presenting early SA-IE were more likely to have self-expanding valves (SEV) (59.4% vs. 47.1%
2 in patients with balloon-expandable valves [BEV], $p=0.041$). TAVR-related complications were
3 more frequent in SA-IE patients, including acute renal failure (SA-IE: 19.2% vs. non-SA-IE:
4 10.4%, $p=0.005$), stroke (SA-IE: 8.5% vs. non-SA-IE: 3.2%, $p=0.008$) and sepsis (SA-IE: 16.3 vs.
5 non-SA-IE: 7.9%, $p=0.001$). While the median length of hospital stay was comparable in both
6 groups, patients with SA-IE presented longer hospitalizations in an acute care facility after TAVR
7 (2 days [IQR: 1-5] vs. 1.5 days [IQR: 1-3], $p=0.011$).

8 **Characteristics and outcomes of the index IE episode post-TAVR.** The features, managing and
9 outcomes of the index IE episode following TAVR comparing SA-IE and non-SA-IE are detailed
10 in **Table 2**. The median time between TAVR and IE diagnosis was lower in SA-IE patients (4.7
11 months [IQR: 1.2-13.9] vs. 6.3 months [IQR: 2.1-14.9]; $p=0.032$). While the most common
12 presenting symptom was fever in both groups, patients with SA-IE showed higher rates of
13 neurological manifestations (SA-IE: 27.0% vs. non-SA-IE: 15.7%, $p=0.003$) and systemic
14 embolism (SA-IE: 18.4% vs. non-SA-IE: 10.7%, $p=0.014$) at admission. Healthcare-associated IE
15 was more frequent in the SA-IE group. (SA-IE: 53.2% vs. non-SA-IE: 40.7%, $p=0.010$). IE
16 episodes with TAVR prosthesis involvement were more likely in the non-SA-IE group (SA-IE:
17 50.4% vs. non-SA-IE: 61.3%, $p=0.013$) whereas the SA-IE group presented a higher proportion
18 of implantable cardiac device (other than TAVR prosthesis) infection (SA-IE: 9.2% vs. non-SA-
19 IE: 2.6%, $p=0.001$). The presence of vegetations as assessed either by transthoracic or
20 transesophageal echocardiography was lower in the SA-IE group (53.0% vs. 66.3%, $p=0.006$).
21 Despite the high proportion of patients with unknown infection foci (SA-IE: 37.6% and non-SA-
22 IE: 43.5%), SA-IE episodes were more likely to be related to TAVR procedures (SA-IE: 7.1% vs.
23 non-SA-IE: 3.2%, $p=0.047$), skin/soft tissue infection (SA-IE: 8.5% vs. non-SA-IE: 1.9%,

1 p<0.001) and vascular access (SA-IE: 9.2% vs. non-SA-IE: 1.4%, p<0.001), whereas
2 gastrointestinal (SA-IE: 1.4% vs. non-SA-IE: 8.3%, p=0.004) and odontological (SA-IE: 0.7% vs.
3 non-SA-IE: 5.3%, p=0.015) foci were more frequent in the non-SA-IE group.

4 The rate of patients presenting at least one IE-related complication during index
5 hospitalization was higher in the SA-IE group (SA-IE: 80.7% vs. non-SA-IE: 66.1%, p=0.001).
6 SA-IE patients complicated more frequently with new-onset heart failure (SA-IE: 53.3% vs. non-
7 SA-IE: 38.2%, p=0.002), acute renal failure (SA-IE: 58.7% vs. non-SA-IE: 35.7%, p<0.001),
8 persistent bacteremia (SA-IE: 41.8% vs. non-SA-IE: 26.9%, p= 0.003) and septic shock (SA-IE:
9 43.3% vs. non-SA-IE: 22.2%, p<0.001). There was an important variability of antibiotic regimens
10 in both groups, with more than 40 different drug combinations. β -Lactam antibiotics alone were
11 less likely used in SA-IE (SA-IE: 11.5% vs. non-SA-IE: 25.3%, p=0.001), whereas the use of
12 vancomycin alone or in combination with other antibiotics were similar (SA-IE: 35.1% vs. non-
13 SA-IE: 27.5%, p=0.116)

14 There were no differences between groups in surgical management rates (SA-IE: 21.0%
15 vs. non-SA-IE: 19.5%, p=0.694). In-hospital mortality was substantially higher in the SA-IE group
16 (SA-IE: 47.8% vs. non-SA-IE: 26.9%, p<0.001).

17 **Factors associated with SA-IE.** The univariate and multivariate-adjusted logistic model
18 determining the factors associated with *S aureus* as causative microorganism among patients with
19 IE post-TAVR are shown in **Supplementary Table S1**. The factors independently associated with
20 SA-IE were TAVR-related complications such as major bleeding (OR_{adj}: 2.82; 95% CI, 1.24-6.43,
21 p=0.013) and sepsis (OR_{adj}: 2.31; 95% CI, 1.13-4.72, p=0.021), neurological symptoms (OR_{adj}:
22 2.16; 95% CI, 1.19-3.92, p=0.011) and systemic embolism (OR_{adj}: 2.06; 95% CI, 1.04-4.08,
23 p=0.038) at IE admission, and IE with non-TAVR implantable cardiac device involvement (OR_{adj}:

1 4.50; 95% CI, 1.93-10.54, $p=0.001$). The likelihood of IE due to *S aureus* in patients with none of
2 the above-mentioned factors was 19.0% (95% CI, 15.2%-23.5%), and it increased to 26.5% (95%
3 CI, 20.3%-33.8%), 37.7% (95% CI, 26.6%-50.3%) and 84.6% (95% CI, 57.8%-95.7%), in the
4 presence of 1, 2 and ≥ 3 factors, respectively (**Figure 2**).

5 **Follow-up outcomes.** The Kaplan–Meier estimate survival curves at 2-year follow-up comparing
6 patients with SA-IE and non-SA-IE are shown in **Figure 3**. The mortality rate was higher in the
7 SA-IE group (71.5% vs. 49.6%, $p<0.001$ by log-rank test). The multivariate-adjusted Cox model
8 determining the independent factors associated with follow-up mortality according to the
9 microbiological etiology (non-SA-IE vs. SA-IE) are shown in **Figure 4** and **Supplementary Table**
10 **S2**. A higher risk profile as determined by the logistic EuroScore, the lack of surgical management
11 during index IE hospitalization, and IE-related complications such as septic shock and persistent
12 bacteremia determined an increased risk of mortality in patients with SA-IE.

13

14 **DISCUSSION**

15 The main findings of this study can be summarized as follows: (i) about 25% of cases of
16 IE post-TAVR had *S aureus* as causative microorganism; (ii) SA-IE patients presented more
17 frequently TAVR-related complications (acute renal failure, stroke, major bleeding and sepsis)
18 and longer intensive unit care hospitalization post-TAVR; (iii) periprocedural TAVR major
19 bleeding or sepsis, neurologic or systemic embolisms as presenting symptoms and IE with signs
20 of cardiac device involvement (other than TAVR prosthesis) were associated with SA-IE, and the
21 presence of such factors (particularly in combination) at index IE admission determined a high
22 likelihood of SA-IE ($>80\%$ in patients with ≥ 3 factors); (iv) SA-IE was associated with a higher
23 incidence of IE-related complications and a very high in-hospital (close to 50%) and follow-up

1 (>70% at 2 years) mortality rates; (v) the lack of surgical management at index IE hospitalization
2 among SA-IE patients determined an increased mortality risk.

3 PVE is the most severe subtype of IE, representing 10–30% of all IE cases.¹⁵ The incidence
4 of IE post-TAVR has been previously reported, ranging from 0.6% to 3.4% per year.^{1,2,16} Of note,
5 despite the evolution of the TAVR procedures over last years with simplified procedures and
6 improved devices, the overall IE incidence remains stable.⁴ There are scarce data comparing IE
7 after surgical aortic valve replacement (SAVR) and TAVR. Although most studies reported similar
8 incidence rates,^{17,18} a recent study analyzing a pooled cohort of 3 randomized clinical trials showed
9 a lower incidence of IE after TAVR compared with SAVR.¹⁹ Of note, the microbiological profile
10 differs between SAVR-IE and TAVR-IE. While enterococci represent only ~10% in SAVR-IE,
11 previous studies using the same cohort of patients revealed this microorganism as the leading cause
12 of TAVR-IE.^{1,4} Our data showed that TAVR-IE was associated with *S aureus* in 1 out of 4 patients.
13 These results are comparable with those reported in SAVR-IE registries. However, the proportion
14 of patients presenting with late SA-IE post-TAVR was slightly higher than those with late SA-IE
15 post-SAVR.⁸ This finding may be related to the particular TAVR patient's profile, leading to more
16 frequent diagnostic and therapeutic invasive procedures during the follow-up period.

17 The diagnosis of PVE is challenging and early diagnosis is essential since delayed
18 treatment is associated with worse clinical outcomes.^{20–22} This issue is even more relevant in
19 patients with suspected IE post-TAVR. First, TAVR recipients represent a particular population
20 with a high comorbidity burden, with patients commonly presenting with atypical symptoms.
21 Previous studies suggest that the modified Duke criteria show a lower diagnostic accuracy for IE-
22 TAVR than native valve IE, mainly related to a higher incidence of negative blood culture and
23 inconclusive echocardiographic findings.^{1,2} Second, IE post-TAVR has been associated with a

1 high incidence of severe IE-related complications and poor outcomes, with a mortality rate at 1-
2 year follow-up close to 50%. To date, no factors associated with *S aureus* as a causative
3 microorganism of IE post-TAVR has been identified. Our data show that TAVR complicated by
4 major bleeding or sepsis, the presence of neurological symptoms or systemic embolism at IE index
5 admission and signs of infection involving implantable cardiac devices other than the TAVR
6 prosthesis were independently associated with SA-IE in TAVR patients. These findings may have
7 important clinical implications since the presence of such factors, particularly in combination,
8 determined a very high likelihood of SA-IE (>80% in patients with ≥ 3 risk factors). Thus, in
9 patients presenting with suspected IE post-TAVR and exhibiting two or more risk factors for SA-
10 IE, treatment should be promptly initiated and oriented towards appropriate antibiotic regimens to
11 cover *S aureus* while waiting for blood culture results. Further studies are warranted to determine
12 if this strategy translates into a lower rate of IE-related complications and improved clinical
13 outcomes. Importantly, there was no association between the prosthesis type and the overall risk
14 of IE. However, patients presenting early SA-IE were more likely to have SEV than patients with
15 BEV. This finding may be partially explained by the higher proportion of patients receiving a
16 permanent pacemaker after the TAVR procedure in the SEV group than the BEV group (25.4% vs
17 10.4%), which increases the risk of bacteremia and consequently the risk of SA-IE.

18 IE post-TAVR has been associated with a poor prognosis and high mortality rate. The
19 current study results also highlight the virulence of SA-IE. Patients developing SA-IE presented
20 even a worse prognosis and higher in-hospital and late mortality rates than those in whom the IE
21 was caused by other microorganisms (47.8% vs. 26.9% and 71.5% vs. 49.6%, respectively). These
22 mortality rates were also substantially higher than those reported in patients presenting surgical
23 SA-IE, with in-hospital mortality $\sim 35\%$.^{23,24} This difference could be partially explained by the

1 higher baseline risk of TAVR patients due to age and comorbidities, in whom any complication
2 would place them at greater risk of mortality than their surgical counterparts. The rate of acute
3 renal failure, acute heart failure and septic shock during index hospitalization in the SA-IE group
4 was twice as much that observed in the non-SA-IE group. PVE management involves complex
5 antibiotic regimens along with surgery (valve explantation) in selected patients. Previous studies
6 reported that approximately half of the patients with IE secondary to *S aureus* undergo surgery
7 during IE index hospitalization.^{7,2526} While current guidelines recommend combined and
8 prolonged antibiotic regimens,^{9,27} the results of our study showed a wide variability of antibiotic
9 regimens in patients with SA-IE post-TAVR. A possible explanation for this finding could be the
10 noteworthy proportion of antimicrobial resistance, renal/hepatic toxicity and drug interactions in
11 the TAVR population that could hamper the application of these recommendations in real-world
12 situations. In addition, the rate of surgical intervention in patients with SA-IE was particularly low.
13 Although surgical treatment of PVE caused by *S aureus* should be considered (if low likelihood
14 of control with antimicrobial therapy), the rate of surgery was similar to that of non-SA-IE patients.
15 Previous studies have failed to demonstrate improved outcomes in patients with TAVR-IE
16 undergoing surgery compared with those treated with antibiotics alone.²⁸ Importantly, our findings
17 suggest that in patients with SA-IE after TAVR, surgery may have a protective effect when
18 adjusting for perioperative mortality risk (logistic EuroScore) and severe IE-related complications
19 (acute renal failure, septic shock, persistent bacteremia). Nevertheless, the role of surgical
20 treatment in TAVR patients is still debated and these results should be interpreted with caution.
21 Until recently, a significant proportion of TAVR recipients exhibited absolute contraindications
22 for surgery. Therefore, universal recommendations of surgery in native or prosthetic-IE could not
23 be extrapolated to TAVR recipients. Nevertheless, the contemporary TAVR patient profile is

1 rapidly changing, with an increasing proportion of low surgical risk patients, that could lead to an
2 increased number of TAVR-IE patients undergoing surgery in the coming years. Dedicated studies
3 are crucial for further substantiated our findings and establish surgery indications in TAVR-IE
4 patients.

5 The population at risk of IE following TAVR is projected to rise exponentially due to the
6 expansion of this treatment to younger patients with higher life expectancies. Consequently,
7 strategies aimed at limiting the incidence and improving IE outcomes in this population become
8 even more relevant, and prevention should be the cornerstone of this life-threatening pathology.
9 First, TAVR should keep moving forward to more simplified (and less invasive) procedures
10 leading to an earlier patient's ambulation and shorter hospital stays. Second, evidence and specific
11 recommendations regarding the most appropriate antimicrobial prophylaxis (in addition to aseptic
12 measures) before some invasive procedures are urgently required. Also, the importance of limiting
13 healthcare-associated procedures that could potentially trigger a bloodstream infection in this
14 population should be highlighted. Third, novel strategies for *S aureus* bacteremia prevention and
15 prosthetic infection would address an important unmet medical need. Device iterations with
16 innovative antibacterial biomaterials that prevent the bacteria adhesion to the prosthetic surfaces
17 could become be important to reduce IE in case of bloodstream infection.

18 **Study limitations:** The present study has certain limitations. First, this is an observational,
19 retrospective study, with the limitations and potential bias inherent to this design. Centers
20 participated voluntarily and there was no external monitoring committee to assess the accuracy of
21 data reported by each center. Second, this study included patients with definite IE after the TAVR
22 procedure regardless of the structure involved. Our cohort comprised ~60% of patients in whom
23 the TAVR prosthesis involvement was clearly identified. The rest were subjects who had isolated

1 cardiac devices IE (other than TAVR), mitral IE, right-side IE or patients in whom TAVR
2 involvement was not confirmed using conventional imaging techniques. Unfortunately, we were
3 unable to determine if some of these latter patients showed any undetected TAVR involvement.
4 Third, detailed information concerning imaging assessment during the follow-up was not available
5 in most patients.

6

7 **CONCLUSIONS**

8 SA-IE after TAVR is a particular life-threatening complication among patients with IE post-
9 TAVR, with a very high in-hospital (~50%, two times higher than non-SA-IE) and long-term
10 (>70% at 2-years) mortality. The presence of some features (periprocedural TAVR complications
11 like major bleeding/sepsis, neurological symptoms/embolism at index IE, involvement of devices
12 other than the TAVR valve) determined a higher likelihood of SA-IE. In patients presenting with
13 suspected IE post-TAVR, the presence of two or more risk factors may prompt an early treatment
14 oriented towards antibiotic regimens to cover *S aureus* while waiting for blood culture results.
15 Although the role of surgery has not been established in TAVR-IE patients yet, the results of this
16 study suggest that surgical treatment may have a protective effect in SA-IE post-TAVR patients.
17 Further studies are warranted.

18

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Table 1. Baseline characteristics, procedural details, and in-hospital TAVR outcomes, according to the causative microorganism (*S aureus* vs. No *S aureus*).

	Non-<i>S. Aureus</i> (n=432)	<i>S aureus</i> IE (n=141)	Unadjusted P value
Baseline characteristics			
Age, median (IQR), years	81 (75-84)	80 (75-84)	0.579
Female, n (%)	154 (35.7)	58 (41.1)	0.241
Body mass index (kg/m ²)	27.2 (24.4-30.9)	25.6 (23.4-28.9)	0.001
Diabetes mellitus, n (%)	160 (37.0)	54 (38.3)	0.788
COPD, n (%)	112 (25.9)	44 (31.2)	0.221
Atrial fibrillation, n (%)	186 (43.1)	56 (39.7)	0.473
Chronic renal failure, n (%)	173 (40.1)	67 (47.5)	0.162
Previous Stroke, n (%)	61 (14.1)	15 (10.6)	0.290
Previous valve surgery, n (%)	48 (11.1)	14 (9.9)	0.683
Previous infectious endocarditis, n (%)	6 (1.4)	3 (2.1)	0.545
Logistic EuroSCORE, % (IQR)	14.0 (8-23.4)	13.5 (8.7-21.4)	0.581
Left ventricular ejection fraction, % (SD)	54.3 (13.1)	51.5 (14.5)	0.067
Mean transaortic gradient, mean (SD), mmHg	46.0 (15.5)	41.7 (16.0)	0.005
Aortic valve area, mean (SD), cm ²	0.73 (0.22)	0.72 (0.25)	0.532
Periprocedural characteristics,			
Implantation site, n (%)			
Catheterization laboratory	181 (41.9)	55 (39.0)	0.659
Operating or hybrid room	251 (58.1)	86 (61.0)	
Approach, n (%)			
Transfemoral	380 (88.0)	128 (90.9)	0.360
Other	52 (12.0)	13 (9.2)	
Conscious sedation, n (%)	213 (49.3)	76 (53.9)	0.272
Prosthesis type, n (%)			
Balloon-expandable	225 (52.1)	73 (51.8)	0.233
Self-expandable	200 (46.3)	65 (46.1)	
Antibiotic prophylaxis, n (%)			
B-Lactam alone	313 (79.0)	109 (87.2)	0.613
Vancomycin (alone or in combination)	17 (4.3)	4 (3.2)	
In-hospital Outcomes (TAVR)			

Acute renal failure, n (%)	45 (10.4)	27 (19.2)	0.005
Stroke, n (%)	14 (3.2)	12 (8.5)	0.008
Major vascular complication, n (%)	25 (5.8)	14 (9.9)	0.082
Major bleeding, n (%)	34 (7.9)	20 (14.2)	0.023
Sepsis, n (%)	34 (7.9)	23 (16.3)	0.001
New pacemaker implantation, n (%)	74 (17.1)	30 (21.3)	0.257
Residual aortic regurgitation >2 at discharge, n (%)	63 (14.6)	19 (13.5)	0.839
Length of ICU stay, median (IQR), days	1.5 (1-3)	2 (1-5)	0.011
Length of hospital stay, median (IQR), days	8.5 (6-14)	9 (7-15)	0.060

Table 2. Main clinical characteristics, management, and outcomes of IE after TAVR, according to the causative microorganism (*S aureus* vs. No *S aureus*)

	Non-<i>S. Aureus</i> (n=432)	<i>S aureus</i> (n=141)	Unadjusted P value
Time from TAVR, median (IQR), months	6.3 (2.1-14.9)	4.7 (1.2-13.9)	0.032
Early IE	291 (67.4)	101 (71.6)	0.379
Late IE	139 (32.2)	40 (28.4)	
Initial symptoms, n (%)			
Fever	326 (75.5)	116 (82.3)	0.058
New-onset heart failure	171 (39.6)	58 (41.1)	0.602
Neurological	68 (15.7)	38 (27.0)	0.003
Systemic embolism	46 (10.7)	26 (18.4)	0.014
Cutaneous	17 (3.9)	9 (6.4)	0.213
Health care-associated infection, n (%)	176 (40.7)	75 (53.2)	0.010
Echocardiographic findings, n (%)			
Vegetation	279 (66.3)	71 (53.0)	0.006
Vegetation size, median (IQR), mm	10 (6-15)	10 (7-17)	0.298
No TAVR platform affection	158 (36.6)	69 (48.9)	0.013
Periannular complication	83 (24.4)	22 (23.4)	0.840
New aortic regurgitation	54 (14.8)	6 (6.2)	0.025
New mitral regurgitation	63 (17.7)	12 (12.9)	0.274
Structure involved, n (%)			
Isolated TAVR prosthesis	221 (51.2)	57 (40.4)	0.027
Mitral (native- or prosthetic valve)	65 (15.1)	21 (14.9)	0.965
Implantable cardiac device	11 (2.6)	13 (9.2)	0.001
Right-sided IE	8 (1.9)	0 (0.0)	0.210
Multi (2 localization at least)	127 (29.4)	50 (35.5)	0.176
Presumed source of entry, n (%)			
Unknown	188 (43.5)	53 (37.6)	0.216
Procedural TAVR related	14 (3.2)	10 (7.1)	0.047
Urological	43 (10.0)	10 (7.1)	0.309
Odontological	23 (5.3)	1 (0.7)	0.018
Gastrointestinal	36 (8.3)	2 (1.4)	0.004
Pacemaker implantation	8 (1.9)	4 (2.8)	0.478
Skin/soft tissue infection	8 (1.9)	12 (8.5)	<0.001

Intravascular source	6 (1.4)	13 (9.2)	<0.001
Other	106 (24.5)	36 (25.5)	0.812
Complications during infective endocarditis hospitalization, No./total (%)			
Any complication	275 (66.1)	109 (80.7)	0.001
Heart failure	159 (38.2)	72 (53.3)	0.002
Acute renal failure	139 (35.7)	74 (58.7)	<0.001
Septic shock	92 (22.2)	58 (43.3)	<0.001
Stroke	41 (9.9)	16 (11.9)	0.508
Other systemic embolization	40 (9.6)	19 (14.2)	0.138
Persistent bacteremia	101 (26.9)	46 (41.8)	0.003
Surgery during IE hospitalization, No./total (%)	82 (19.5)	29 (21.0)	0.694
Time to surgery, median (IQR), days	17 (7-37)	11.5 (5-22)	0.094
Isolated Aortic valve replacement	44/77 (57.1)	11/29 (37.9)	0.078
Isolated mitral valve replacement	1/77 (1.3)	2/29 (6.9)	0.121
Isolated cardiac device extraction	7/77 (9.1)	11/29 (37.9)	<0.001
Combined surgery	25/77 (32.5)	5/29 (17.2)	0.121
Follow-up outcomes			
Follow-up, median (IQR), months ^a	15.4 (4.8-35.6)	13.1 (3.7-24.3)	0.077
In-hospital mortality, n (%)	113 (26.9)	66 (47.8)	<0.001
1-year mortality rate, (95% CI), %	43.7 (38.8-48.9)	62.1 (53.8-70.5)	<0.001 ^b
2-year mortality rate, (95% CI), %	49.6 (44.5-55.1)	71.5 (62.9-79.7)	<0.001 ^b
Recurrence of IE, No./total (%)	41/307 (13.4)	7/72 (9.7)	0.312

^aPatients who survived in-hospital period

^bby log-rank test

FIGURE LEGENDS:**Figure 1. Study population**

Flow-chart of study population of patients with IE after TAVR.

Figure 2: SA-IE rate according to the presence of associated factors for SA-IE in patients with IE after TAVR.

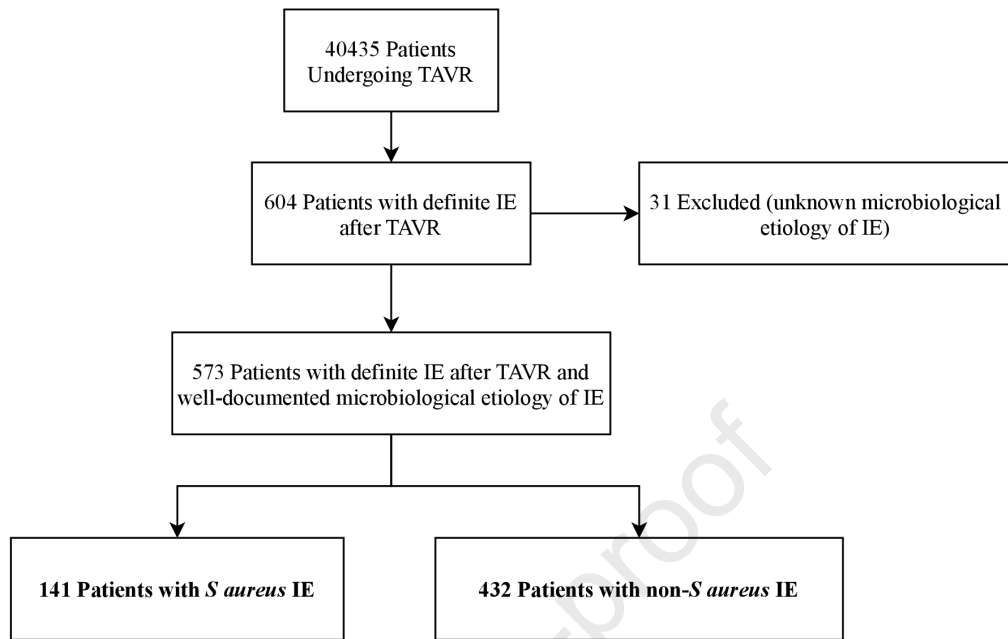
Figure representing the likelihood of SA-IE in patients with infective endocarditis (IE) after transcatheter aortic valve replacement (TAVR) according to the presence of associated factors.

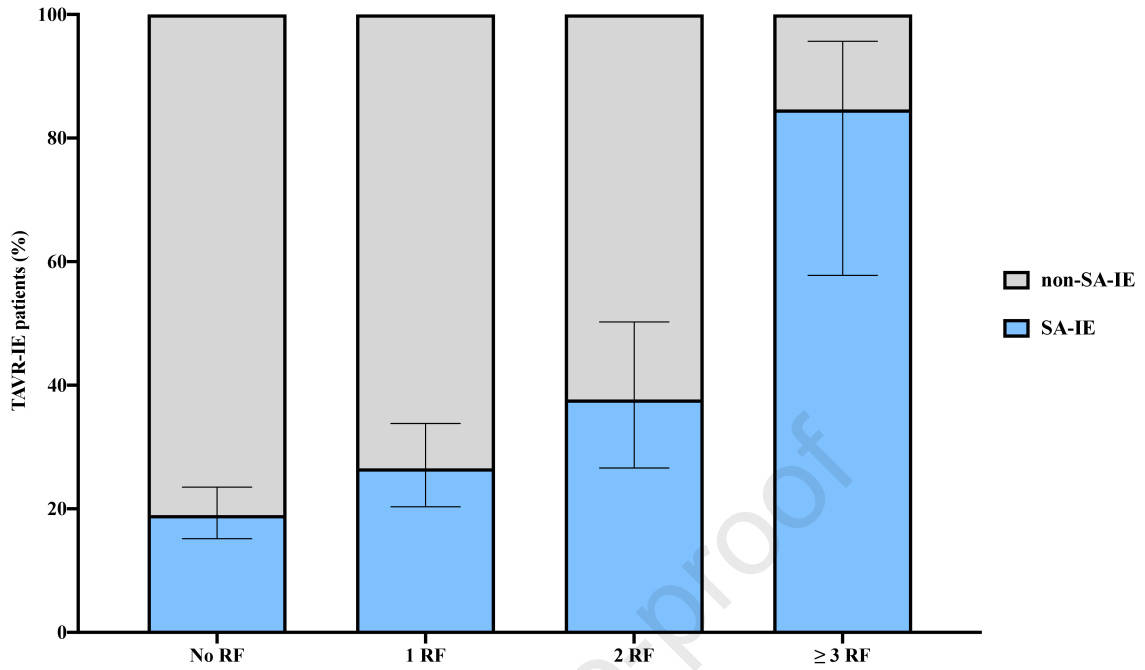
RF indicates risk factor.

Figure 3. Survival analysis.

Kaplan–Meier estimate survival curve at 2-year follow-up comparing patients with SA-IE and non-SA-IE.

Figure 4: Factors associated with cumulative follow-up mortality in patients with infective endocarditis comparing SA-IE and non-SA-IE.





Incidence (95% CI) 18.99% (15.16-23.52) 26.54% (20.34-33.83) 37.70% (26.61-50.25) 84.62% (57.77-95.67)

No. of patients

non-SA-IE	273	119	38	2
SA-IE	64	43	23	11

